Clinical Trial Protocol

Clinical Trial Protocol Number	MS200527-0060
Title	A Phase IIb, Randomized, Double-blind Study in Subjects with Rheumatoid Arthritis Evaluating the Safety and Efficacy of Evobrutinib Compared with Placebo in Subjects with an Inadequate Response to Methotrexate
Phase	IIb
IND Number	CCI
EudraCT Number	2017-000384-32
Coordinating Investigator	PPD
Sponsor	For all countries except the USA and Japan: Merck KGaA, Frankfurter Str. 250 64293 Darmstadt, Germany For Japan only: Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan And For the USA EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821 USA Medical Responsible: PPD EMD Serono Research & Development Institute 45A Middlesex Turnpike, Billerica, MA 01821, USA Telephone: PPD

Clinical Trial Protocol Version	12 July 2018/Version 3.0 (Amendment 4)
Replaces Version	13 December 2017/Version 2.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	11 May 2017
1.1	Amendment specific for US	03 July 2017
2.0	Global Amendment	13 December 2017
2.1	Amendment specific for US	16 November 2017
3.0	Global Amendment	12 July 2018

Protocol Version [3.0] (12-July-2018)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

After receiving feedback from multiple regulatory agencies, the Sponsor has decided not to initiate the Open-label Extension (OLE) Period.

Section # and Name	Description of Change	Brief Rationale
Throughout	All mention of OLE and related procedures, objectives, and duration estimates were removed	Implementing Sponsor decision to not initiate the OLE Period
Synopsis	Removed Table 2 and Table 3	No longer required given Sponsor decision to not initiate the OLE Period
8.6. Planned Analysis	Removed 12-week analysis and moved consistency analysis to be part of the final analysis	Without the OLE, there is no need to run an interim analysis before the final analysis
Synopsis	Added text to explain removal of OLE Period and provide procedure for subjects already in the OLE Period	Give guidance for subjects who enroll in the OLE Period prior to implementation of Protocol Version 3.0.
7.1.3. Open-label Extension Period	Added text to explain removal of OLE Period and provide procedure for subjects already in the OLE Period	Give guidance for subjects who enroll in the OLE Period prior to implementation of Protocol version 3.0.

[redacted]

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CCI [redacted]

List of Abbreviations

ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% Response Criteria
ACR50	American College of Rheumatology 50% Response Criteria
ACR70	American College of Rheumatology 70% Response Criteria
AE	Adverse event
ALT	Alanine aminotransferase
APRIL	A proliferation-inducing ligand
AST	Aspartate aminotransferase
AUC	Area under the curve
β-hCG	Beta-human chorionic gonadotropin
bDMARD	Biologic disease-modifying anti-rheumatic drugs
bDMARD-IR	RA subjects with inadequate response to methotrexate and ≥ 1 bDMARD
BID	Twice daily
BlyS	B lymphocyte stimulator (also called B-cell activating factor or BAFF)
BTK	Bruton's tyrosine kinase
C	Collect
CARLOS	Cartilage Loss Scale
CAT	Computer adaptive testing
CCP	Cyclic citrullinated protein
CDAI	Clinical Disease Activity Index
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical trial report
CXR	Chest X-ray
CYP	Cytochrome P450
CYP3A	Cytochrome P450 isozyme 3A
CYP3A4/5	Cytochrome P450 isozyme 3A4/5

DAS	Disease Activity Score
DAS28	Disease Activity Score Based on a 28 Joint Count
DMARD	Disease-modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-Glutamyl-transferase
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
CCI	[redacted]
hsCRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IMP	Investigational Medicinal Product

IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
JAK	Janus kinase
JSN	Joint space narrowing
LDA	Low disease activity
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver Function Test
LLN	Lower limit of normal
LTBI	Latent tuberculosis infection
MAR	Missing at random
MCP	Metacarpophalangeal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MOP	Manual of Procedures
MRI	Magnetic resonance imaging
mRNA	Messenger Ribonucleic Acid
MTX	Methotrexate
MTX-IR	RA subjects with inadequate response to methotrexate
NIH	National Institute of Health
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PCR	Polymerase chain reaction
PD	Pharmacodynamics
CCI	[redacted]
PK	Pharmacokinetics
PO	Orally
PP	Per-Protocol
CCI	[redacted]
Q2W	Every 14 days
QD	Once daily

R	Review
RA	Rheumatoid arthritis
RAMRIQ	Rheumatoid Arthritis Magnetic Resonance Image Quantification
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System
RF	Rheumatoid factor
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDAI	Simplified Disease Activity Index
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SJC	Swollen joint count
SLE	Systemic lupus erythematosus
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TJC	Tender joint count
TNF	Tumor necrosis factor
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drugs
ULN	Upper limit of normal
VAS	Visual analog scale
WOCBP	Women of childbearing potential

1 Synopsis

Clinical Trial Protocol Number	MS200527-0060
Title	A Phase IIb, Randomized, Double-blind Study in Subjects with Rheumatoid Arthritis Evaluating the Safety and Efficacy of Evobrutinib Compared with Placebo in Subjects with an Inadequate Response to Methotrexate
Trial Phase	IIb
IND Number	CCI
FDA covered trial	Yes
EudraCT Number	2017-000384-32
Coordinating Investigator	PPD Telephone: PPD E-mail: PPD
Sponsor	For all countries except the USA and Japan: Merck KGaA, Frankfurter Str. 250 64293 Darmstadt, Germany For Japan only: Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan And For the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA Medical Responsible: PPD EMD Serono Research & Development Institute 45A Middlesex Turnpike, Billerica, MA 01821, USA Telephone: PPD

Trial centers/countries	Approximately 160 sites in 17 countries
Planned trial period (first subject in-last subject out)	June 2017 to June 2020
Trial Registry	ClinicalTrials.gov, EudraCT

Objectives:

Primary objective:

- To evaluate the efficacy and dose response of 12 weeks of treatment with evobrutinib compared with placebo in subjects with rheumatoid arthritis (RA) with inadequate response to methotrexate (MTX-IR) on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by American College of Rheumatology (ACR) 20% (ACR20) response assessed using high-sensitivity C-reactive protein (hsCRP) at Week 12.

Key secondary objectives:

- To further evaluate the efficacy and dose response of 12 weeks of treatment with evobrutinib in MTX-IR subjects with RA on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by DAS28-hsCRP low disease activity (DAS28 < 3.2) rate at Week 12
- To further evaluate the efficacy of 12 weeks of treatment with evobrutinib compared to placebo in MTX-IR subjects with RA on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by DAS28-hsCRP remission (DAS28 < 2.6) rate at Week 12
- To further evaluate the efficacy and dose response of 12 weeks of treatment with evobrutinib in MTX-IR subjects with RA on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by ACR50 and ACR70 at Week 12
- To evaluate the safety of evobrutinib in MTX-IR subjects with RA on stable MTX therapy.

Other secondary objectives:

- To further evaluate the efficacy of evobrutinib on the signs and symptoms of RA with inadequate response to MTX
- To evaluate the effect of evobrutinib on joint structures and inflammation, at Weeks 4 and 12 in the MRI substudy, as assessed by magnetic resonance imaging (MRI)
- To evaluate the effect of evobrutinib on physical function in RA subjects
- To evaluate the effect of evobrutinib on subject-reported health-related quality of life (HRQoL)
- To evaluate the effect of evobrutinib on subject-reported fatigue (using Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue).

Exploratory objectives:

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Methodology:

This is a Phase IIb, multicenter, international, randomized, double-blind, placebo-controlled parallel-arm trial, designed to determine the efficacy, dose response, and safety of evobrutinib (also known as M2951) in subjects 18 to 75 years of age with moderate to severe RA, and to consider a dose to take forward into Phase III development.

Enrollment will include approximately 360 MTX-IR subjects with no prior treatment with biologic disease-modifying anti-rheumatic drugs (bDMARD) or targeted synthetic DMARD (tsDMARD).

Approximately 50% of the subjects will participate in a substudy using MRI to evaluate the ability of evobrutinib to prevent the progression of joint structural damage.

Eligible subjects will be randomly assigned in a 1:1:1:1 ratio to receive, in combination with their stable background MTX therapy, evobrutinib 25 mg once daily, evobrutinib 75 mg once daily, evobrutinib 50 mg twice daily, or placebo.

Randomization will be stratified by whether or not subjects are in the MRI substudy and by region.

The trial is composed of a Screening Period of 4 weeks, a Treatment Period of 12 weeks, and a Safety Follow-up Period of 4 weeks. After completing the 12-week Treatment Period, subjects will enter into safety follow up period.

In Protocol version 2.0, subjects completing the Treatment Period could have entered an optional Open-label Extension (OLE) Period, but the Sponsor made the decision to not initiate the OLE Period. As of the effective date of Protocol version 3.0 at study sites, all subjects completing the Treatment Period will enter the Safety Follow-up Period, and any subjects already participating in the OLE Period at that time will be immediately withdrawn from the study following the protocol-specified withdrawal procedures: subjects would return for an End of Treatment Visit and return 4 weeks later for an End of Study/Safety Follow-up Visit.

During the trial, clinical efficacy endpoints will be evaluated using assessments of clinical response, disease activity and remission, prevention of joint structural damage progression, physical function, fatigue, and HRQoL. Safety will be evaluated through the nature,

occurrence, severity and outcome of adverse events (AEs), and assessment of physical examination findings, electrocardiograms (ECGs), hematology and chemistry laboratory assessments, vital signs, and absolute values and change from Baseline in serum total immunoglobulin (Ig) levels (IgG, IgA, and IgM) and total B cell counts.

Planned number of subjects: 360 subjects with RA (to achieve 320 evaluable subjects)

Primary endpoint:

Primary efficacy endpoint: ACR20 response assessed using hsCRP (ACR20) at Week 12.

Key secondary endpoints:

Key secondary efficacy endpoints:

- DAS28-hsCRP low disease activity (DAS28 < 3.2) rate at Week 12
- DAS28-hsCRP remission (DAS28 < 2.6) rate at Week 12
- ACR 50% (ACR50) response assessed using hsCRP at Week 12
- ACR 70% (ACR70) response assessed using hsCRP at Week 12.

Key secondary safety endpoints:

- The nature, severity, and occurrence of AEs and serious AEs (SAEs)
- Absolute values and change from Baseline in:
  - Vital signs
  - ECG parameters including RR interval, PR interval, QRS duration, QT interval, and QTcF interval
  - Serum Ig levels (IgG, IgA, IgM)
  - Total B cell counts
  - Clinical laboratory parameters.

Other secondary efficacy endpoints:

At Week 12:

- Achieving American College of Rheumatology/European League Against Rheumatism (EULAR) Boolean remission
- Achieving Clinical Disease Activity Index (CDAI) score ≤ 2.8 (CDAI remission)
- Achieving Simplified Disease Activity Index (SDAI) score ≤ 3.3 (SDAI remission)
- EULAR Responder Index (based on DAS-hsCRP)
- ACR hybrid scores computed using hsCRP
- Change from Baseline in DAS28-hsCRP
- Change from Baseline in CDAI and SDAI

- Changes and percentage changes from Baseline of individual components of the ACR Core Set
- Imaging:
  - Change from Baseline in Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) scores (designated hand, minimal assessed joints: wrist, metacarpophalangeal [MCP] joints #1 to #5) for subjects in the MRI substudy:
    - Synovitis score
    - Bone marrow edema (osteitis) score.
- Changes from Baseline of Physical Function:
  - Health Assessment Questionnaire – Disability Index (HAQ-DI).
- Changes from Baseline of HRQoL:
  - Medical Outcomes Study 36-item Short Form Health Survey (SF-36)
  - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.

Exploratory endpoints:

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[redacted]

Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria (all subjects):

The current trial will enroll subjects who fulfill the following key inclusion criteria:

- Consenting male or female subjects, 18 to 75 years of age (In Japan, if a subject is < 20 years, the written informed consent from the subject's parent or guardian will be required in addition to the subject's written consent.)
- Confirmed diagnosis of RA according to 2010 ACR/EULAR RA classification criteria of at least 6 months duration prior to Screening

- Persistently active moderate to severe RA at both Screening and Randomization (if significant surgical treatment of a joint has been performed, that joint cannot be counted for entry or enrollment purposes), as defined by:
  - ≥ 6 swollen joints (of 66 assessed) **and**
  - ≥ 6 tender joints (of 68 assessed).
- An hsCRP ≥ 5.0 mg/L (≥ 0.50 mg/dL) at Screening
- Treatment for ≥ 16 weeks with 7.5 to 25 mg/week MTX at a stable dose and route of administration (oral or parenteral) for at least 8 weeks prior to dosing with the IMP and maintained throughout the trial
- For subjects entering the trial on MTX doses < 15 mg/week (< 10 mg/week in Japan), there must be clear documentation in the medical record that higher doses of MTX were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines.

MRI Substudy Subjects:

In addition to meeting the inclusion criteria for the study, subjects must have palpable synovitis of the wrist and/or ≥ 1 of MCP joints #1 to #5, defined as loss of bony contours with palpable joint effusion and/or swelling, in the MRI-designated hand (ie, the hand being used in MRI assessments).

Key exclusion criteria (all subjects):

Subjects who fulfill any of the following key exclusion criteria should not be enrolled into this trial:

- ACR functional class IV as defined by the ACR classification of functional status or wheelchair/bedbound
- Use of oral corticosteroids > 10 mg daily prednisone equivalent, or change in dose of corticosteroids within 2 weeks prior to Screening or during Screening
- Use of injectable corticosteroids (including intra-articular corticosteroids) or intra-articular hyaluronic acid within 4 weeks prior to Screening or during Screening
- Initiation or change in dose for nonsteroidal anti-inflammatory drugs (NSAIDs) (including low-dose aspirin and COX-2 inhibitors) within 2 weeks prior to dosing with the IMP
- High potency opioid analgesics are prohibited within 2 weeks prior to Screening and during the trial; other analgesics are allowed (eg, acetaminophen, codeine, hydrocodone*, propoxyphene*, or tramadol), although not within 24 hours of study visits with clinical assessments (*not approved in Japan).
- Current or prior treatment with **ANY** of the following:
  - Biologic DMARDs (approved or investigational), including but not limited to:
    - TNF antagonists or biosimilars of these agents (approved or investigational), or any investigational TNF antagonist

- Interleukin-6 antagonists
- Abatacept (CTLA4-Fc)
- Anakinra* (IL-1 receptor antagonist) (*not approved in Japan)
- B cell-depleting antibodies (eg, rituximab, ocrelizumab*, ofatumumab, obinutuzumab*, ocaratuzumab*, veltuzumab*, or any biosimilars of these agents [approved or investigational]) (*not approved in Japan)
- Anti-BLyS (B lymphocyte stimulator) agents (eg, belimumab, tabalumab*) (*not approved in Japan)
- Dual BLyS/A proliferation-inducing ligand (APRIL) neutralizing agents (eg, atacicept*, RCT-18*) (*not approved in Japan).

o Targeted synthetic DMARDs (approved or investigational), specifically:

- Janus kinase inhibitors
- Other Bruton's tyrosine kinase (BTK) inhibitors

o Alkylating agents (eg, chlorambucil*, cyclophosphamide) (*not approved in Japan).

- The following restrictions on nonbiologic DMARD must be followed, otherwise the subject is excluded:
  - o Auranofin (Ridaura®), minocycline, penicillamine, sulfasalazine, cyclosporine, mycophenolate (mycophenolate sodium not approved in Japan), tacrolimus, azathioprine: must have been discontinued for 4 weeks prior to dosing with the IMP
  - o Leflunomide (Arava®) must have been discontinued 12 weeks prior to dosing with the IMP if no elimination procedure is followed. Alternately, it should have been discontinued with the following elimination procedure at least 4 weeks prior to dosing with the IMP: Cholestyramine at a dosage of 8 g 3 times a day for at least 24 hours, or activated charcoal at a dosage of 50 g 4 times a day for at least 24 hours.
  - o Injectable Gold (aurothioglucose* or aurothiomalate): must have been discontinued for 8 weeks prior to dosing with the IMP (*not approved in Japan)
  - o Anti-malarials (hydroxychloroquine, chloroquine*) will be allowed in this trial. Subjects may be taking oral hydroxychloroquine (≤ 400 mg/day) or chloroquine* (≤ 250 mg/day), doses must have been stable for at least 12 weeks prior to dosing with the IMP, and will need to be continued at that stable dose for the duration of the trial. If discontinued prior to this trial, they must have been discontinued for 4 weeks prior to dosing with the IMP (*not approved in Japan).

MRI Substudy Subjects:

- Inability to comply with MRI scanning, including contraindications to MRI such as known allergy to gadolinium contrast media, claustrophobia (if the site does not have ability to scan extremities only), presence of a pacemaker, cochlear implants, ferromagnetic devices or clips, intracranial vascular clips, insulin pumps, and nerve stimulators.

- More than 25% of applicable joints of the target hand and wrist having had prior surgery or showing maximum Genant-modified Sharp erosion (3.0) or joint-space narrowing (4.0) scores, based on single posteroanterior radiographs of target hand and wrist read centrally.

Investigational Medicinal Product: dose/mode of administration/dosing schedule:

Subjects randomized into the trial will receive 1 of 3 doses of evobrutinib (also known as M2951) (25 mg once daily, 75 mg once daily, or 50 mg twice daily) or placebo, taken orally.

Reference therapy: dose/mode of administration/dosing schedule:

Not applicable.

Planned trial and treatment duration per subject:

Total duration of subject participation is approximately 5 months (approximately 20 weeks) which includes:

- Screening: 28 days (4 weeks)
- Treatment: 84 days (12 weeks)
- Safety Follow-up: 28 days (4 weeks).

Statistical methods:

A sample size of 80 evaluable subjects per group will provide adequate (approximately 90%) power to detect a difference in ACR20 response proportion at Week 12 between evobrutinib and placebo-treated subjects at an $\alpha = 0.05$ 2-sided significance level, assuming a placebo response proportion of 30% to 45% and an expected treatment benefit of 30%, after adjusting for multiple comparisons of 3 dose comparisons with placebo. For the same range of placebo response rate, the sample size of 80 evaluable subjects per group will also provide adequate power (approximately 80%) for the expected difference of 25%. To account for reduced information provided by the Modified Intent-to-Treat (mITT) analysis set, due to subject dropout and protocol noncompliance, occurring at a rate of approximately 11% over a 12-week period, approximately 90 subjects per group will be enrolled. The study includes a Japanese cohort: 32 evaluable Japanese subjects total, increased to 36 randomized Japanese subjects total to protect against loss of information.

For the evaluation of MRI data, assuming an effect size of 0.7 for change from Baseline in the OMERACT RAMRIS individual scores for osteitis or synovitis at Week 12, at a 2-sided $\alpha = 0.05$, a sample size of 40 evaluable subjects per group with MRI data will provide approximately 80% power using the Wilcoxon rank-sum test. To account for approximately 11% dropout and nonevaluable MRI data, approximately 45 subjects per arm will be enrolled in the MRI study.

There is 1 planned analysis from this study. The final analysis will be triggered when 100% of subjects randomized complete the safety follow-up or discontinue prematurely from the study, the protocol violations are determined, and the database is locked. All data collected up to and including the Safety Follow-up Visit will be included in this analysis. A consistency analysis is also planned to be performed as part of the final analysis to evaluate the consistency of efficacy at Week 12 between the Japan and non-Japan subjects. If the Japanese cohort

enrollment is too slow to have n = 32 to 36 evaluable subjects included in the consistency analysis, then the consistency analysis will not occur.

For the primary and key secondary efficacy analyses, ACR20 (ACR50/ACR70) response rate, the estimate of the odds ratio (OR), together with the associated 2-sided 95% CI and p-value, comparing each evobrutinib dose group to placebo, is based on a logistic regression model for the odds of ACR20 (ACR50/ACR70) response, with evobrutinib dose group or placebo as a factor and adjustment for covariates based on randomization strata (region, MRI-substudy participation).

The dose response will be assessed via a modeling approach as an additional supportive analysis.

Analysis of the change from Baseline scores of the MRI data will be performed on the appropriate analysis sets (eg, MRI analysis set for the RAMRIS scores) using a mixed-effect model for repeated measures, with treatment arm as factors, and randomization strata, and Baseline as covariates.

Analyses of all other secondary endpoints will be exploratory in nature.

Safety data will be listed and summarized using descriptive statistics.

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Table 1 Schedule of Assessments – Screening to Safety Follow-up Visit

Activity/Assessment	Screening			Treatment Period							Safety Follow-up[a]/End of Trial Visit
Trial Visit Number	***1a***	***1b***	***1c***	***2***	***3***	***4***	***4a***	***5***	***5a***	***6/End of Treatment/Early Withdrawal***	
Trial Week				**1 (Baseline)**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Trial Day	**-28 to -1**			**1**	**14**	**28**	**42**	**56**	**70**	**84**	**112**
Visit Window (Days)	**+ 7**				**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**- 5**	**+ 5**
Informed consent	X										
Inclusion/Exclusion criteria	X			X[b]							
Demographics	X										
Medical history[c]	X										
Physical examination	X			X						X	X
Abbreviated physical examination					X	X		X			
Vital signs[d]	X			X	X	X		X		X	X
12-lead ECG[e]	X			X				X		X	
Chest X-ray[f]	X										
Concomitant medicines and procedures[g]	X			X	X	X	X	X	X	X	X
Tuberculosis test	X										
HIV/Hepatitis B/ Hepatitis C test	X										
Reflex testing for HBV DNA[h]	X					X		X		X	X
MRI[i]			X			X				X	
Posteroanterior radiograph of target hand and wrist[j]		X									
TSH	X										

Activity/Assessment	**Screening**			**Treatment Period**							**Safety Follow-up[a]/End of Trial Visit**
Trial Visit Number	***1a***	***1b***	***1c***	***2***	***3***	***4***	***4a***	***5***	***5a***	***6/End of Treatment/Early Withdrawal***	
Trial Week				**1 (Baseline)**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Trial Day	**-28 to -1**			**1**	**14**	**28**	**42**	**56**	**70**	**84**	**112**
Visit Window (Days)	**+ 7**				**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**- 5**	**+ 5**
Pregnancy test (serum β-hCG) and FSH[k]	X										
Highly sensitive urine pregnancy test				X		X		X		X	X
Serum β-D-glucan[l]	X										
Randomization				X							
Dispense/review/collect subject diary				D	R	R		R		R/C	
SF-36[m]				X		X		X		X	
FACIT-Fatigue[m]				X		X		X		X	
CCI											
IMP dispensation[o]				X	X	X		X		X	
IMP administration[p]				X	Daily administration of evobrutinib or placebo						
IMP compliance[q]					X	X		X		X	
Patient's Assessment of Arthritis Pain VAS[r,m]	X			X	X	X		X		X	
Patient's Global Assessment of Disease Activity VAS[r,m]	X			X	X	X		X		X	
Tender/Swollen Joint Count (68/66 joints)[r]	X			X	X	X		X		X	
Physician's Global Assessment of Disease Activity VAS[r]	X			X	X	X		X		X	
HAQ-DI[r]				X	X	X		X		X	

Activity/Assessment	**Screening**			**Treatment Period**							**Safety Follow-up[a]/End of Trial Visit**
Trial Visit Number	***1a***	***1b***	***1c***	***2***	***3***	***4***	***4a***	***5***	***5a***	***6/End of Treatment/Early Withdrawal***	
Trial Week				**1 (Baseline)**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Trial Day	**-28 to -1**			**1**	**14**	**28**	**42**	**56**	**70**	**84**	**112**
Visit Window (Days)	**+ 7**				**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**- 5**	**+ 5**
AE evaluation[s]	X			X	X	X	X	X	X	X	X
IgG, IgA, IgM, and IgG subclasses	X			X	X	X		X		X	X
Total B cell counts[t]	X			X	X	X		X		X	X
Hematology[v]	X			X[u]	X	X		X		X	X
Biochemistry	X			X[u]	X	X		X		X	X
CCI											
Coagulation	X										
Lipid panel[x]				X							
Urinalysis, Urine Microscopy[y]	X			X				X		X	
hsCRP[r]	X[z]	X[z]		X	X	X		X		X	X
ESR[r]				X						X	
CCI											
B cell subsets[t]				X[u]		X				X	X
Whole blood/T cells, NK cells, monocytes, and T cell subsets[t]				X[u]						X	
CCI											
Anti-CCP	X			X[u]						X	
RF	X			X						X	
14-3-3η				X						X	
Whole blood RNA[bb]				X						X	

Activity/Assessment	Screening			Treatment Period							Safety Follow-up[a]/End of Trial Visit
Trial Visit Number	*1a*	*1b*	*1c*	*2*	*3*	*4*	*4a*	*5*	*5a*	*6/End of Treatment/Early Withdrawal*	
Trial Week				1 (Baseline)	2	4	6	8	10	12	16
Trial Day	-28 to -1			1	14	28	42	56	70	84	112
Visit Window (Days)	+ 7				± 2	± 2	± 2	± 2	± 2	- 5	+ 5
CCI											

ACR = American College of Rheumatology, AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, C = collect, CAT = Computer adaptive testing, CCP = cyclic citrullinated protein, CXR = chest X-ray, D = Dispense, DNA = deoxyribonucleic acid, ECG = electrocardiogram, ESR = erythrocyte sedimentation rate, FACIT = Functional Assessment of Chronic Illness Therapy, FSH = follicle-stimulating hormone, GGT = γ-Glutamyl-transferase, HAQ-DI = Health Assessment Questionnaire – Disability Index, HBsAg = hepatitis B surface antigen, HBV = hepatitis B Virus; HIV = Human Immunodeficiency Virus, CCI, hsCRP = high-sensitivity C-reactive protein, ICF = Informed Consent Form, Ig = immunoglobulin, IMP = investigational medicinal product, LFT = liver function test, MRI = magnetic resonance imaging, NK = natural killer, CCI, R = review, R/C = review/collect, RA = rheumatoid arthritis, RF = rheumatoid factor, RNA = ribonucleic acid, SF-36 = Medical Outcomes Study 36-item Short Form Health Survey, TSH = thyroid stimulating hormone, US = United States, VAS = visual analog scale, WOCBP = women of childbearing potential.

[a] The Safety Follow-up Visit will be performed 28 days (+ 5-day window) after the Week 12/End of Treatment Visit. Subjects who discontinue the IMP or withdraw from the trial early will attend the Safety Follow-up Visit according to procedures described in Sections 5.5.1 or 5.5.2, respectively.

[b] Subject eligibility to be confirmed on Day 1 prior to randomization. For WOCBP, the highly sensitive urine pregnancy test on Day 1 must be negative prior to randomization.

[c] Medical history includes documentation of general medical history, RA classification criteria, RA medical history, medications, and surgery/procedures.

[d] Vital signs including height, weight, oral temperature, seated blood pressure, pulse rate, and respiratory rate will be assessed predose at each indicated visit (height measured only at Screening), including the Safety Follow-up Visit.

[e] At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs assessments slightly before the specific time point, ECG assessment as close to protocol-specified time as possible, and CCI blood sampling immediately following ECG.

[f] Subjects who have previously had a normal CXR for clinical reasons within the last 3 months prior to Screening do not need to have the CXR repeated. In Germany, only subjects with CXR taken within 3 months of screening with results available and normal will be considered for this study. See Section 7.4.4.3 for details.

[g] Concomitant medications will be recorded at Screening and Day 1, and any changes solicited/recorded at every trial visit, and during any ad hoc telephone contacts.

[h] For subjects who are negative for HBsAg but are anti-hepatitis B surface antibody positive and/or anti-hepatitis B core antibody positive at Screening, an HBV DNA PCR reflex test will be completed at Screening. If the subject is able to enter the study (ie, subject is either HBV DNA-negative OR has detectable HBV DNA < 20 IU/mL only), additional HBV DNA PCR testing must be performed (see Exclusion Criterion 17 in Section 5.3.2).

[i] For subjects participating in the MRI substudy, MRI of wrist and hand must to be completed within 7 days prior to Day 1 (Baseline), and at the Weeks 4 and 12 study visit. All other inclusion/exclusion criteria should be verified prior to completing the baseline MRI image (including the second hsCRP test).

[j] For subjects participating in the MRI substudy, a posteroanterior radiograph of target hand and wrist must to be completed at least 7 days before the Baseline MRI. In Germany, only subjects with posteroanterior radiographs taken within 3 months of screening with radiograph available for submission to central reader will be considered for this study. All radiographs must be read centrally.

[k] For women who are postmenopausal, see Appendix I. A sample for FSH must be drawn at Screening to confirm postmenopausal status.

[l] For Japan only.

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[o] The IMP will be dispensed after randomization on Day 1 and thereafter at each indicated trial visit during the Treatment Period. All remaining IMP will be collected at Week 12 for all subjects.

[p] At the indicated visits, the IMP will be administered during the trial visit after trial visit procedures are completed (other than postdose CCI [redacted] sampling); otherwise, the IMP will be self-administered at a set time each day (± 2 hours).

[q] At the indicated visits after Day 1, IMP compliance for the intervals since the previous visit will be documented using pill counts.

[r] These assessments are part of the American College of Rheumatology Core Set of Disease Activity Measures for Rheumatoid Arthritis Clinical Trials (Felson 1993), commonly referred to as the ACR Core Set (see Sections 7.3.1 and 7.3.2).

[s] Any AEs occurring during the Screening Period (for subjects who have signed the ICF) will be recorded, and AEs will be solicited/recorded at all remaining trial visits and during any ad hoc contacts (eg, telephone calls).

[t] For visits including subsets, flow cytometry will be performed on the same sample for counts of: total T cell, total B cell, total NK cell, monocytes, B cell subsets, and T cell subsets – total B cells will not be counted separately (see Section 7.6.1). For visits where only total B cell counts are being performed, flow cytometry for the other cell types and subsets, including B-cell subsets, will not be performed.

[u] Blood samples on Day 1 are to be collected predose for hematology, chemistry, coagulation (partial thromboplastin time and international normalized ratio), hsCRP, ESR, samples for exploratory CCI [redacted], anti-CCP and RF are to be collected predose on Day 1. See Table 10 for detailed assessments.

[v] Hemoglobin A1C evaluated only for subjects with a diagnosis of diabetes; only at Screening.

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[x] Lipid panel includes HDL-C, LDL-C, total cholesterol, and triglycerides (see Table 10). Subjects are required to fast for a minimum of 8 hours prior to lipid panel.

[y] Microscopy will be performed if urinalysis results are abnormal for blood, protein, or nitrite.

[z] During the Screening Period, two hsCRP level measurements must be obtained and both results must meet the inclusion criterion in the study (see Section 5.3.1). The second hsCRP must be collected: a) at least 7 days after the initial screening hsCRP **and** b) at least 7 days prior to randomization or baseline MRI (for subjects in the MRI substudy), **and** c) no more than 14 days prior to randomization (21 days for MRI sites that are not able to transfer X-rays electronically) or baseline MRI (for subjects in the MRI substudy).

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[redacted]

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

- EMD Serono Research & Development Institute, Inc., Billerica, Massachusetts, USA, in the USA.
- Merck Serono Co., Ltd., (Affiliate of Merck KGaA, Darmstadt, Germany) in Japan.
- Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany in countries outside the USA and Japan.

Study Organization in Japan: Refer to Study Organization in Japan in supporting documentation for additional information.

The trial will be conducted at approximately 160 sites in the USA (15 sites), Europe, South America, Africa, and Japan. The Coordinating Investigator, PPD , 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 (CTR).

Trial Sites in Japan: Refer to the Trial Sites in Japan supporting documentation.

An Independent Data Monitoring Committee (IDMC) will be established to continually review available data and safeguard the interests of trial subjects. The IDMC will be composed of a minimum of 3 members who do not have any conflicts of interest with the trial Sponsor, and are not Investigators for this study, or any other study of evobrutinib in rheumatoid arthritis, including 2 clinicians and a biostatistician. The full membership, mandate, and processes of the IDMC will be detailed in the IDMC Charter.

In addition, the trial will be advised and monitored by a Study Steering Committee, chaired by the Coordinating Investigator and comprised of, at minimum, 3-5 Study Investigators, the Clinical Program Lead, and the Medical Responsible. Recommended optional members of the Study Steering Committee include the Study Statistician and the Operational Lead from the contract research organization (CRO). Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are provided in Appendix III.

The trial will appear in the following clinical trial registries: clinicaltrials.gov and www.clinicaltrialsregister.eu.

The Sponsor will enlist the support of PPD , a CRO, to conduct the clinical part of the trial including trial set-up, coordination, monitoring, medical oversight, data capture, data management, statistical analysis, and clinical trial reporting. PPD , will undertake operational aspects in Japan. The Sponsor will also make use of the CRO's central

laboratory for sample analyses, storage, and shipment to specialized bioanalytical laboratories. The Sponsor will supervise all outsourced activities.

The investigational medicinal product (IMP) will be supplied by the Clinical Trial Supply Department of the Sponsor, and packaged, labeled and distributed by a designated contract manufacturing organization.

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 Rheumatoid Arthritis

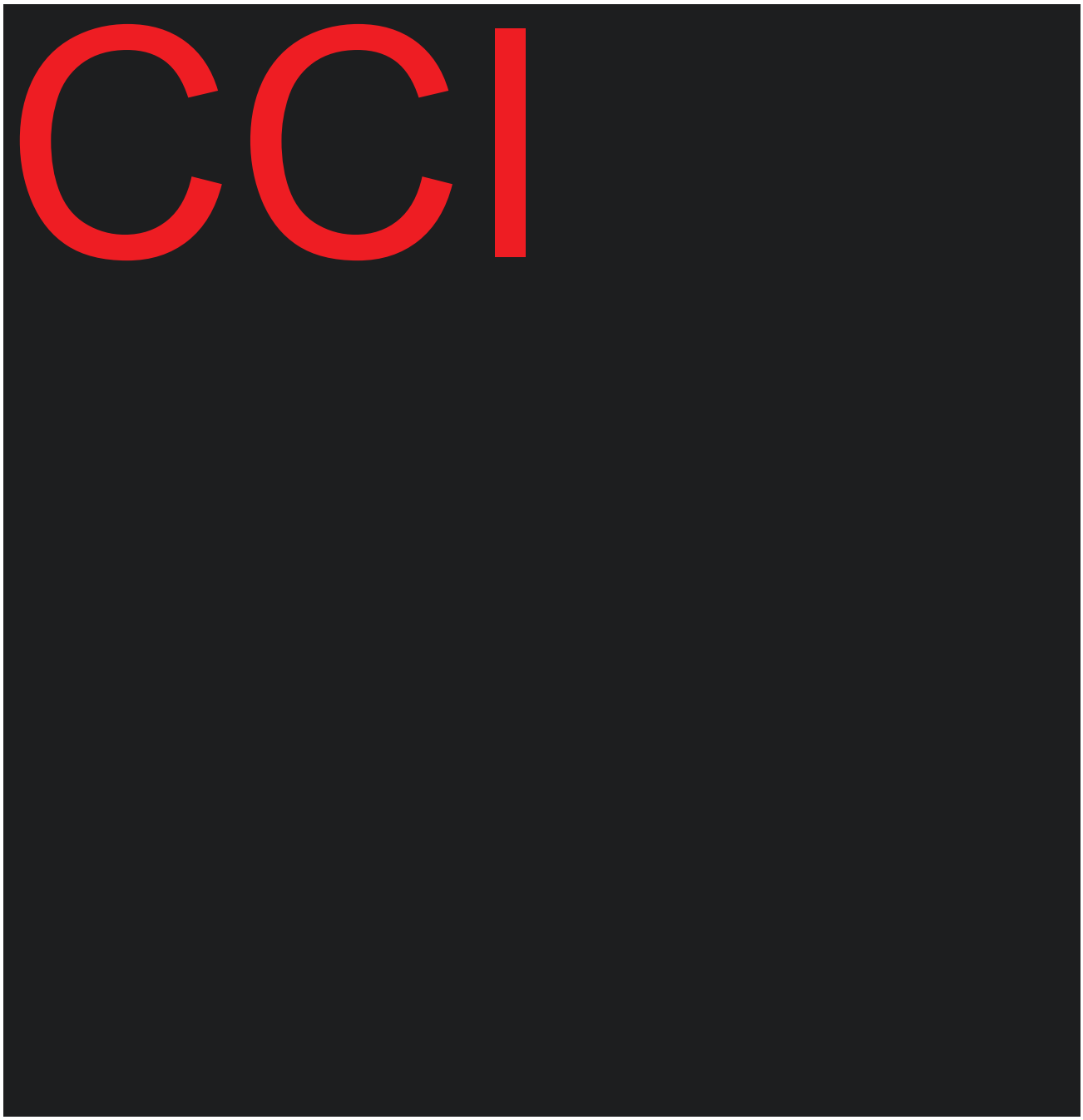
Conventional rheumatoid arthritis (RA) therapy consists of treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARD). Methotrexate (MTX) represents one of the most widely used DMARD for RA, yet less than half of patients with RA show substantial and sustained clinical improvement in disease signs and symptoms (Blumberg 2001).

The emergence of biologic therapies for RA, such as tumor necrosis factor (TNF)-α inhibitors, represent treatment options that mitigate the clinical manifestations of RA by selectively targeting key inflammatory mediators. Approximately 30% of patients with RA, usually those with more severe disease, will not experience satisfactory clinical improvement with use of currently available therapies (Rindfleisch 2005). Patients with RA prefer the oral route of administration, with some refusing injected therapies, despite the benefit (Louder 2016). Janus kinase (JAK) inhibitors are efficacious, but are associated with adverse reactions including increased risk of infections and malignancies, which cause concern (Nakayamada 2016). Accordingly, a significant unmet need remains for more effective treatments for RA.

3.2 Evobrutinib

Evobrutinib (also known as M2951) is a novel inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib, the only approved molecule in this class, is used in the treatment of hematological malignancies. Several BTK inhibitors have been evaluated in preclinical models of RA, with some of these advancing to clinical development for treatment of RA (Akinleye 2013, Norman 2016, Whang 2014). Evobrutinib is being developed for the treatment of RA due to the known role of B cells and autoantibodies in RA. As inhibition of BTK has been shown to inhibit key B cell functions (eg, antigen presentation, proliferation, differentiation and cytokine production), and has also been shown to inhibit signaling via autoantibody/antigen engagement of the Fc receptor on non-B cells—all factors felt to contribute to RA disease biology—blockade of BTK is expected to provide clinical benefit to patients with RA. The expectation that BTK inhibition will be beneficial in RA is supported by recently reported data showing clinical efficacy in a small, early clinical trial of another BTK inhibitor, CC-292 (Kivitz 2016). As BTK inhibition is a different mechanism of action than currently available treatments for RA, the expectation is that treatment with

evobrutinib will help patients that are not responsive to current therapies. Additionally, as evobrutinib is a highly selective BTK inhibitor, it may have a more favorable safety profile than ibrutinib.



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, the Japanese ministerial ordinance on GCP (for Japan only), and any additional applicable regulatory requirements.

Based on the available nonclinical and clinical data to date, the conduct of the trial specified in this protocol is considered justifiable.

3.4 Risk/Benefit

No identified risks or new potential risks have emerged from the completed Studies EMR200527-001 or MS200527-0019 in healthy volunteers or SLE Study EMR200527-002. No new safety signals have been confirmed from ongoing Study MS200527-0081 as of an IDMC data review meeting on 24 October 2017.

Important potential risks to subjects are based on nonclinical safety data of evobrutinib and clinical data on adverse drug effects associated with compounds of a similar pharmacological class. They include infection, leukopenia, thrombocytopenia, hemorrhage, gastrointestinal intolerance, renal toxicity, hepatocellular injury, atrial fibrillation, and embryo-fetal toxicity. The potential risk of infection relates to the immunomodulatory actions of evobrutinib. Women of childbearing potential participating in clinical studies with evobrutinib must agree to adhere to the use of highly effective contraception as specified in the clinical study protocol. CCI

Risk minimization measures routinely implemented in early phase clinical trials, including exclusion criteria for hematological cytopenias and stopping rules based on grade changes in specific laboratory parameters, are considered adequate for planned clinical trials in patients with autoimmune diseases. No additional risk minimization measures are proposed.

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Taking the above information into account, benefit-risk considerations support the proposed clinical trial of evobrutinib in patients with RA.

For the Japanese population, a Phase I trial (MS200527-0017) has been conducted to evaluate safety, pharmacokinetics (PK), and pharmacodynamics (PD) of evobrutinib as a bridging trial between Japanese and non-Japanese healthy subjects.

Refer to the Investigator's Brochure for more details of each trial.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, the Japanese ministerial ordinance on GCP (for Japan only), and any additional applicable regulatory requirements.

4 Trial Objectives

4.1 Primary Objective

The primary objective is:

- To evaluate the efficacy and dose response of 12 weeks of treatment with evobrutinib compared with placebo in subjects with rheumatoid arthritis (RA) with inadequate response to methotrexate (MTX-IR) on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by American College of Rheumatology (ACR) 20% (ACR20) response assessed using high-sensitivity C-reactive protein (hsCRP) at Week 12.

4.2 Key Secondary Objective

The key secondary objectives are:

- To further evaluate the efficacy and dose response of 12 weeks of treatment with evobrutinib in MTX-IR subjects with RA on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by DAS28-hsCRP low disease activity (DAS28 < 3.2) rate at Week 12
- To further evaluate the efficacy of 12 weeks of treatment with evobrutinib compared to placebo in MTX-IR subjects with RA on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by DAS28-hsCRP remission (DAS28 < 2.6) rate at Week 12
- To further evaluate the efficacy and dose response of 12 weeks of treatment with evobrutinib in MTX-IR subjects with RA on stable MTX therapy by assessment of the signs and symptoms of RA, as measured by ACR50 and ACR70 at Week 12
- To evaluate the safety of evobrutinib in MTX-IR subjects with RA on stable MTX therapy.

4.3 Other Secondary Objectives

The other secondary objectives are:

- To further evaluate the efficacy of evobrutinib on the signs and symptoms of RA with inadequate response to MTX
- To evaluate the effect of evobrutinib on joint structures and inflammation, at Weeks 4 and 12 in the MRI substudy, as assessed by magnetic resonance imaging (MRI)
- To evaluate the effect of evobrutinib on physical function in RA subjects
- To evaluate the effect of evobrutinib on subject-reported health-related quality of life (HRQoL)
- To evaluate the effect of evobrutinib on subject-reported fatigue (using Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue).

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase IIb, multicenter, international, randomized, double-blind, placebo-controlled parallel-arm trial, designed to determine the efficacy, dose response, and safety of evobrutinib in subjects with RA, and to consider a dose to take forward into Phase III development. Approximately 360 total subjects 18 to 75 years of age with RA planned to be randomized (to obtain 320 evaluable subjects). The study includes a Japanese cohort (approximately 36 Japanese subjects). This trial will be conducted at approximately 160 sites across 17 countries. Schematic

presentations of the trial design are presented in Figure 1. A detailed schedule of trial procedures/assessments is provided in Table 1. Details of the study population are presented in Table 2.

Table 2 Trial Study Population

Diagnosis:	Moderate to severe RA
Methotrexate Therapy:	MTX-IR, on a stable dose of methotrexate
Prior exposure to bDMARD? (eg, TNF antagonists, IL-6 antagonists, anakinra[a], abatacept, rituximab, etc.)	No prior exposure to approved or investigational bDMARD allowed.
Prior exposure to tsDMARD? (eg, JAK inhibitors, BTK inhibitors)	No prior treatment with investigational or approved tsDMARD(s) allowed.

bDMARD = biologic disease-modifying anti-rheumatic drug, BTK = Bruton's tyrosine kinase, IL = interleukin, JAK = Janus kinase, MTX-IR = inadequate response to methotrexate, RA = rheumatoid arthritis, TNF = tumor necrosis factor, tsDMARD = targeted synthetic disease-modifying anti-rheumatic drug.

[a] Not approved in Japan.

Approximately 50% of subjects will participate in a substudy using magnetic resonance imaging (MRI) to evaluate the ability of evobrutinib to prevent the progression of joint structural damage. These subjects will have hand and wrist MRI images and X-rays at the times indicated in the Schedule of Assessments (Table 1).

Treatment Sequences

Eligible subjects will be randomly assigned in a 1:1:1:1 ratio to 1 of the 4 parallel treatment groups (N = 90/group), as detailed in Table 3, in combination with their stable background MTX therapy. Subjects and Investigators will be blinded to the initial treatment assignment.

Table 3 Treatment Groups and Regimens

Treatment Group	Regimen[a,b]
1	Evobrutinib 25 mg QD
2	Evobrutinib 75 mg QD
3	Evobrutinib 50 mg BID
4	Placebo

MTX = methotrexate.

[a] All subjects will continue to take their MTX background therapy along with trial treatment per treatment group.

[b] To maintain the study blind, all subjects will receive BID treatment. For subjects with QD treatment assignments, 1 dose a day will be study drug and 1 will be placebo.

Trial Duration

Total duration of subject participation is approximately 5 months (approximately 20 weeks), which includes:

- Screening: 28 days (4 weeks)
- Treatment: 84 days (12 weeks)
- Safety Follow-up: 28 days (4 weeks).

The trial will be conducted on an outpatient basis. Subjects will attend clinic visits at regular intervals as indicated in the Schedule of Assessments (Table 1).

Screening Period

The first visit will be a Screening Visit and will include a review of the inclusion/exclusion criteria (see Section 5.3). Subjects should undergo the Day 1 visit as soon as possible after eligibility for the trial has been confirmed. Subjects who do not meet all inclusion criteria or meet one or more of the exclusion criteria within the first Screening Period and are considered screen failures. If inclusion/exclusion criteria are not met at the end of the 28-day Screening Period (+ 7-day window), either the initial Screening Period or the single Rescreening Period, based on the results of the repeated tests, the subject should be considered a screen failure and not be enrolled in the study.

Rescreening:

Subjects who are considered screen failures after a first Screening Period may undergo rescreening once, after approval by the Medical Monitor (see Section 5.3). If a subject is rescreened, all screening tests will need to be repeated except as follows:

a. Documented chest X-ray (CXR), hand and wrist X-ray if applicable, and TB testing must have occurred within 3 months of the initial rescreening visit, or need to be repeated during the Rescreening Period.

b. Hepatitis and Human Immunodeficiency Virus (HIV) testing must have occurred within 1 month of the initial rescreening visit, or need to be repeated during the Rescreening Period.

Retesting:

During the initial Screening Period, or single Rescreening Period, testing may be repeated for subjects if test results, would preclude enrollment in the study, and are thought to represent a laboratory error or a reversible, clinically insignificant intermittent condition, or are inconsistent with the subject's historical values (see Inclusion Criteria 12 and 13 for specifics regarding tuberculosis [TB] testing), after discussion with the Medical Monitor. When a test needs to be repeated during the Screening Period, the Screening Period can be extended to 8 weeks after discussion with the Medical Monitor.

In addition, if the initial MRI quality check at Screening indicates a repeat MRI is necessary, the Screening Period may be extended up to 7 days after discussion with the Medical Monitor.

Treatment Period (Double-blind Placebo-controlled)

The duration of the Treatment Period will be 12 weeks starting at randomization (Day 1). The Day 1 visit will be considered the Baseline for disease activity assessments (eg, ACR20/50/70, ACR hybrid, Disease Activity Score Based on a 28 Joint Count [DAS28], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]). Subject eligibility and a negative pregnancy test (if applicable) must be reviewed on Day 1 prior to randomization, and the first dose of IMP will be given while the subject is still on site for Day 1. Subjects must then return to the site for trial visits as indicated in the Schedule of Assessments Table 1.

Treatment decisions will be made by Investigator assessment for the purpose of subject management.

Any subjects permanently withdrawn from IMP will be expected to complete the End of Treatment/Early Withdrawal Visit within 5 days of IMP withdrawal, followed by the Safety Follow-up Visit.

Safety Follow-up Period

Subjects will enter the Safety Follow-up Period after the Week 12/End of Treatment Visit. For subjects who discontinue the Treatment Period (discontinue IMP) during the main study, an End of Treatment/Early Withdrawal Visit should occur with the subject then entering the Safety Follow-up Period. The Safety Follow-up Visit/End of Trial visit is scheduled 28 days (+ 5-day window) after the End of Treatment/Early Withdrawal Visit.

Assessment of Endpoints

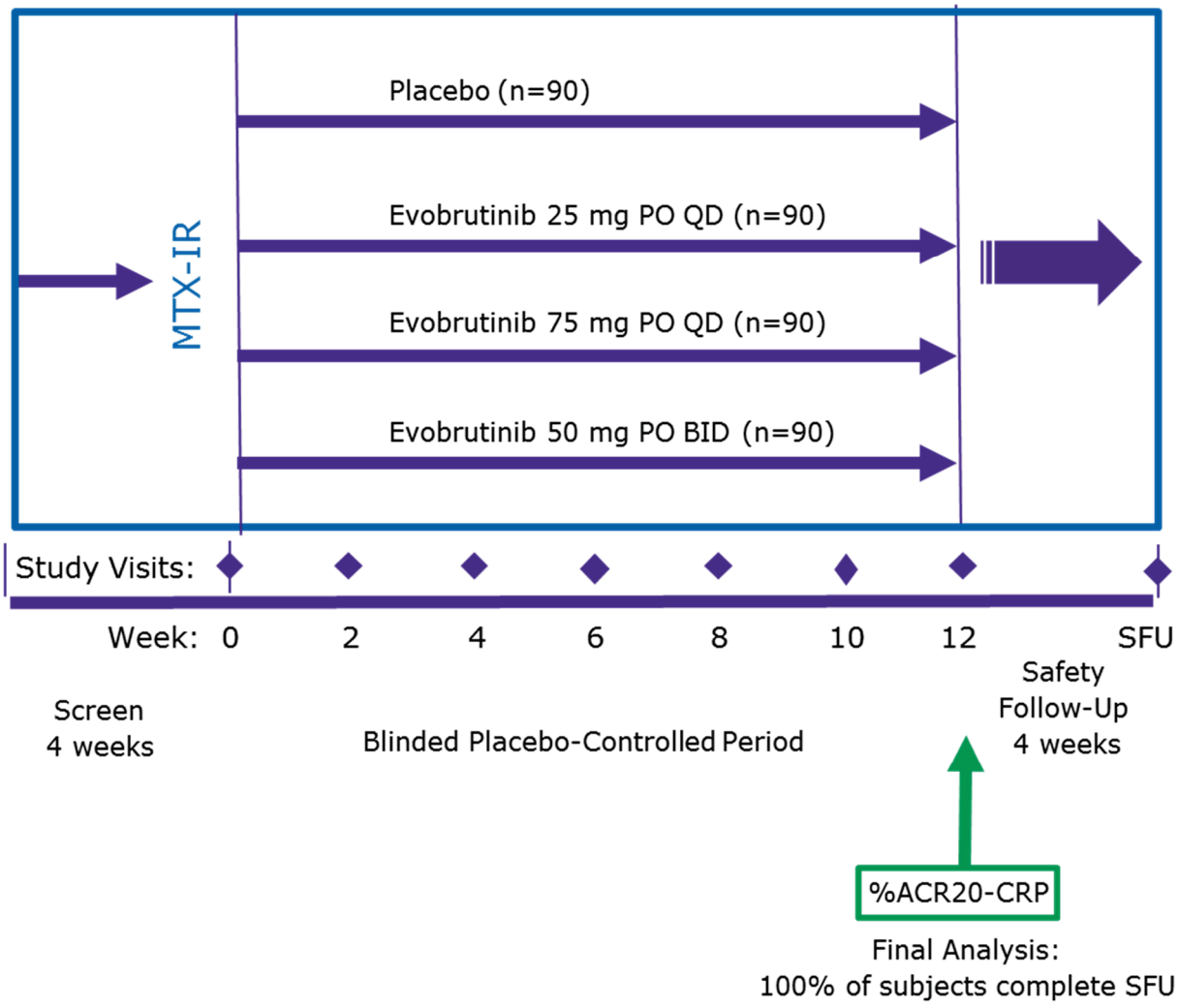
During the trial, clinical efficacy endpoints will be evaluated using several assessments, such as the ACR20/50/70, hybrid ACR, DAS28, CDAI, SDAI, and others. Efficacy in terms of prevention of joint structural damage progression will be assessed using MRI, scored using the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) and other MRI scoring systems. Efficacy in terms of physical function will be assessed using the Health Assessment Questionnaire – Disability Index (HAQ-DI). Effects of treatment on HRQoL will be examined using subject-reported outcome measures including but not limited to: Medical Outcomes Study 36-item Short Form Health Survey (SF-36v2) and FACIT-Fatigue.

Safety will be evaluated through the nature, occurrence, severity, and outcome of adverse events (AEs), and assessment of physical examination findings, ECGs, hematology and chemistry laboratory assessments, vital signs, and absolute values and change from Baseline in serum immunoglobulin (Ig) levels (IgA, IgG, IgM, and IgG subclasses) and total B cell counts.

Statistical Methods

Statistical methods including sample size justification are provided in Section 8.

Figure 1 Schematic of the Trial Design – Screening to Safety Follow-up Visit



ACR = American College of Rheumatology, ACR20 = ACR 20% Response Criteria, %ACR20-CRP = Proportion of subjects achieving an ACR20 response, where the acute phase reactant criterion is based on hsCRP, D1 = Day 1, MTX-IR = RA subjects with inadequate response to methotrexate, PO = Orally, RA = rheumatoid arthritis, SFU = Safety Follow-up Visit.

5.2 Discussion of Trial Design

5.2.1 Scientific Rationale for the Trial

The proposed Phase IIb trial design is based on experience with evobrutinib in the Phase IIa trial for RA (MS200527-0081), studies of other treatments for RA, consensus guidelines for treatment of RA (refer to American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis [2015]), Food and Drug Administration (FDA) draft guidance (refer to FDA Guidance

for Rheumatoid Arthritis: Developing Drug Products for Treatment [2013]), and European Medicines Agency (EMA) draft guidance (refer to EMA Evaluation of Medicines for Human Use: Points to Consider on Clinical Investigation of Medicinal Products Other Than NSAIDs for Treatment of Rheumatoid Arthritis [2015]).

Study Population

The proposed trial will evaluate RA subjects with inadequate response to MTX and no prior treatment with biologic DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD [eg, JAK inhibitors, BTK inhibitors]), which we will refer to as the MTX-IR population. Subjects will be randomized to 1 of 3 doses of evobrutinib or placebo.

The MTX-IR population represents a well characterized segment of the total population of individuals with RA, and is one of the populations in which efficacy must be evaluated to obtain approval in the EU per EMA guidance.

Beyond assessing efficacy on clinical endpoints (eg, ACR20 response at 12 weeks, DAS28, ACR core set measures, ACR-EULAR remission), efficacy will also be assessed on physical function (HAQ-DI), pain (VAS), fatigue (FACIT-Fatigue), and HRQoL (SF-36), as these patient-reported concepts are relevant in patients' lives and treatment is expected to impact these variables. Efficacy in preventing structural damage progression will be assessed using MRI in the MRI substudy. Other than the inclusion/exclusion criteria for MRI substudy eligibility, participation in the MRI substudy is purely random, based on MRI availability at a particular site.

Endpoint Selection

The primary endpoint, ACR20 response at Week 12, is in accordance with FDA and EMA regulatory guidance documents for dose-ranging studies in RA. Clinical response will also be assessed using ACR50 response and ACR 70 response, as well as measures of low disease activity (LDA [eg, DAS28-CRP < 2.6]) and remission (eg, ACR/European League Against Rheumatism [EULAR] remission). Physical function will be assessed using HAQ-DI. Prevention of structural damage progression will be assessed using MRI at Weeks 4 and 12 in the MRI substudy.

Dose Range Finding

As all agents approved since the introduction of TNF antagonists in RA have used the same doses in patient populations with inadequate response to either MTX (MTX-IR) or to MTX and at least one bDMARD (bDMARD-IR), we will study the efficacy of evobrutinib with 3 doses in the MTX-IR to allow the assessment of dose response in this population, and will plan to evaluate the dose(s) identified on the basis of this study for subsequent development in all of the RA subpopulations to be studied (MTX-IR, bDMARD-IR, DMARD-naïve).

Stratification Factors at Randomization

Subjects will be stratified by whether or not they are in the MRI substudy and by region to account for the impact on study outcomes of these factors.

Use of Magnetic Resonance Imaging to Evaluate Joint Structural Damage Progression

Classically, joint structural damage in RA has been evaluated with radiographic methods, such as the modified Total Sharp Score (mTSS) (van der Heijde 2000). However, these methods are insensitive to early changes, requiring either 1- and 2-year study durations or large studies of shorter duration enriched for patients with documented erosions at Baseline, to assess the ability of an agent to prevent progression of joint structural damage. Due to these limitations, OMERACT developed the RAMRIS, which evaluates wrist and hand MRI images and scores them for erosions, synovitis, tenosynovitis, and osteitis (Ostergaard 2004, Ostergaard 2017). Unlike the mTSS, the OMERACT RAMRIS scores have been shown to be sensitive to changes as early as 12 weeks, and these changes predict radiographic progression as measured by the mTSS (Baker 2014, Baker 2016, Conaghan 2016, Genovese 2016b). Further, these changes have been shown to predict efficacy in longer studies using the mTSS. A validated 9-point scale for the assessment of cartilage loss (CARLOS) (Peterfy 2012) will also be used.

In the proposed trial, approximately 50% of the subjects will be evaluated using MRI to assess treatment effect on the MRI scores at 4 and 12 weeks when compared to Baseline, which we refer to as the MRI substudy. Barring subjects with contraindications to MRI imaging (eg, allergy to MRI contrast, presence of a non-MRI compatible metal medical device or foreign body), participation in the MRI substudy will be required for enrollment at MRI capable sites, in order to avoid selection bias. To ensure an adequate sample size in the MRI substudy, enrollment of non-MRI subjects may be capped. As the non-MRI subjects are projected to be recruited faster than the MRI subjects, capping recruitment of MRI subjects is unlikely to be required. However, if during the course of the study, it appears that MRI subjects will reach 45/arm in advance of the non-MRI subjects reaching 45/arm, we may limit enrollment of further MRI subjects to prevent over enrollment in the MRI substudy.

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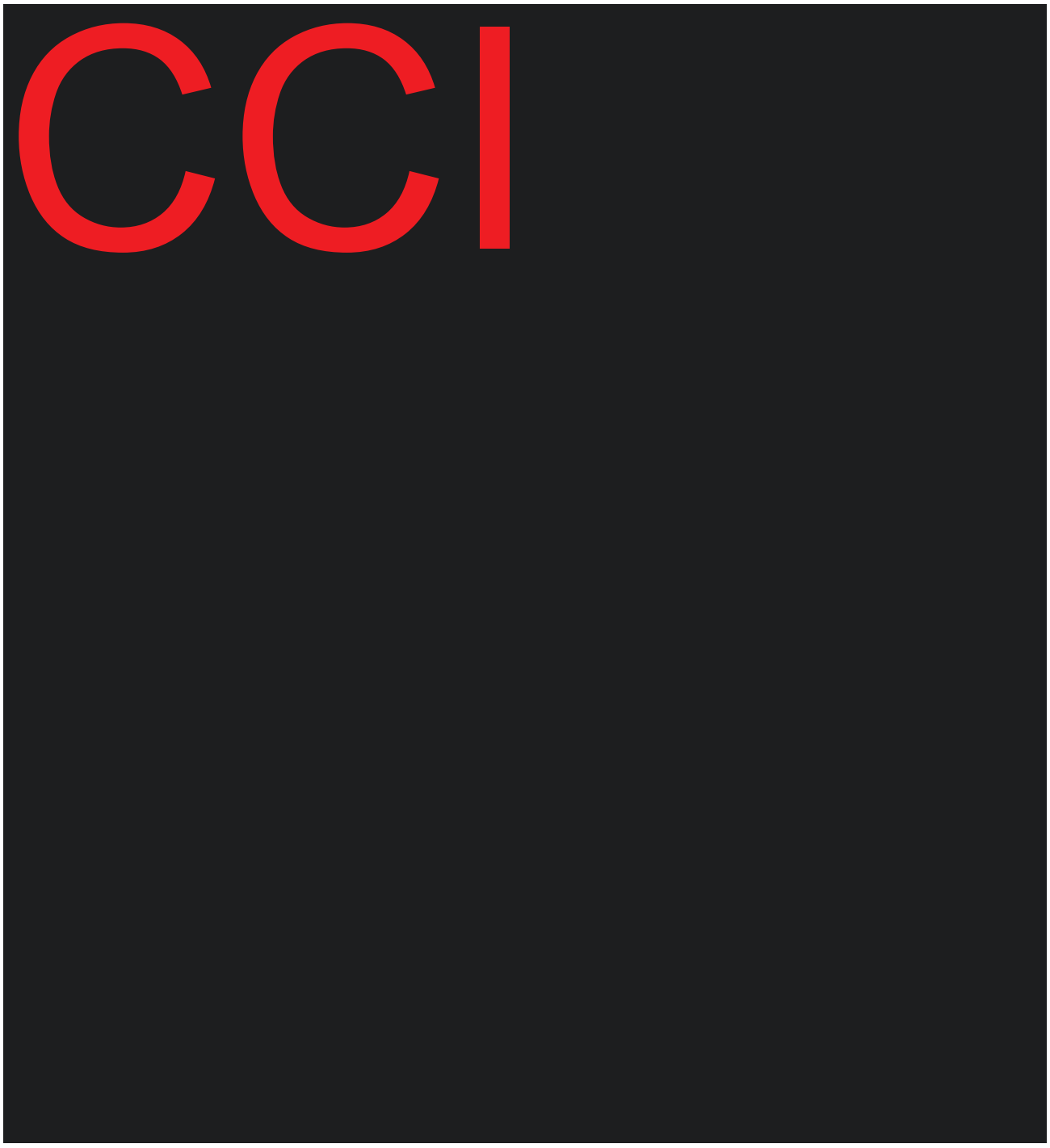

5.2.3 Rationale for Endpoints

5.2.3.1 Primary Efficacy Endpoints

The ACR20 response at Week 12 is the primary efficacy endpoint.

The endpoints and schedule for the efficacy assessments reflect the most updated FDA regulatory guidance and evidence-based recommendations for this indication. As the placebo-controlled period is limited to the first 12 weeks of the trial, due to ethical concerns regarding longer use of placebo in subjects given the availability of other approved, effective therapies (bDMARD and tsDMARD) for the MTX-IR population, the primary endpoint, ACR20, is assessed at 12 weeks (American College of Rheumatology Clinical Trial Priorities and Design Conference 2010, Boers 2009).

Efficacy in RA as evaluated in clinical trials is measured using the American College of Rheumatology Core Set of Disease Activity Measures for Rheumatoid Arthritis Clinical Trials (Felson 1993), commonly referred to as the ACR Core Set. The ACR Core Set consists of:

1. Swollen Joint Count (of 66 joints assessed)
2. Tender Joint Count (of 68 joints assessed)
3. Physician's Global Assessment of RA Disease Activity (generally assessed using a visual analog scale [VAS])
4. Acute Phase Reactant – erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
5. Physical function (as assessed using the HAQ-DI or other validated instrument)
6. Pain (as assessed using the Patient's Assessment of Arthritis Pain VAS)
7. Patient's Global Assessment of RA Disease Activity

The definition of an ACR20 response, and many other assessments in RA (eg, ACR50, ACR70, CDAI, SDAI, DAS28, EULAR Responder Index), are calculated from evaluation of the ACR Core Set. Criteria for remission and LDA are also assessed using items from the ACR Core Set or indices derived thereof (eg, ACR/EULAR remission criteria, CDAI $\leq$ 3.3, DAS28 $\leq$ 3.2, SDAI $\leq$ 3.3).

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 pain, patient and physician's global assessment, physical function, acute phase reactants). ACR20 is the FDA-recommended efficacy endpoint for dose-ranging studies in RA in the FDA guidance, and is in line with EMA guidance for dose-ranging studies in RA. In this trial, the acute phase reactant for assessing ACR20 response for the primary endpoint is the high-sensitivity C-reactive protein (hsCRP).

5.2.3.2 Secondary Endpoints

5.2.3.2.1 Key Secondary Endpoints

5.2.3.2.1.1 Efficacy

DAS28-hsCRP low disease activity (DAS28 < 3.2) rate, DAS28-hsCRP remission (DAS28 < 2.6) rate, and ACR50 and ACR70 responses at Week 12 are the key secondary efficacy endpoints.

DAS28 – The DAS28 is a composite score derived from 4 measures (Aletaha 2008, Vander Cruyssen 2005). The components of DAS28 are:

- The number of swollen joints (out of the 28)
- The number of tender joints (out of the 28)
- Erythrocyte sedimentation rate or hsCRP
- Patient's Global Assessment of Disease Activity (0-10 scale).

In this study, DAS28-hsCRP will be used for determination of any endpoint that includes the DAS28 (eg, DAS28 remission, DAS28 LDA). DAS28-hsCRP is computed as follows, with hsCRP expressed in units of mg/L:

$$\text{DAS28-hsCRP} = 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.36 \times \ln(\text{hsCRP} + 1) + 0.014 \times \text{GH} + 0.96$$

CCI [redacted]

Thresholds for disease severity grading, including remission, have been established for the DAS28 and other composite disease activity measures used in the assessment of RA (Anderson 2012), and are presented in Table 5 for the DAS28, CDAI, and SDAI.

Table 5 Disease Activity Cutoffs for Select American College of Rheumatology - Recommended Disease Activity Measures

Disease Activity Measure	Scale	Remission	Low/Minimal	Moderate	High/Severe
CDAI	0 – 76	≤ 2.8	> 2.8 to ≤ 10.0	> 10.0 to ≤ 22.0	> 22.0
DAS28 (CCI or CRP)	0 – 9.4	< 2.6	≥ 2.6 to < 3.2	≥ 3.2 to ≤ 5.1	> 5.1
SDAI	0 – 86	≤ 3.3	> 3.3 to ≤ 11.0	> 11 to ≤ 26	> 26

Source: Anderson 2012.

CDAI = Clinical Disease Activity Index, CRP = C-reactive protein, DAS28 = Disease Activity Score with 28-Joint Counts, ESR = erythrocyte sedimentation rate, SDAI = Simplified Disease Activity Index.

A change of 1.2 (twice the measurement error) is defined as a significant change of the disease activity state (Prevoo 1995). Yet, a change of 0.6 may be already 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 (den Broeder 2002). DAS28 remission and DAS28 LDA are also being assessed as secondary endpoints.

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% and 70% improvement in 3 out of the remaining 5 ACR core-set measures (patient pain, patient and physician's global assessment, physical function, and acute phase reactants). In this trial, the acute phase reactant for assessing ACR50 and ACR70 responses is the hsCRP.

5.2.3.2.1.2 Safety

The nature, severity, and occurrence of AEs and SAEs

Absolute values and change from Baseline in:

- Vital signs
- ECG parameters including RR interval, PR interval, QRS duration, QT interval, and QTcF interval
- Serum Ig levels (IgG, IgA, IgM)
- Total B cell counts
- Clinical laboratory parameters.

5.2.3.2.2 Other Secondary Endpoints

5.2.3.2.2.1 Efficacy Endpoints

ACR Hybrid - The ACR hybrid score was developed to provide a quasi-continuous score that can detect smaller changes between treatments than the categorical ACR20/50/70 scores by combining the continuous score of the mean improvement in the core set measures combining the ACR20, ACR50, and ACR70 scores with the mean percent change from Baseline in all 7 ACR response core set components (Felson 2007, American College of Rheumatology Clinical Trial Priorities and Design Conference 2010, van Vollenhoven 2011). ACR hybrid, along with the DAS28, is recommended by the FDA regulatory guidance as a way to support dose-response assessment. It is calculated according to Table 6 (Felson 2007).

Table 6 **Scoring Method for the Hybrid American College of Rheumatology Response Measure**

ACR Status	Mean % Change in Core Set Measures			
	< 20	≥ 20, < 50	≥ 50, < 70	≥ 70
Not ACR20	Mean % change	19.99	19.99	19.99
ACR20 but not ACR50	20	Mean % change	49.99	49.99
ACR50 but not ACR70	50	50	Mean % change	69.99
ACR70	70	70	70	Mean % change

Source: Felson 2007.

ACR = American College of Rheumatology, ACR20 = American College of Rheumatology 20% Response Criteria, ACR50 = American College of Rheumatology 50% Response Criteria, ACR70 = American College of Rheumatology 70% Response Criteria.

Note: 1) Calculate the average percentage change in core set measures. For each core set measure, subtract score after treatment from Baseline score and determine percentage improvement in each measure. Next, if a core set measure worsened by > 100%, limit that percentage change to 100% (a - 100% bound). Then average the percentage changes for all core set measures. 2) Determine whether the subject has achieved ACR20, ACR50, or ACR70. 3) Using the table above, obtain the Hybrid ACR response measure. To use the table, take the ACR20, ACR50, or ACR70 status of the subject (left column) and the mean percentage improvement in core set items; the Hybrid ACR score is where they intersect in the table.

DAS28 – as described above.

EULAR Responses – Assessments of subjects with RA by EULAR response criteria will be used to categorize subjects as having had no response, moderate response, good response, or any response (moderate + good responders) according to Table 7 (van Gestel 1998).

Table 7 **Categorization of Subject Responses as No Response, Moderate Response, or Good Response Based on EULAR Response Criteria**

Post-baseline Level of DAS28	Improvement Since Baseline in DAS28		
	> 1.2	≤ 1.2 and > 0.6	≤ 0.6
DAS28 ≤ 3.2	Good response		
3.2 < DAS28 ≤ 5.1		Moderate response	
DAS28 > 5.1			No response

Source: van Gestel 1996 and van Gestel 1998.

DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count.

SDAI – The SDAI is the numerical sum of 5 outcome parameters: tender and swollen joint count (based on a 28-joint assessment), the Patient's and the Physician's Global Assessments of disease activity (0–10 cm VAS), and level of CRP (expressed in units of mg/dL). The SDAI is a valid and sensitive assessment of disease activity (Aletaha 2005, Smolen 2014) 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 (Fransen 2005, Smolen 2014). The

ACR/EULAR 2011 Index-based definition of remission is based on SDAI (SDAI ≤ 3.3), and is being assessed as a secondary endpoint (Felson 2011, Smolen 2014).

CDAI – The 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 the Patient's and Physician's Global Assessments (0–10 cm VAS) for estimating disease activity. The greater advantage associated with CDAI is its potential to be employed in evaluation of subjects 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 subjects with RA (Aletaha 2005, Smolen 2014). Thresholds for disease severity grading are included in Anderson (Anderson 2012). Remission based on CDAI is also being assessed as a secondary endpoint.

EULAR/ACR Boolean Remission – Following the Boolean-based definition of remission of ACR/EULAR, at any time point, a subject must satisfy all of the following: tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, CRP ≤ 1 mg/dL and Patient's Global Assessment ≤ 1 (on a 0–10 scale). The Patient's Global Assessment must be elicited as follows: "Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today? (0–10, where 0 = very well and 10 = very poorly)". The Boolean criteria appear more stringent than the DAS28 remission and have been specifically created for use in clinical trials (Bykerk 2012, Felson 2011).

5.2.3.2.2.2 Physical Function

HAQ-DI – The HAQ-DI is a validated tool 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, ie, 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 DI or FDI, the disability index or functional disability index (Emery 2011). The HAQ-DI has been validated for use in RA over 3 decades (Bruce 2003).

5.2.3.2.2.3 Quality of Life

Medical Outcomes Study 36-item Short-Form Health Survey – The SF-36 is a validated 36-item, subject-reported indication of overall health status not specific to any age, disease, or treatment group (Ware 1992). The SF-36 has been extensively studied in RA, and a significant association has been shown between the physical functioning score of the SF-36 and the HAQ-DI score, as well as with other measures of disease activity and severity, and comorbidities (Fries 1980).

The SF-36 includes multi-item scales 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. These are summarized in two summary measures of physical and mental health: the Physical Component Summary and Mental Component Summary.

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.

Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue – FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function (Wolfe 1996). It uses a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). As each of the 13 items of the FACIT-Fatigue scale ranges from 0–4, the range of possible scores is 0–52, with 0 being the worst possible score and 52 the best. To obtain the 0–52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score.

5.2.3.2.2.4 Prevention of Joint Structural Damage Progression

Rheumatoid Arthritis MRI Scoring System Scores – Images of the MRI-designated hand and wrist (the hand being used in the MRI assessments) will be acquired using an MRI scanner as specified in the imaging guidelines. OMERACT RAMRIS scores for synovitis, tenosynovitis, bone marrow edema (osteitis), and erosions (Ostergaard 2004, Ostergaard 2017) will be read centrally by 2 independent readers, who are blinded to treatment and dose assignment and to chronology of each time point. Discrepancies in RAMRIS scores between the 2 readers will be reviewed at a consensus adjudication session with both readers to reach a consensus score for the designated cases. At a minimum, the images with the top 10% discrepancies in scores between the 2 readers will be reviewed (refer to Imaging Guidelines for details of Adjudication and Selection of Cases for Adjudication). Unlike conventional radiography scored using the mTSS, which is generally sensitive to changes in joint structure over 52 weeks or more, the OMERACT RAMRIS scores have been shown to be sensitive to changes as early as 12 weeks, and these changes predict radiographic progression as measured by the mTSS (Baker 2014, Baker 2016, Conaghan 2016, Genovese 2016b).

Cartilage Loss Scale (CARLOS) – The images used for RAMRIS scoring above will also be evaluated using the validated 9-point cartilage loss scale (Peterfy 2012), to provide another assessment of the impact of study interventions on joint structural damage progression.

CCI [redacted]

5.2.4 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

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

5.3.1 Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled:

1. Ability to understand the purposes and risks of the trial
2. Has signed the appropriate written Informed Consent Form (ICF), approved by the Investigator's Institutional Review Board (IRB)/Independent Ethics Committee (IEC), prior to the performance of any trial activities. In Japan, if a subject is < 20 years of age, the written informed consent from the subject's parent or guardian will be required in addition to the subject's written consent.
3. Male or female subjects, 18 to 75 years of age
4. Subjects should be able to complete (read and write) the PRO questionnaires
5. Confirmed diagnosis of RA according to 2010 ACR/EULAR RA classification criteria of at least 6 months duration prior to Screening
6. Persistently active moderate to severe RA at **both** Screening and Randomization (if significant surgical treatment of a joint has been performed, that joint cannot be counted for entry or enrollment purposes), as defined by (see Appendix II):
    a. ≥ 6 swollen joints (of 66 assessed) **and**
    b. ≥ 6 tender joints (of 68 assessed).
7. An hsCRP ≥ 5.0 mg/L (≥ 0.50 mg/dL) from 2 samples collected during Screening. The second hsCRP must be collected:
    a. At least 7 days after the initial screening hsCRP, **and**
    b. At least 7 days prior to randomization or baseline MRI (for subjects in the MRI substudy), **and**
    c. No more than 14 days prior to randomization (21 days for MRI sites that are not able to transfer X-rays electronically) or baseline MRI (for subjects in the MRI substudy).
8. Positive rheumatoid factor (RF) and/or anti-cyclic citrullinated protein (anti-CCP)
9. Treatment for ≥ 16 weeks with 7.5 to 25 mg/week MTX. MTX at a stable dose and route of administration (oral or parenteral) for at least 8 weeks prior to dosing with the IMP and maintained throughout the trial
10. For subjects entering the trial on MTX doses < 15 mg/week (< 10 mg/week in Japan), there must be clear documentation in the medical record that higher doses of MTX were not tolerated or that the dose of MTX is the highest acceptable dose based on local clinical practice guidelines
11. Subjects should be on an adequate and stable dose of folic acid (not less than 5 mg total dose weekly [800 µg to 1 mg per day], unless this would violate the local label) for at least 2 weeks prior to the first dose of the IMP
12. No evidence of active TB as defined by all of the following:

a. A negative QuantiFERON®-TB test at Screening

b. No signs or symptoms consistent with the diagnosis of active TB upon medical history and/or physical examination

c. Normal CXR at Screening or within the 3 months prior to Screening

d. No household contacts with active TB.

NOTE: Individuals that have completed appropriate LTBI treatment, and provide documentation thereof, are eligible and are not required to be tested for TB. Individuals with indeterminate or positive QuantiFERON-TB test results during Screening that are felt to represent a false positive result by the Investigator, with no clinical features consistent with active TB, will be subsequently evaluated with T-SPOT.TB at the request of the Investigator. In this case, if the T-SPOT.TB is negative, the individual may be enrolled after approval by the Medical Monitor. Sites that are not able to process T.SPOT.TB should contact the Medical Monitor for additional guidance.

13. No evidence of latent TB infection (LTBI) that is undergoing treatment, is inadequately treated, or is untreated as defined by all of the following:

a. A negative QuantiFERON-TB test at Screening

b. No clinical symptoms consistent with active TB

c. Normal CXR at Screening or within the 3 months prior to Screening.

NOTE: Individuals that have completed appropriate LTBI treatment, and provide documentation thereof, are eligible and are not required to be tested for TB. Individuals with indeterminate or positive QuantiFERON-TB GOLD test results during Screening that are felt to represent a false positive result by the Investigator will be subsequently evaluated with T-SPOT.TB at the request of the Investigator. In this case, if the T-SPOT.TB is negative, the individual may be enrolled after approval by the Medical Monitor. Sites that are not able to process T.SPOT.TB should contact the Medical Monitor for additional guidance.

14. Female participants:

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

a. Not a woman of childbearing potential (WOCBP) as defined in Appendix I of this protocol **OR**

b. A WOCBP who agrees to use 2 methods of birth control: a barrier method together with a highly effective method (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix I of this protocol, at least 28 days before start of first dose of the IMP (as appropriate), during the Treatment Period, and for 90 days after the last dose of the IMP.

15. History of vaccinations, as required per local guidelines:

a. Vaccination against Streptococcus pneumoniae with PPSV23 and/or PCV13 or local equivalent with repeat administration as necessary to be up to date. If vaccinated during screening, there must be at least 2 weeks between vaccination and randomization.

b. Vaccination against influenza virus (as seasonally required, as per local guidelines); or vaccination against these pathogens during Screening (as seasonally required for influenza virus, as per local guidelines). If vaccinated during screening, there must be at least 2 weeks between vaccination and randomization. If the subject is screened after the most recent influenza season and/or the influenza vaccine is no longer available, the influenza vaccine should be given during the study once available, as required per local guidelines.

MRI Substudy Subjects:

16. In addition to meeting inclusion criteria 1–15 above and the criteria for inclusion into the study, subjects must have palpable synovitis of the wrist and/or ≥ 1 of metacarpophalangeal (MCP) joints #1 to #5, defined as loss of bony contours with palpable joint effusion and/or swelling, in the MRI-designated hand (ie, the hand being used in MRI assessments).

5.3.2 Exclusion Criteria

Subjects who fulfill any of the following should not be enrolled into this trial:

1. ACR functional class IV as defined by the ACR classification of functional status or wheelchair/bedbound
2. Use of oral corticosteroids > 10 mg daily prednisone equivalent, or change in dose of corticosteroids within 2 weeks prior to Screening or during Screening
3. Use of injectable corticosteroids (including intra-articular corticosteroids) or intra-articular hyaluronic acid within 4 weeks prior to Screening or during Screening
4. Initiation or change in dose for NSAIDs (including low-dose aspirin and COX-2 inhibitors) within 2 weeks prior to dosing with the IMP
5. High potency opioid analgesics (eg, methadone, hydromorphone, oxycodone, fentanyl, or morphine) are prohibited within 2 weeks prior to Screening and during the trial; other analgesics are allowed (eg, acetaminophen, codeine, hydrocodone*, propoxyphene*, or tramadol), although not within 24 hours of study visits with clinical assessments (*not approved in Japan).
6. Current or prior treatment with **any** of the following:
    a. Biologic DMARDs (approved or investigational), including but not limited to:
        i. TNF antagonists (eg, adalimumab, infliximab, certolizumab pegol, golimumab, etanercept, or any biosimilars of these agents [approved or investigational], or any investigational TNF antagonist)
        ii. Interleukin-6 antagonists (eg, tocilizumab, sarilumab, sirukumab, vobarilizumab*) (*not approved in Japan)

iii. Abatacept (CTLA4-Fc)

iv. Anakinra* (IL-1 receptor antagonist) (*not approved in Japan)

v. B cell-depleting antibodies (eg, rituximab, ocrelizumab*, ofatumumab, obinutuzumab*, ocaratuzumab*, veltuzumab*, or any biosimilars of these agents [approved or investigational]) (*not approved in Japan)

vi. Anti-BLyS (B lymphocyte stimulator) agents (eg, belimumab, tabalumab*) (*not approved in Japan)

vii. Dual BLyS/ A proliferation-inducing ligand (APRIL) neutralizing agents (eg, atacicept*, RCT-18*) (*not approved in Japan).

b. Targeted synthetic DMARDs (approved or investigational), specifically:

i. JAK inhibitors (eg, tofacitinib, baricitinib, ruxolitinib, filgotinib*, ABT-494*, etc.) (*not approved in Japan)

ii. Other BTK inhibitors (eg, CC-292, GDC-0853, BMS-986142, etc.).

c. Alkylating agents (eg, chlorambucil*, cyclophosphamide) (*not approved in Japan).

7. The following restrictions on nonbiologic DMARD must be followed, otherwise the subject is excluded:

a. Auranofin (Ridaura®), minocycline, penicillamine, sulfasalazine, cyclosporine, mycophenolate (mycophenolate sodium not approved in Japan), tacrolimus, azathioprine: must have been discontinued for 4 weeks prior to dosing with the IMP

b. Leflunomide (Arava®) must have been discontinued 12 weeks prior to dosing with the IMP if no elimination procedure is followed. Alternately, it should have been discontinued with the following elimination procedure at least 4 weeks prior to dosing with the IMP: Cholestyramine at a dosage of 8 g 3 times a day for at least 24 hours, or activated charcoal at a dosage of 50 g 4 times a day for at least 24 hours

c. Injectable Gold (aurothioglucose* or aurothiomalate): must have been discontinued for 8 weeks prior to dosing with the IMP (*not approved in Japan)

d. Anti-malarials (hydroxychloroquine, chloroquine*) will be allowed in this trial. Subjects may be taking oral hydroxychloroquine (≤ 400 mg/day) or chloroquine* (≤ 250 mg/day), doses must have been stable for at least 12 weeks prior to dosing with the IMP, and will need to be continued at that stable dose for the duration of the trial. If discontinued prior to this trial, they must have been discontinued for 4 weeks prior to dosing with the IMP (*not approved in Japan).

8. **MRI Substudy Subjects:**

a. Inability to comply with MRI scanning, including contraindications to MRI such as known allergy to gadolinium contrast media, claustrophobia (if the site does not have ability to scan extremities only), presence of a pacemaker, cochlear implants, ferromagnetic devices or clips, intracranial vascular clips, insulin pumps, and nerve stimulators.

b. More than 25% of applicable joints of the target hand and wrist having had prior surgery or showing maximum Genant-modified Sharp erosion (3.0) or joint-space narrowing (4.0) scores, based on single posteroanterior radiographs of target hand and wrist read centrally.

9. Immunologic disorder other than RA, with the exception of secondary Sjogren's syndrome associated with RA, and well-controlled diabetes or thyroid disorder
    a. Thyroid Disorder: See exclusion criterion #29
    b. Diabetes: For purposes of this study, subjects with diabetes with Hemoglobin A1C ≥ 10% at Screening are excluded.
10. Any condition other than RA or Sjogren's syndrome associated with RA that requires oral, intravenous, intramuscular, or intra-articular corticosteroid therapy
11. Diagnosis of Felty's syndrome
12. Vaccination with live or live-attenuated virus vaccine within 1 month prior to Screening or during Screening
13. Vaccination with Bacille Calmette-Guérin (BCG) within 12 months of Screening
14. Known hypersensitivity to any trial treatment, diluents, excipients, latex, including placebo

16. Active, clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks of Screening or during Screening, or completion of oral anti-infectives within 2 weeks before or during Screening, or a history of recurrent infections (ie, 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled would not be exclusionary.
17. Any of the following:
    a. History of or positive testing for Human Immunodeficiency Virus (HIV) at Screening
    b. History of or positive testing for hepatitis C antibody and/or hepatitis C ribonucleic acid (RNA) by polymerase chain reaction (PCR) at Screening
    c. Positive for hepatitis B surface antigen (HBsAg) at Screening
    d. For subjects who are negative for HBsAg at Screening, but are anti-hepatitis B surface antibody positive and/or anti-hepatitis B core antibody positive at Screening, reflex testing for hepatitis B virus (HBV) deoxyribonucleic acid (DNA) by PCR will be performed:
        i. Hepatitis B antibody-positive subjects who have detectable HBV DNA ≥ 20 IU/mL are excluded
        ii. Hepatitis B antibody-positive subjects who are HBV DNA-negative OR have detectable HBV DNA < 20 IU/mL are not excluded from the study. However, these subjects will need HBV DNA measured by PCR and liver function tests at Weeks 4, 8, 12/End of Treatment/Early Withdrawal, and 16/Safety Follow-up/End of Trial Visit.
    e. Testing for HIV, hepatitis C Virus (HCV), and HBV is required for participation in the study. Individuals unwilling to have this testing done are excluded.
18. History of:
    a. Latent or active granulomatous infection other than TB (eg, nontuberculous mycobacteria) within 6 months prior to randomization
    b. Any opportunistic infection (eg, histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infections) within 6 months prior to randomization
    c. Symptomatic herpes zoster within 3 months prior to randomization
    d. Disseminated/complicated herpes zoster (eg, multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or postherpetic neuralgia).

19. Presence of uncontrolled or New York Heart Association (NYHA) Class 3 or 4 congestive heart failure.

    a. NYHA Class 3: Cardiac disease resulting in marked limitation of physical activity. Subjects are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain

    b. NYHA Class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

20. History of splenectomy at any time and/or history of infected joint prosthesis if that joint prosthesis is still in place

21. History of any major surgery or joint surgery within 2 months prior to Screening, or will require major surgery or any planned joint surgery during trial

22. History of myocardial infarction or cerebrovascular event within 6 months prior to Screening, or current active angina pectoris, symptomatic heart failure, seizures, untreated hypertension, gastrointestinal bleeding, or any other significant medical condition in the Investigator's opinion

23. On anti-coagulation or anti-platelet therapy other than low dose daily aspirin for cardioprotection

24. On fish oil (unless discontinued prior to first dose)

25. History of cancer, except adequately treated basal cell or squamous cell carcinoma of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix, unless considered cured > 5 years

26. Breastfeeding/lactating or pregnant, or discontinued lactation within 3 months of randomization. Lactating women are excluded regardless of whether or not they are nursing infant(s).

27. Clinically significant abnormality on ECG, or an active infective process or any other clinically significant abnormality on Screening CXR. If a CXR has been taken within the previous 3 months prior to Screening and results are available and normal, the CXR does not need to be carried out.

28. Estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 as calculated by the 4 component Modification of Diet in Renal Disease (MDRD) equation by the central laboratory:

    a. The 4-component Modification of Diet in Renal Disease equation (Levey 2006): eGFR = 175 × (serum creatinine in mg/dL) – 1.154 × (age in years) – 0.203 × 0.742 (if female) × 1.212 (if race is black).

29. TSH < 0.01 or ≥ 7.1 mIU/L. Subjects receiving thyroxine as replacement therapy may participate in the study provided that thyroxine has been at a stable dose for ≥ 12 weeks, and

TSH is within the reference range. TSH may be repeated once within approximately 2 weeks of the initial testing, if the first result is exclusionary, and the value from repeat testing may be accepted for eligibility to participate in the study if it is within the reference range.

30. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, or lipase > 2 × above upper limit of normal (ULN) of laboratory reference range, total bilirubin > 1.5 × ULN, any other clinically significant laboratory abnormality
31. B cell (CD19) count < 50% of the lower limit of normal (LLN)
32. Significant cytopenia, including absolute neutrophil count < 1,500/mm^3, platelet count < 100,000/mm^3, or absolute lymphocyte count < 1,000/mm^3
33. Has taken an investigational drug within 1 month or 5 half-lives of the investigational drug, whichever is longer, prior to Screening (exclusion criteria 6 to 8 and 10 take priority)
34. Subjects currently receiving (or unable to stop using prior to receiving the first dose of IMP) medications or herbal supplements known to be potent (strong or moderate) inhibitors of cytochrome P450 isozyme 3A (CYP3A) (must stop at least 1 week prior to dosing), potent (strong or moderate) inducers of CYP3A (must stop at least 3 weeks prior to dosing), or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least 1 day prior to dosing), see Table 9.
35. History of/or current alcohol, substance, or drug abuse:
    a. Excessive alcohol use is defined as alcohol and/or substance abuse or dependence (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text revision) in the past year **OR**
    b. A history of alcohol or substance abuse, as determined by the Investigator.
36. Legal incapacity or limited legal capacity.
37. Positive serum β-D-glucan test (Japan only).

5.4 Criteria for Randomization and Initiation of Trial Treatment

Randomization should occur on Day 1 after all Screening procedures have been completed; subject eligibility must be reviewed again and confirmed at the site on Day 1 prior to randomization. If a subject does not meet eligibility criteria, the subject can be retested and rescreened once at the Investigator's discretion as described in Section 7.1.1.

Eligible subjects will be randomized to treatment through a central randomization process by an IWRS. This will be a double-blind trial. Subjects will be stratified by whether or not they are in the MRI substudy and by region. There are no systematic differences between MRI and non-MRI sites beyond the availability and suitability of MRI for study purposes, to avoid potential selection bias. Participation in the MRI substudy will be mandatory for subjects participating at designated MRI sites.

5.5 Criteria for Subject Withdrawal

Subjects will be informed they have the right to withdraw from the trial at any time, without prejudice to their medical care, and they are not obliged to state a reason for withdrawing. Any withdrawal must be fully documented in the eCRF and source documents, and should be followed up by the Investigator.

The Investigator may withdraw a subject at any time if this is considered to be in the subject's best interest.

5.5.1 Withdrawal from Trial Therapy

Subjects who withdraw from therapy must return for an End of Treatment/Early Withdrawal Visit followed by a Safety Follow-up Visit. At the time of early withdrawal from trial therapy, all information/assessments noted at the End of Treatment Visit in the Schedule of Assessments are to be completed. For any subject that withdraws from the MRI substudy prior to Week 12, contact the Study Sponsor. If the IMP is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the eCRF, and all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made and any AEs followed up until resolution or a period of 30 days after the last Safety Visit (or withdrawal from the trial).

A subject must be withdrawn from IMP if any of the following occur:

- Adverse events, if permanent discontinuation of the IMP is desired or considered necessary by the Investigator and/or subject
- Use of prohibited medications, as defined in Section 6.5.2. However, any medications may be administered to address adverse reactions, or emergency situations. Should a prohibited medication be needed during the study, the subject would be withdrawn from the trial. All medications other than study therapy given during the course of the trial must be recorded (see Section 6.5.1).
- Interruption of MTX more than twice in a period of 4 weeks
- Pregnancy (for further details in case of pregnancy, see Section 7.4.2)
- Protocol noncompliance judged as significant by the Investigator and/or the Sponsor. If a subject has failed to attend scheduled trial assessments or had failed to comply with the trial protocol otherwise, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.
- Subject withdrawal of consent
- Loss to follow-up; at least 3 attempts (2 telephone calls, 1 Acknowledgement of Receipt letter) should be made to contact the subject to ensure the reason for not returning is not an AE
- Death

- Participation in another clinical trial, with the exception of noninterventional studies
- Any event(s) that endanger the safety of the subject, with the exception of AEs that will be handled as above
- If during the study, in the opinion of the Investigator, the subject's RA disease level is unacceptably high requiring therapy not permitted per the protocol, the subject may withdraw from the study treatment and initiate therapy recommended per the treating physician. In this case, the subject will be considered a nonresponder.

5.5.1.1 Stopping Rules

The severity of AEs will be graded using the NCI-Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grading scale (Hahn 2012).

The IMP should be temporarily withheld or permanently withdrawn if the following abnormalities occur or re-occur, as relevant, and re-initiation following temporarily withholding of IMP should be discussed with the Medical Monitor. If a subject's predose baseline value falls within any of the below criteria, consult with the Medical Monitor regarding potential withdrawal, continued participation in study, and additional monitoring if needed:

- For a neutrophil count $< 500/mm^3$ or platelet count $< 25,000/mm^3$ or lymphocyte count $<200/mm^3$ (Grade 4) or neutrophil count 500 to $999/mm^3$ (Grade 3) with fever or platelet count 25,000 to $49,999/mm^3$ (Grade 3) with bleeding, the IMP should be permanently withdrawn.
  - For a Grade 3 decrease in neutrophil count without fever or Grade 3 decrease in platelet count without bleeding, temporarily hold the IMP and recheck the value. If the value is still Grade 3, permanently discontinue the IMP.
  - For a decrease to Grade 2, temporarily hold the IMP and recheck the value. Discontinue the IMP if the neutrophil or platelet count continues to decrease, and re-initiate the IMP if no downward trend is observed.

- For an increase in serum creatinine to > 3 × Baseline (Grade 3 or higher), the IMP should be permanently withdrawn.
    - For any other increase in serum creatinine > 1.5 × Baseline, temporarily hold the IMP and recheck the value. Discontinue the IMP if the value does not decrease, or re-initiate the IMP if a downward trend is observed.
- For any serum IgG level < 3 g/L, confirmed by repeat testing, the IMP should be permanently withdrawn.
- For any increase in HBV DNA by PCR from negative/undetectable to detectable, AND/OR increase in HBV DNA by PCR from < 20 IU/mL to ≥ 20 IU/mL, the IMP should be permanently withdrawn. The subject should be followed with additional testing and hepatitis B treatment, as indicated per local guidelines, including consultations with a specialist, such as a Hepatologist, at the Investigator's discretion and in conjunction with the Medical Monitor.
- For any other laboratory abnormality of Grade 4 severity, the IMP should be temporarily withdrawn, and the subject discussed with the Medical Monitor and Sponsor prior to re-initiation.
- For any other laboratory increase/decrease of Grade 3 from Baseline, discuss with the Medical Monitor and consider temporarily holding the IMP.

Unscheduled duplicate blood samples will be collected for selected safety laboratories to be processed by both the central laboratory and local laboratories to permit rapid confirmation of a central laboratory test result that requires an action such as drug interruption. A detailed list of these tests is provided in the laboratory manual. The Investigator should review local laboratory results within 24 hours and should base decisions regarding retesting or IMP dose interruption or discontinuation on local laboratory results if local laboratory results are obtained prior to the central laboratory results and show an abnormality requiring action. The local laboratory reference range should be used to determine grade in this case. Only the central laboratory results will be automatically reported and used for analyses. If an action is taken to retest or adjust the IMP dose based on local laboratory results, the results should be entered in the eCRF (with date, time and result, and local reference range) on an unscheduled visit page to document why the decision was made.

The reason for IMP withdrawal and the nature, duration, and results of any planned follow-up observations should be recorded in the appropriate section of the eCRF.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. In addition to voluntary withdrawal from the trial, a subject must be withdrawn if the subject is permanently withdrawn from trial therapy (see Section 5.5.1). Subjects withdrawn from the trial while still on the IMP should return immediately for an End of Treatment/Early Withdrawal Visit upon discontinuation of the IMP and a Safety Follow-up Visit (see Section 5.5.1). Subjects who are withdrawn from the trial and are no longer on the IMP must complete the Safety Follow-up Visit assessments described in Section 7.1.4.

If a subject fails to return for the post-treatment Safety Visit, at least 3 attempts (2 telephone calls, 1 Acknowledgement of Receipt letter) should be made to contact the subject to ensure the reason for not returning is not an AE. Likewise, if a subject wishes to discontinue from the trial (eg, for personal reasons), an attempt should be made to establish the true reason is not an AE (bearing in mind the subject is not obliged to state the reasons). A complete final evaluation at the time of the subject's withdrawal should be made and any AEs followed up until resolution or a period of 30 days after the last Safety Visit (or withdrawal from the trial).

Subjects who are withdrawn after randomization (eg, due to AEs or lack of efficacy) will not be replaced. Subjects who are withdrawn from the trial will not be allowed to re-enroll in the trial.

5.6 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 for any IMP. 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 an IMP or withdrawal of an IMP from the market for safety reasons.

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

5.7 Definition of End of Trial

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

A clinical trial protocol may not be considered closed as long as:

- Any subject is still receiving any IMP as part of this protocol
- Visits specified by the protocol are still taking place
- Procedures or interventions according to the protocol are still being undertaken in any subject
- The post-treatment follow-up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

6.1 Description of the Investigational Medicinal Product

Investigational Medicinal Product:

The term "Investigational Medicinal Product" 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 formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

The IMPs to be administered in this trial are evobrutinib (also known as M2951) and evobrutinib placebo.

Evobrutinib will be administered as film-coated tablets for oral administration and containing 25 mg of drug substance (chemical name 1-(4-{[6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propenone) formulated with excipients. The evobrutinib placebo will be administered as tablets ready for oral administration matching the active tablets in color, size, and shape.

The Sponsor will provide IMP to the trial sites.

Specific Rules for Treatment Modifications:

Not applicable.

6.2 Dosage and Administration

Details describing evobrutinib dosing and administration are provided in Table 8. Subjects will receive oral evobrutinib or placebo tablets daily as detailed in Table 8. Treatment regimens and sequences are detailed in Table 3.

Table 8 Dosage and Administration of Evobrutinib

Product Description	Dosage Form	Evobrutinib Dose	Number of Tablets (Morning Dose)		Number of Tablets (Evening Dose)	
			25 mg		25 mg	
			Evobrutinib	Placebo	Evobrutinib	Placebo
Evobrutinib	Oral	25 mg QD	1	2	0	2
Evobrutinib	Oral	75 mg QD	3	0	0	2
Evobrutinib	Oral	50 mg BID	2	1	2	0
Placebo	Oral	0 mg	0	3	0	2

Note: To maintain the blind, all subjects will receive BID treatment. Subjects will self-administer 3 tablets in the morning and 2 tablets in the evening (every 12 hours ± 2 hours).

At the visits indicated in the Schedule of Assessments (Table 1), IMP should be administered during the trial visit.

Subjects should take each dose more than 1 hour prior to a meal or snack and more than 2 hours after a meal or snack. Clear fluids are allowed at any time.

6.3 Assignment to Treatment Groups

Eligible subjects will be randomized through a central stratified randomization process by the IWRS prior to dosing on Day 1.

The trial is fully controlled by the IWRS, which assigns treatment individual (unique) kit numbers for each subject. The kit number is linked via the Good Manufacturing Practice qualified system to the corresponding treatment as well as to the subject.

Subject identifiers will be comprised of 3 sets of numbers representing the trial number, the site number, and the subject number, which is allocated sequentially at each site starting with PPD.

Treatment kits will contain enough medication for administration for 1 week (+ 2 days). In addition to the subject and Investigator/site, all Sponsor and CRO trial staff will be blinded to the treatment group assignment.

6.4 Noninvestigational Medicinal Products to be Used

Throughout the trial, subjects will remain on their chronic stable doses of MTX at the time of Screening (see Section 5.3.1), along with other permitted medications (see Section 6.5.1) as part of their standard of care and adjusted only for safety reasons.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration (ie, start and end dates), dosing regimen (eg, once daily, twice daily, etc.), and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Permitted medications are any medications required per the medical history and not specifically prohibited by the protocol during the trial. These standard of care medications are part of the subject's previous RA treatment and will therefore not be provided by the Sponsor. Any such medications prescribed or used should be recorded in the eCRF.

Methotrexate: All subjects should maintain a stable MTX dose (up to 25 mg/week, via oral, intramuscular, or subcutaneous administration) during the trial period. Any modification of the route of administration is not allowed. However, if modification to the route of administration is determined by the Investigator to be in the best interest of the subject at any time, please contact the Medical Monitor to discuss. However, a dose reduction of MTX will be allowed in case of AEs attributed to MTX. Temporary interruptions of administration are allowed for up to 14 days (can be interrupted up to twice because MTX is administered once weekly).

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

Anti-malarials (hydroxychloroquine or chloroquine*): Subjects may be taking oral hydroxychloroquine (≤ 400 mg/day) or chloroquine* (≤ 250 mg/day). The dose must have been stable for at least 12 weeks prior to dosing with the IMP, and will need to be continued at that stable dose for the duration of the trial. If discontinued prior to this trial, they must have been discontinued for 4 weeks prior to dosing with the IMP. Dose adjustment of anti-malarials is not allowed. Subjects who were not previously on anti-malarials should not initiate anti-malarial therapy during the trial (*not approved in Japan).

Oral corticosteroids: Oral corticosteroids are permitted at a dose of ≤ 10 mg/day prednisone or equivalent. The dose of oral corticosteroids must remain stable. Subjects who were not previously

on oral corticosteroids should not initiate corticosteroid therapy during the trial. Any changes must be discussed with a Medical Monitor to determine if the changes are compatible with continued participation in the trial.

NSAID: Subjects may be treated with NSAIDs (including low-dose aspirin and COX-2 inhibitors) for symptomatic treatment of arthritis up to the maximum recommended dose per local labeling during the trial (including COX-2 inhibitors). Drug(s) must be at a stable dose, route, and regimen for at least 2 weeks prior to Baseline. Increases in the NSAID dose during the trial are not allowed. Discontinuation or reduction is allowed in case of NSAID-related toxicity/to protect the subject's safety. In subjects who receive NSAIDs, prophylactic treatment with proton pump inhibitors or H2 receptor blockers is recommended (per local guidelines). NSAIDs are also allowed for the management of AEs not related to RA such as colds or sprains throughout the trial (including COX-2 inhibitors); however, the daily dosage of NSAIDs must not be modified within 24 hours prior to any study visit, except if an adjustment is needed to protect a patient's safety.

Non-NSAID Analgesics: High potency opioids (eg, methadone, hydromorphone, oxycodone, fentanyl, or morphine) are prohibited during the trial. Other analgesics (eg, acetaminophen, codeine, hydrocodone*, propoxyphene*, or tramadol), up to the maximum recommended doses, may be used for pain control as required. Subjects should not take non-NSAID analgesics within 24 hours prior to a visit where clinical efficacy assessments are performed with the exception of those subjects who entered the trial on a stable dose, route, and regimen of non-NSAID analgesics (at least 28 days prior to Screening). (*not approved in Japan)

Any concomitant medications (including over-the-counter medications, herbal medications, preventive vaccines, vitamins, proton pump inhibitors [prescription or over-the-counter], and food supplements) and procedures must be recorded. A description of the type of drug or procedure, name of the active substance, dosage, frequency, duration, reason for administration of drug, and 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.

Any medications (other than those excluded as per exclusion criteria in Section 5.3.2 or prohibited as per Section 6.5.2) that are considered necessary for the subjects' welfare and will not interfere with the trial medication may be given at the Investigator's discretion. Any medications may be administered to address adverse reactions, or emergency situations. Should a prohibited medication be needed during the study, the subject would be withdrawn from the trial.

6.5.2 Prohibited Medicines

The following medications and therapies are not permitted during the trial and would require discontinuation of trial treatment:

- Oral corticosteroid dose > 10 mg/day
- Intramuscular or intravenous corticosteroids

- Intra-articular corticosteroids. Intra-articular hyaluronic acid, although this option may be discussed with the Medical Monitor if required to prevent early discontinuation. Any injected joints will be censored from joint counts for the duration of the study.
- Biologic therapies for treatment of RA (bDMARDs) are strictly prohibited. Biologic therapies for other indications must be discussed with the medical monitor on a case-by-case basis, with the exception of insulin and antibodies used for bone density (eg, denosumab), which are permitted
- tsDMARD (eg, JAK inhibitors, other BTK inhibitors)
- Intravenous Ig therapy and/or plasmapheresis
- Live and live-attenuated vaccines
- Anticoagulants and anti-platelet therapy other than low dose daily aspirin for cardioprotection
- Fish oil
- Herbal supplements including, but not limited to, St. John's wort, grapefruit, Seville oranges, cranberries, or juices of these fruits
- Moderate or strong inhibitors of CYP3A (see Table 9). The additive effects of weak inhibitors taken in combination must also be taken into account
- Moderate or strong inducers of CYP3A (see Table 9)
- Drugs mainly metabolized by CYP3A with a narrow therapeutic index (see Table 9).

New therapies for RA should not be initiated during the trial. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and should result in withdrawal of the subject from the IMP (see Section 5.5.1).

Table 9 Examples of Inhibitors or Inducers of CYP3A Enzymes or Substrates with Narrow Therapeutic Range

Inhibitors		
Strong	**Moderate**	**Weak**
Boceprevir, clarithromycin, conivaptan, grapefruit juice,[a] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[a] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
Inducers		
Strong	**Moderate**	**Weak**
Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, rufinamide
Substrates With a Narrow Therapeutic Range		
Alfentanil, astemizole,[b] cisapride,[b] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[b]		

AUC = area under the curve, CYP = cytochrome P450, CYP3A = cytochrome P450 isozyme 3A.

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation is used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation is used (eg, low dose, single strength).

[b] Withdrawn from the US and certain other markets because of safety reasons.

Notes:

- This is not an exhaustive list. For an updated list, see Tables 5, 6, and 7 in the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
- A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 5-fold or decreases clearance by > 80%, and a strong inducer decreases AUC of a substrate by ≥ 80%.
- A moderate inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 2-fold but < 5-fold or decreases clearance by 50% to 80%, and a strong inducer decreases AUC by 50% to 80%.
- A weak inhibitor is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP < 2-fold or decreases clearance 20% to 50%, and a weak inducer decreases AUC by 20% to 50%.
- CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de pointes).

6.5.3 Other Interventions

6.5.3.1 Other Trial Considerations

Women of childbearing potential must be willing to follow very specific requirements for birth control as indicated in Section 5.3.1. While there is no requirement for contraception in male

participants based on the nonclinical data, it is recommended that conception be avoided during exposure to evobrutinib as there is limited experience in humans.

6.5.3.2 Other Interventions/Therapies

Use of potentially excluded procedures such as acupuncture or joint replacement therapy is to be discussed with the Sponsor or designee on a case-by-case basis. Use of acupuncture is allowed to continue if it is started before Screening. Major elective surgeries such as abdominal, thoracic, or joint replacement surgeries should not be planned to occur during the Trial Period. Unplanned joint replacement surgery should be discussed at the earliest opportunity prior to the surgery with the Medical Monitor regarding continuation of the subject in the trial. Surgical procedures involving the hands, wrists, or feet are prohibited during the trial due to their likely effects on imaging endpoints. Unplanned procedures involving the hands, wrists, or feet should be discussed at the earliest opportunity prior to the surgery with the Medical Monitor regarding continuation of the subject in the trial.

6.6 Packaging and Labeling of the Investigational Medicinal Product

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

Evobrutinib and matching placebo are supplied by the Sponsor. A description of the pharmaceutical properties and composition of the formulation of evobrutinib is provided in the Investigator's Brochure. Additional details of packaging and labeling of the IMP will be defined in a separate Operations Manual.

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

The IMP must be carefully stored at the trial site in a location with restricted access and separately from other drugs. Storage conditions for evobrutinib will be specified in the Manual of Procedures (MOP). Any deviations from the recommended storage conditions should be immediately reported to the Sponsor, and the medication should not be used until authorization has been received from the Sponsor.

The IMPs must not be used for any purpose other than the trial. The administration of the IMPs to subjects who have not been enrolled into the trial is not covered by the trial insurance.

Disposal of the IMPs should be according to local regulations and institutional guidelines.

6.8 Investigational Medicinal Product Accountability

The Investigator or designee (or head of the trial site, in Japan only) is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records. (In Japan only, the head of the trial site can delegate the control of and accountability for the study drug to an investigational product storage manager.) Upon receipt of IMP, the responsible person (in Japan only: the head of the trial site or the investigational product storage manager) will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.

IMP dispensing 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 and prepared at the site
- The use of each dose by each subject
- The disposition (including return, if applicable) of any unused IMP
- Dates, quantities, batch numbers, vial numbers, expiry dates, and the individual subject trial numbers.

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

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a subject may be redispensed to a different subject.

A Trial Monitor will periodically collect the IMP accountability forms.

6.9 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered at the site on trial visit days as defined in Table 1. All other dosing will be done by the subject at home throughout the rest of the trial. Compliance may be assessed via the subject diary for dosing and food intake around dosing. Diaries will be collected and reviewed at the trial visits specified in Table 1.

Subjects 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, subjects will be given sufficient IMP for at-home dosing until the next scheduled visit during the Treatment Period.

Insufficient compliance with the protocol-specified dosing regimen is defined as receiving < 80% of the required number of scheduled doses of study medication. If a subject has insufficient compliance, the Investigator or designee is to counsel the subject and ensure steps are taken to improve compliance.

6.10 Blinding

This will be a double-blind trial. After Day 1, the trial site staff, the Sponsor, and the CRO trial team will be blinded to results that can reveal the CCI effects of evobrutinib in an individual subject (ie, hsCRP, ESR).

Blinding to treatment codes or laboratory results capable of revealing treatment will be maintained throughout the trial duration, except for the unblinded IDMC, or in the event that emergency unblinding is necessary for subject safety or the reporting of SUSARs.

In order to maintain the blinded nature of the trial, only the randomization statistician, an independent person at the trial site responsible for receiving local laboratory ESR results and conveying those results to the central laboratory, and an independent statistical team (independent of the PPD trial team) responsible for production of the IDMC analyses, will be fully unblinded during trial conduct.

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The procedures of database lock and unblinding for the statistical analysis will be documented in the Data Management Plan and Unblinding Plan.

The IDMC will also be unblinded to treatment, and as such, will have unblinded access to all laboratory data for the duration of the trial, as described in the IDMC Charter.

All breaks of the trial blind must be adequately documented in the Unblinding Plan.

6.11 Emergency Unblinding

The Investigator will have the ability to break the blind with regard to IMP for any subject at any time through the IWRS. However, the Investigator should make every effort to contact the responsible Medical Monitor or their designee to discuss the subject's emergency situation and the need to unblind prior to unblinding any subject and must contact the Sponsor or designee within 1 working day after the event occurs without revealing to the Sponsor personnel the result of the code break. The Investigator will be able to access the subject's treatment assignment 24 hours a day through the IWRS using a unique access code and user number (different from those used to assign subjects to treatment through the IWRS). Should the IWRS be unavailable for any reason, the Investigator will be able to break the blind via a telephone call to the IWRS help desk, which is available 24 hours a day. The help desk can access the database manually to perform the unblinding via telephone in the event that the IWRS is not operational. The Investigator must record the date of unblinding and the reason in the eCRF and source documents. Contact information for breaking the blind in an emergency is given on the subject emergency card provided to each subject (see Section 9.4).

Under certain circumstances, Drug Safety may be required to unblind the treatment assignment for an individual subject following an SAE or other serious event; for example, if an expedited regulatory report is required. See Section 7.4.1.4 for further details on expedited reporting and SAEs.

If emergency unblinding is required, discontinuation of the affected subject from the IMP and/or trial is not mandatory unless there are other circumstances that require subject discontinuation. If the affected subject is discontinued from the IMP, the subject must immediately complete the End of Treatment/Early Withdrawal Visit, followed by the Safety Follow-up Visit 28 days (+ 5-day window) later.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the study. Any overdose must be recorded in the study medication section of the eCRF.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or nonserious) – must be reported to the Sponsor's Global Drug Safety department or designee in an expedited manner using the appropriate reporting form (see Section 7.4).

The effects of an overdose of evobrutinib are unknown, and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be considered for hospitalization for observation if clinically indicated, and the Investigator or treating physician should use appropriate clinical judgment for the management of any clinical or investigational findings.

6.13 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, the subject is free to access further treatment as deemed appropriate by the Treating Investigator.

7 Trial Procedures and Assessments

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

Throughout the trial, subjects will undergo the assessments detailed in Table 1 including blood sampling. Details of the blood volumes to be collected for each sample/visit will be detailed in the laboratory manual. Instructions on how samples will be collected, labeled, processed, stored, and shipped as well as specification on bioanalytical methods will be detailed in the laboratory manual.

All blood and urine tests will be analyzed by a central laboratory, with the following exceptions:

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- Blood samples will be sent for duplicate analysis of selected safety tests by both central and local laboratories. These duplicate safety samples are listed in the laboratory manual.
- Erythrocyte sedimentation rate will be analyzed by local laboratories.
- T.SPOT.TB test, if applicable at Screening, will be analyzed at local laboratories.

Every effort should be made to perform assessments as close as possible to the scheduled time points, within the range of days noted for each day on trial as noted in Table 1. The details of efficacy assessments and safety assessments are described in Sections 7.3 and 7.4, respectively.

The Schedule of Assessments for the trial is presented in Table 1 and details of the trial procedures are provided in Section 7.1.1 for the Screening Period, Section 7.1.2 for the Treatment Period, Section 7.1.2.1 for the End of Treatment Visit, and Section 7.1.4 for the Safety Follow-up Visit.

The Sponsor and CRO should be notified immediately of any major violations of the trial procedures. Major and minor protocol violations will be defined in the MOP and in the SAP (relevant only). Procedures for documenting protocol violations will be provided in the MOP.

7.1 Schedule of Assessments

Assessments during the trial will be performed according to Table 1. It is strongly recommended that patient-reported outcome measures be performed prior to any other assessments and should only be conducted after ICF has been signed. For volumes of blood collected, see laboratory manual.

7.1.1 Screening Period

At Screening, the prospective subject will be informed of the trial objectives and overall requirements, and informed consent will be obtained prior to initiating any Screening procedures or collecting any data. Screening procedures will be performed according to assessments in Table 1, within 28 days prior to the first administration of the IMP (or within 8 weeks if a screening test needs to be repeated, as applicable; see Section 5.1).

After signing of informed consent, Screening assessments will include, but are not limited to, recording of demographic information and other Baseline characteristics, detailed RA history, medical history, and medications history and reviewing of inclusion/exclusion criteria. If a subject does not meet eligibility criteria, the subject can be retested and rescreened once within the Screening Period at the Investigator's discretion and on discussion with the Medical Monitor.

If a subject is rescreened, the subject will be assigned a new subject number and reconsented.

Subjects who have completed the Screening assessments and have fulfilled all of the eligibility criteria will be entered into the trial.

7.1.2 Treatment Period

At all applicable visits, patient-reported outcome questionnaires must be performed prior to any other assessments. At the Day 1 visit, assessments should be performed prior to randomization and the administration of the IMP. Scheduled assessments will be performed according to Table 1 before administration of the IMP, with the exception of relevant postdose blood draws (eg, CCI). The first dose of the IMP will be given while the subject is still on site for the Day 1 visit.

At subsequent visits (Weeks 2 through 12), all scheduled visits during the Treatment Period may take place within the visit windows specified in Table 1. Subjects who discontinue early must return for the End of Treatment/Early Withdrawal Visit and Safety Follow-up Visit.

7.1.2.1 End of Treatment Visit

The End of Treatment Visit will be performed at Week 12 or within 5 days of early discontinuation of treatment with the IMP. Subjects will undergo assessments as described in Table 1. In case of premature discontinuation, the PRO assessments have to be completed at the End of Treatment visit.

7.1.3 Open-label Extension Period (Only Applicable Prior to Protocol Version 3.0)

In Protocol version 2.0, subjects completing the Treatment Period could have entered an optional Open-label Extension (OLE) Period, but the Sponsor made the decision to not initiate the OLE Period. As of the effective date of Protocol version 3.0 at study sites, all subjects completing the Treatment Period will enter the Safety Follow-up Period, and any subjects already participating in

the OLE Period at that time will be immediately withdrawn from the study following the protocol-specified withdrawal procedures outlined in Section 5.5.2: subjects would return for an End of Treatment Visit and return 4 weeks later for an End of Study/Safety Follow-up Visit.

7.1.4 Safety Follow-up Visit

The Safety Follow-up Visit will be performed 28 days (+ 5-day window) after the End of Treatment/Early Withdrawal Visit.

Subjects who discontinue the IMP or withdraw from the trial early will attend the Safety Follow-up Visit according to procedures described in Sections 5.5.1 or 5.5.2, respectively.

Any ongoing SAEs must be followed up until the SAE/AE has resolved, is considered stable, or is considered no longer clinically relevant by the Investigator.

7.2 Demographic and Other Baseline Characteristics

7.2.1 Demography

At Screening, the following demographic data will be collected: date of birth, sex (gender), race, ethnicity, smoking history and current smoking status (if former smoker, capture date of discontinuation).

7.2.2 Medical History

To determine the subject's eligibility for the trial, a complete medical history of each subject will be collected and documented during Screening, which will include, but may not be limited to, the following:

- Past and concomitant diseases
- Full Physical examination
- Laboratory assessments
- All medications (including herbal medications) taken and procedures carried out within 28 days prior to Screening. RA-related medications and procedures from within 1 year prior to Screening should be documented. Additional medications and procedures (with particular attention to RA-related medications and procedures), should be included as deemed relevant by the Investigator.

For the trial entry, all of the subjects must fulfill all inclusion criteria described in Section 5.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 5.3.2.

7.3 Efficacy Assessments

The following tests and procedures have been selected to evaluate the efficacy of evobrutinib and describe clinical improvement in subjects 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, hsCRP analyses, DAS28-hsCRP, DAS28-ESR, and subject and physician VAS, which are described below.

7.3.1.1 American College of Rheumatology Response Rates

The primary efficacy endpoint is ACR20 at Week 12 in subjects with RA. 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 hsCRP level (see Appendix II).

a. Tender Joint Count

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 subject's body; see Appendix II). 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 MCP 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 subject 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 subject 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 Screening and will be excluded from evaluation during the trial. The locations (or a listing) of surgical procedures should be documented in the subject's source documents/eCRF pages.

b. Swollen Joint Count

For ACR measures, the number of swollen joints will be determined by examination of 66 joints (33 joints on each side of the subject'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 MCP 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 subject 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 Screening and will be excluded from evaluation during the trial. The locations (or a listing) of surgical procedures should be documented in the subject's source documents/eCRF pages.

c. High sensitivity C-Reactive Protein

High-sensitivity C-reactive protein 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 evobrutinib on the subject's RA.

ACR20

The ACR20 is a primary efficacy measure for which, at Week 12, a subject 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 (see Section 7.3.1.7):

- Patient's Global Assessment of Disease Activity
- Patient's Assessment of 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 hsCRP.

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

ACR50 and ACR70

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

ACR Hybrid

The ACR hybrid score provides a quasi-continuous score that can detect smaller changes between treatments than the categorical ACR20/50/70 scores by combining the ACR20, ACR50, and ACR70 scores with the mean percent change from Baseline in all 7 ACR core set components. It is calculated according to Table 6.

7.3.1.2 European League Against Rheumatism Responder Index

Assessments of subjects with RA by EULAR response criteria will be used to categorize subjects as nonresponders, moderate responders, good responders, or responders (moderate + good responders) according to Table 7 (van Gestel 1998). In this study, DAS28-hsCRP will be used to determine EULAR response.

7.3.1.3 American College of Rheumatology/European League Against Rheumatism Boolean Remission

Following the Boolean-based definition of remission of ACR/EULAR, at any time point, a subject must satisfy all of the following: TJC ≤ 1, SJC ≤ 1, CRP ≤ 1 mg/dL and Patient's Global Assessment of Disease Activity ≤ 1 (on a 0–10 scale). The Boolean criteria appear more stringent than the DAS28 remission and have been specifically created for use in clinical trials (Felson 2011, Bykerk 2012).

7.3.1.4 Disease Activity Score - high-sensitivity-C-Reactive Protein

The DAS28-hsCRP is a measure of disease activity in 28 joints that consists of a composite numerical score of the following variables: TJC, SJC, hsCRP, and Patient's Global Assessment of Disease Activity (Vander Cruyssen 2005).

For DAS28-hsCRP, 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 subject's body: 2 shoulders, 2 elbows, 2 wrists, 10 MCP joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints, and 2 knees (Smolen 1995).

In this trial, the acute phase reactant for computing DAS28 is the hsCRP. DAS28-hsCRP will be derived using the following formula from the DAS28 website (DAS 2016):

$$DAS28\text{-}hsCRP = 0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.014 \times GH + 0.36 \times ln(hsCRP + 1) + 0.96$$

Where:

- TJC28 = 28 joint count for tenderness
- SJC28 = 28 joint count for swelling
- ln(hsCRP) = natural logarithm of hsCRP
- GH = the general health component of the Disease Activity Score (DAS) (ie, Patient's Global Assessment of Disease Activity).

7.3.1.5 Clinical Disease Activity Index

The CDAI is calculated based on the following formula (Smolen 2014):

$$CDAI = SJC28 + TJC28 + GH + PhGA$$

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 100-mm horizontal VAS, where the left end represents "very well", and the right end represents "very poor", converted to a cm scale [0 to 10 cm]).
- PhGA = Physician's Global Assessment of Disease Activity on a 100-mm horizontal VAS, where the left end represents "very well", and the right end represents "very poor", converted to a cm scale (0 to 10 cm).

7.3.1.6 Simplified Disease Activity Index

The SDAI is calculated based on the following formula (Smolen 2014):

$$SDAI = SJC28 + TJC28 + GH + PhGA + hsCRP$$

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 100-mm horizontal VAS, where the left end represents "very well", and the right end represents "very poor", converted to a cm scale [0 to 10 cm])
- PhGA = Physician's Global Assessment of Disease Activity on a 100-mm horizontal VAS, where the left end represents "very well", and the right end represents "very poor", converted to a cm scale (0 to 10 cm)
- hsCRP = high sensitivity C-reactive protein in mg/dL.

7.3.1.7 Visual Analog Scales

Visual analog scales will include the patient's assessment of pain, the patient's assessment of disease activity, and the physician's assessment of disease activity. Patient-reported outcome questionnaires must be performed prior to any other assessments at all visits.

Patient's Assessment of Arthritis Pain: The subject's assessment of his or her current level of pain related to arthritis over the previous 7 days will be recorded using the 100-mm horizontal VAS where the left end represents "no pain" and the right end represents "severe pain." The scale should be administered prior to the tender and swollen joint count examination.

Patient's Global Assessment of Disease Activity: The subject's overall assessment of his or her disease activity during the last 24 hours will be recorded using a 100-mm horizontal VAS, where the left end represents "very well", and the right end represents "very poor." The subject will be asked "considering all the ways that your arthritis affects you, draw a single vertical line (|) through the line below to indicate how your arthritis is today."

Physician's Global Assessment of Disease Activity: The Investigator's assessment of the subject's current arthritis disease activity will be recorded using a 100-mm horizontal VAS, where the left end represents "no arthritis activity", and the right end represents "extremely active arthritis."

7.3.2 Physical Function Assessments

7.3.2.1 Health Assessment Questionnaire – Disability Index

The HAQ-DI is a subject-reported questionnaire that is commonly used in RA to measure disease associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities (Fries 1980, Fries 1982, Ramey 1996).

The disability section of the questionnaire scores the subject'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.

Validated translated versions of the HAQ-DI will be used for each country participating in this trial.

7.3.3 Prevention of Joint Structural Damage Progression

Joint structural damage will be assessed using MRI at Baseline and Weeks 4 and 12 in subjects participating in the MRI substudy.

7.3.3.1 Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS)

Images of the MRI-designated hand and wrist (the hand being used in the MRI assessments will be assigned at Baseline and used consistently for the duration of the study) will be acquired using an MRI scanner as specified in the imaging guidelines. OMERACT RAMRIS scores for synovitis, bone marrow edema (osteitis), and erosions (Ostergaard 2004) will be read centrally by 2 independent readers, who are blinded to dose assignment and to chronology of each time point. Discrepancies in RAMRIS scores between the 2 readers will be reviewed at a consensus adjudication session with both readers to reach a consensus score for the designated cases. At a minimum, the images with the top 10% discrepancies in scores between the 2 readers will be reviewed (refer to Imaging Guidelines for details of Adjudication and Selection of Cases for Adjudication).

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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, ECGs, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject 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 subject (see Section 7.4.1.2).

The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject 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.

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

Investigators will reference the CTCAE, version 4.03 (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.

Only 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.

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets 1 of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IMP/trial 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, de-challenge or re-challenge, concomitant medication, course of the underlying disease, concomitant disease and relevant history, and trial procedures.

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (eg, 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 (eg, 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 subject 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 subject or may require medical or surgical intervention to prevent 1 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 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (eg, an overnight stay to facilitate the administration of intravenous fluids) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, 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.

Predefined Adverse Events of Special Interest

No adverse events of special interest have been designated for evobrutinib.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject 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 eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as described in Section 7.4.1.4.

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 eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues until the Safety Follow-up Visit (see Section 7.1.4). SAEs occurring after a subject has taken the last dose of IMP will be collected throughout the subject's participation until the Safety Follow-up Visit, regardless of the Investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the Investigator determines the SAE was related to IMP, or protocol procedure.

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

7.4.1.4 Procedure for Reporting Serious Adverse Events

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 eCRF may be provided in parallel (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, 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 eCRF.

The Investigator must respond to any request for follow-up information (eg, additional information, outcome, final evaluation, or 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 Medical Monitor, although in exceptional circumstances, the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

7.4.1.5 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 subjects 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 subjects, 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.

For Japan only: In accordance with ICH GCP and the Japanese ministerial ordinance on GCP, the Sponsor/designee will inform the Investigator and the head of the trial site of "findings that could adversely affect the safety of subjects, 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 and the head of the trial sites 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. The head of the trial site should also maintain copies of safety reports appropriately.

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.

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the Safety Follow-up Visit. All SAEs ongoing at the Safety Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject 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.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (eg, 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 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. 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 7.4.1.4.

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

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

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

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

7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Table 10, following the timing noted in the Schedule of Assessments (Table 1). For the lipid panel, fasting for a minimum of 8 hours is required. All samples should be clearly identified. Sample collection, preparation, and handling/shipment procedures are described in the laboratory manual. For WOCBP, including those who are postmenopausal for less than 12 months, serum pregnancy tests will be performed at initial screening, and high sensitivity urine pregnancy tests will be performed at the visits specified in Table 1. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active Treatment Period (or when potential pregnancy is otherwise suspected), and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Additional laboratory tests may be performed after abnormal findings.

Table 10 Clinical Safety Laboratory Evaluations

Screening virology[a]	▪ Human immunodeficiency virus I and II antigen and antibodies ▪ Hepatitis C antibody ▪ Hepatitis C virus polymerase chain reaction (reflex test if hepatitis C antibody positive) ▪ Hepatitis B core total and IgM antibody ▪ Hepatitis B surface antigen ▪ Hepatitis B surface antibody		
Biochemistry	▪ Albumin ▪ Aspartate aminotransferase ▪ Alanine aminotransferase ▪ Alkaline phosphatase ▪ γ-Glutamyl-transferase ▪ Lactate dehydrogenase	▪ Bilirubin (total) ▪ Protein (total) ▪ Creatinine[b] ▪ Amylase[c] ▪ Lipase[c] ▪ Total carbon dioxide ▪ Blood urea nitrogen ▪ Glucose	▪ Sodium ▪ Potassium ▪ Chloride ▪ Calcium ▪ Magnesium ▪ Phosphate ▪ Uric Acid
[redacted]			

Hematology	▪ Hematocrit ▪ Hemoglobin ▪ Hemoglobin A1C[d] ▪ Red blood cell count ▪ Mean corpuscular volume ▪ Mean corpuscular hemoglobin ▪ Mean corpuscular hemoglobin concentration ▪ Reticulocyte count	▪ Platelet count ▪ White blood cell count	▪ White blood cell differentials and absolute counts: ○ Basophils ○ Eosinophils ○ Lymphocytes ○ Monocytes ○ Neutrophils
Coagulation[a]	▪ International normalized ratio ▪ Partial thromboplastin time		
Lipid panel[e]	▪ HDL-C ▪ LDL-C	▪ Total cholesterol ▪ Triglycerides	
Urinalysis/ microscopy	▪ pH ▪ Nitrite ▪ Protein ▪ Blood	▪ Glucose ▪ Ketone bodies ▪ Urobilinogen	▪ Bilirubin ▪ Specific gravity ▪ Microscopy (white blood cells, red blood cells, casts)[f]
Other screening tests[a]	▪ QuantiFERON® tuberculosis test ▪ Serum β-D-glucan (Japan only)	▪ Thyroid-stimulating hormone	▪ Serum β-hCG (women only) ▪ FSH (women who are postmenopausal only)
Reflex Testing for HBV DNA	▪ HBV DNA PCR		
Urine	▪ Highly sensitive urine β-hCG (WOCBP only)		

β-hCG = beta-human chorionic gonadotropin, DNA = deoxyribonucleic acid, FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen, HBV = hepatitis B Virus, HCV = hepatitis C Virus, HDL-C = high-density lipoprotein cholesterol, hsCRP = high sensitivity C-reactive protein, Ig = immunoglobulin, LDL-C = low-density lipoprotein cholesterol, PCR = polymerase chain reaction, WOCBP = women of childbearing potential.

[a] Performed only at Screening.

[b] Estimated glomerular filtration rate will be derived from serum creatinine.

[c] Reflex test for iso-enzymes if results are > 2 × upper limit of normal.

[d] Only for subjects with a diagnosis of diabetes; only at Screening.

[e] Subjects required to fast for a minimum of 8 hours prior to lipid panel.

[f] Microscopy will be performed if urinalysis results are abnormal for blood, protein, or nitrite.

7.4.3.1 Immunological Assessments

Blood samples for Ig levels (IgA, IgG, and IgM) and for B cell number will be collected as safety evaluations according to the Schedule of Assessments in Table 1. The actual date and time of each sample will be recorded.

Samples will be analyzed by the central analytical laboratory selected under the responsibility of the Sponsor using an appropriately validated bioanalytical method.

For blood sample volumes, see laboratory manual.

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7.4.3.2 High-Sensitivity C-Reactive Protein and Erythrocyte Sedimentation Rate

Samples for hsCRP and ESR will be collected at visits indicated in Table 1.

Samples for hsCRP will be analyzed by the central laboratory; ESR will be analyzed by local laboratories. Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the laboratory manual.

7.4.3.3 B Cell Counts

Blood samples will be collected for counts of total B cells (as outlined in the laboratory manual) as indicated in Table 1. This population will be counted using flow cytometry.

The actual date and time of each sample will be recorded. Samples will be analyzed by the laboratory selected by the Sponsor using an appropriately validated method. Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the laboratory manual.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs, including seated blood pressure, pulse rate, respiratory rate, weight, height, and oral temperature will be assessed predose at all trial visits (except height, only at Screening) (see Table 1).

A semiautomated pulse rate and blood pressure recording device with an appropriate cuff size will be utilized. Pulse rate and blood pressure will be measured after 10 minutes rest with the subject's arm unconstrained by clothing or other material. The blood pressure should be assessed in a seated position on the same arm for each subject throughout the trial.

7.4.4.2 Physical Examinations

Physical examinations will be assessed as indicated in Table 1.

Physical examination includes assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and musculoskeletal, cardiovascular, and respiratory systems. Physical examination findings during Screening will be recorded as medical history events and new findings during the trial as AEs.

An abbreviated physical examination should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, and extremities and other systems as required by symptoms.

7.4.4.3 12-lead ECG and Chest X-ray

A single 12-lead ECG will be performed as indicated in Table 1. The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semisupine position. CCI blood sampling should be collected immediately following ECG assessment.

The following ECG parameters will be obtained from the computerized 12-lead ECG recordings: rhythm, heart rate (as measured by RR interval), PR interval, QRS duration, and QT interval. The corrected QT interval (QTcF) will be calculated using Fridericia's formula. The overall evaluation (normal/abnormal) will be recorded on the eCRF, and if abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator.

The printout of the ECG is to be signed, dated, and filed in the Investigator's Site File along with a signed and dated copy (if the printouts are not on archive-quality paper). In addition, ECGs will also be stored digitally by the Sponsor.

Posterioanterior CXRs will be performed during Screening according to local standard practice. Subjects who had a CXR performed for clinical reasons within the last 3 months of Screening do not need to have the CXR repeated. The CXR should show no evidence of active infective process, or any other clinically significant abnormalities. The overall evaluation (normal/abnormal) will be recorded on the eCRF, and if abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator.

The 12-lead ECG and CXR will be performed and read locally.

Every effort should be made to collect CCI according to the Schedule of Assessments at the exact nominal time relative to dosing. Samples will not be considered protocol deviations as long as the actual collection date and time is recorded and is within the window referenced in the Schedule of Assessments.

For subjects randomized to placebo treatment, CCI samples will be collected but not analyzed unless determined necessary by the Investigator and/or Sponsor. CCI

Samples will be collected, labeled, processed, stored, and shipped as detailed in the laboratory manual.

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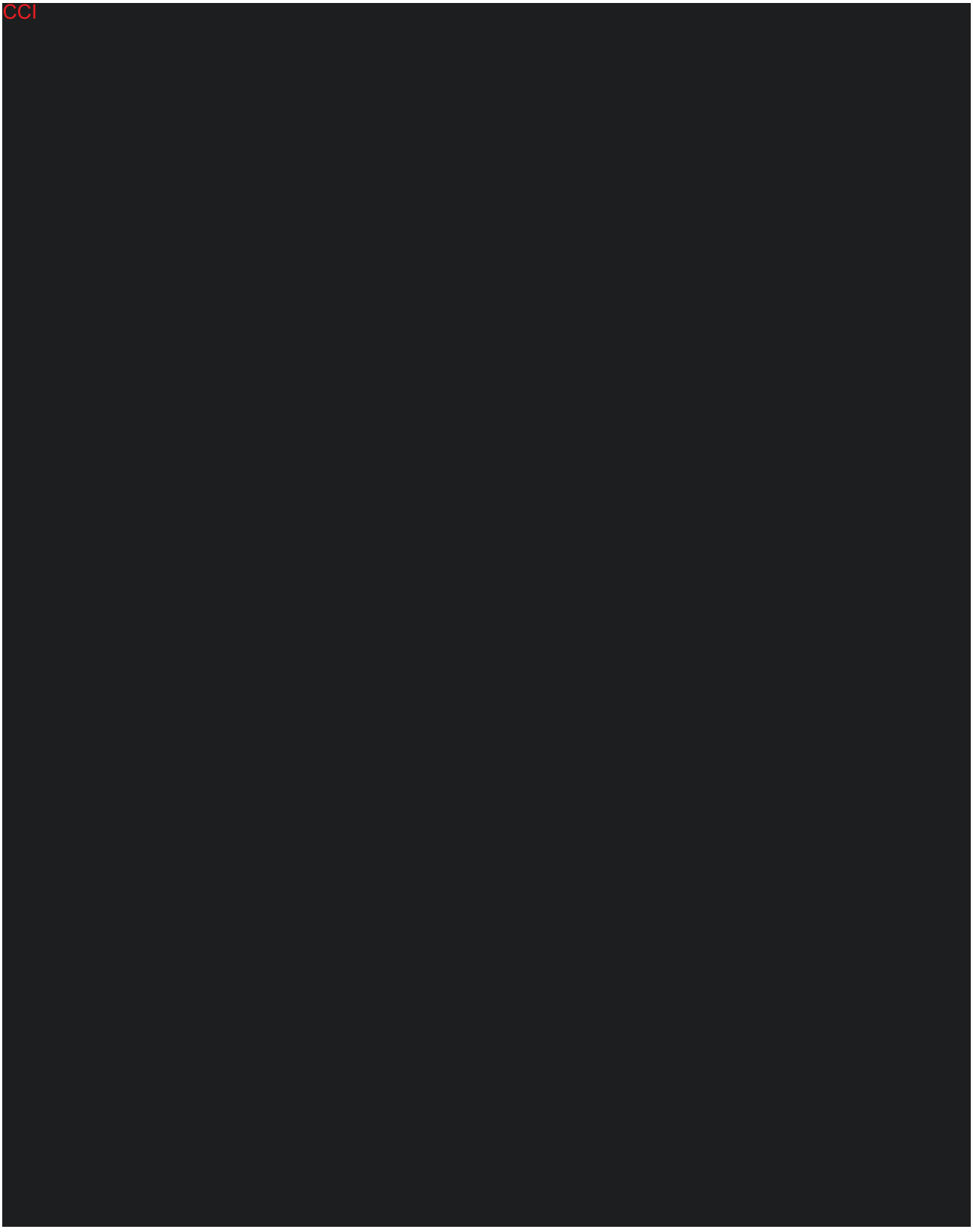

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7.7 Assessment of Symptoms and Health Related Quality of Life (HRQoL)

7.7.1 Medical Outcomes Study 36-item Short-Form Health Survey

The SF-36v2 is a 36-item scale constructed to survey HRQoL on eight domains: limitations in physical activities due to health problems; limitations in social activities due to physical or emotional problems; limitations in usual role activities due to physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities due to emotional problems; vitality (energy and fatigue); and general health perceptions (Ware 1992).

The SF-36v2 has a 4 weeks recall period and yields scale scores for each of the eight health domains, and 2 summary measures of physical and mental health: the Physical Component Summary and Mental Component Summary.

7.7.2 Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function

(Wolfe 1996). It uses a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). As each of the 13 items of the FACIT-Fatigue scale ranges from 0–4, the range of possible scores is 0–52, with 0 being the worst possible score and 52 the best. To obtain the 0–52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score.

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7.8 Other Assessments

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8 Statistics

8.1 Sample Size

The primary endpoint of the trial is the ACR20 response at Week 12.

A sample size of 80 evaluable subjects per group will provide approximately 90% power at an α of 0.05, 2-sided significance level to detect a difference in Week 12 ACR20 response proportion between evobrutinib- and placebo-treated subjects, assuming a placebo response proportion of 30% to 45% and an expected treatment benefit of 30%, after adjusting for multiple comparisons

of 3 dose comparisons with placebo. For the same range of placebo response rate, the sample size of 80 evaluable subjects per group will also provide adequate power (approximately 80%) for the expected difference of 25%.

To account for reduced information provided by the Modified Intent-to-Treat (mITT) analysis set, due to subject dropout and protocol noncompliance, occurring at a rate of approximately 11% over a 12-week period, approximately 90 subjects per group will be enrolled. The sample size was calculated using a chi-squared test of the odds ratio in nQuery Advisor® 7.0.

The Japanese cohort size was determined to provide an evaluation of consistency in the Week 12 ACR20 response proportion between the non-Japan and Japan regions. Assuming that:

(i) the Week 12 ACR20 response proportion in the placebo group is 0.30 for both the non-Japan and Japan regions,

(ii) the Week 12 ACR20 response proportion due to each of the 3 evobrutinib dose groups is 0.60 for both regions, so that the true underlying effect size is 0.30 for both regions,

(iii) a total evaluable sample size of 320 (ie, 240:80 randomization for evobrutinib:placebo) is involved in analysis of the two regions,

and applying "Method 2" from the Pharmaceuticals and Medical Devices Agency Guidance, 32 evaluable subjects in the Japanese cohort are required so that both observed region-specific effect sizes exceed 0.10 with probability of approximately 80%. Taking into account a loss of information due to 10% dropout at Week 12, the total number of Japanese subjects to be randomized is 36, or 10% of the total planned enrollment of 360 subjects. The sample size was calculated via simulations with SAS version 9.3. The power is the average of 3 estimated probabilities, with each estimate based on 10,000 simulations.

For the evaluation of MRI data, assuming a minimum effect size of 0.7 for the difference in the change from Baseline in the OMERACT RAMRIS individual scores for osteitis or synovitis at Week 12 between at least one dose and placebo, at a 2-sided $\alpha = 0.05$, a sample size of 40 evaluable subjects per group with MRI data will provide approximately 80% power using the Wilcoxon rank-sum test in nQuery Advisor® 7.0. The same sample size will provide approximately 70% power for an effect size of 0.6. To account for approximately 11% dropout and nonevaluable MRI data, approximately 45 subjects per arm will be enrolled in the MRI study. Since there were no high-quality data available to form the basis for accurate sample size calculations for RAMRIS scores involving a study population similar to that planned for the present study, the assumed effect size of 0.7 is considered comparable to those reported in the published studies (Conaghan 2011, Genovese 2016a, Genovese 2016b).

8.2 Randomization

A randomized allocation schedule for IMP assignment will be generated by a third party vendor who is not on the study team. Randomization will occur using the IWRS.

Eligible subjects will be randomized into 1 of 3 evobrutinib arms (25 mg once daily, 75 mg once daily, or 50 mg twice daily) or the placebo arm in a ratio of 1:1:1:1 stratified by whether or not they are in the MRI substudy (Yes, No) and by region (US, Western Europe, Japan, and the rest of world), so that within each treatment arm, there will be approximately 90 subjects, with approximately 45 subjects included in the MRI substudy to ensure approximately 80 evaluable subjects per arm for the primary analysis, and approximately 40 evaluable subjects per arm for the MRI analysis.

To ensure an adequate number of evaluable MRI subjects in the MRI substudy, recruitment of non-MRI subjects into the study may be capped. If a subject's baseline MRI indicates lack of osteitis and synovitis, additional subjects may be added to the MRI stratum to account for these subjects. Should the MRI substudy recruitment prove more difficult than anticipated, the Sponsor reserves the right to terminate the MRI substudy. Should this be done, all sites would be allowed to recruit non-MRI subjects into the study.

8.3 Endpoints

8.3.1 Primary Endpoint

The primary efficacy endpoint is ACR20 response assessed using hsCRP (ACR20) at Week 12.

8.3.2 Secondary Endpoints

The key secondary efficacy endpoints are:

- DAS28-hsCRP low disease activity (DAS28 < 3.2) rate at Week 12
- DAS28-hsCRP remission (DAS28 < 2.6) rate at Week 12
- ACR 50% (ACR50) response assessed using hsCRP at Week 12
- ACR 70% (ACR70) response assessed using hsCRP at Week 12.

The key secondary safety endpoints are:

- The nature, severity, and occurrence of AEs and serious AEs (SAEs)
- Absolute values and change from Baseline in:
  - Vital signs
  - ECG parameters including RR interval, PR interval, QRS duration, QT interval, and QTcF interval
  - Serum Ig levels (IgG, IgA, IgM)
  - Total B cell counts
  - Clinical laboratory parameters.

Other secondary efficacy endpoints are:

At Week 12:

- Achieving American College of Rheumatology/European League Against Rheumatism (EULAR) Boolean remission
- Achieving Clinical Disease Activity Index (CDAI) score ≤ 2.8 (CDAI remission)
- Achieving Simplified Disease Activity Index (SDAI) score ≤ 3.3 (SDAI remission)
- EULAR Responder Index (based on DAS-hsCRP)
- ACR hybrid scores computed using hsCRP
- Change from Baseline in DAS28-hsCRP
- Change from Baseline in CDAI and SDAI
- Changes and percentage changes from Baseline of individual components of the ACR Core Set
- Imaging:
  - Change from Baseline in Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) scores (designated hand, minimal assessed joints: wrist, metacarpophalangeal (MCP) joints #1 to #5) for subjects in the MRI substudy:
    - Synovitis score
    - Bone marrow edema (osteitis) score.
- Changes from Baseline of Physical Function:
  - Health Assessment Questionnaire – Disability Index (HAQ-DI).
- Changes from Baseline of HRQoL:
  - Medical Outcomes Study 36-item Short Form Health Survey (SF-36)
  - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.

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8.4 Analysis Sets

For the purposes of analysis, the following analysis sets are defined in the following table:

Population	Description
Enrolled	All participants who sign informed consent
Intent-to-treat (ITT)	The ITT analysis set will include all subjects 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).
Modified intent-to-treat (mITT)	The mITT analysis set will include all randomized subjects who received at least one dose of IMP (evobrutinib or placebo). Subjects in the mITT analysis set will be included in the treatment group as randomized.
Per-Protocol (PP)	The PP analysis set will include all randomized and treated subjects who do not have any clinically important protocol deviations.
MRI	The MRI analysis set will include all randomized subjects who have at least 1 post dose MRI assessment.
Safety (SAF)	The SAF analysis set will include all subjects who receive at least 1 dose of IMP (evobrutinib or placebo). Subjects will be analyzed according to the actual treatment they receive.

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The mITT analysis set will be used for the purpose of efficacy analysis unless otherwise stated; the SAF analysis set will be used for the purpose of safety analysis; and the PP analysis set will be used for the purpose of sensitivity analysis of the primary efficacy endpoint.

8.4.1 Subgroups

The following subgroups may be considered for primary/key secondary efficacy analyses:

- Region: US, Western Europe, Japan, the rest of world
- MRI substudy participation: Yes/No
- Ethnicity: Japanese/Non-Japanese
- Gender: Male/Female.

Other subgroups may be defined in the SAP.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Prior to locking of the database for the study, a detailed SAP will be finalized.

Any changes to the data analysis methods described in the protocol will require an amendment only if a principal feature of the protocol is affected. Any other changes to the planned data analysis that does not require a protocol amendment will be described in the SAP and the CTR. Additional exploratory analyses will be conducted as deemed appropriate.

A 2-sided α level of 0.05 will be applied for tests of treatment effect within the study.

For the purpose of statistical analyses, baseline is defined as the last assessment prior to first dose.

In general, continuous variables will be summarized descriptively using the number of observations (N), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Statistical analysis will be performed using the computer program package SAS® System for Windows (version 9.4 or higher; SAS Institute, Cary North Carolina, USA).

Missing Data Handling:

For the primary and key secondary endpoints of ACR response, the Last Observation Carried Forward will be used as the primary method for the imputation of missing values of the ACR components. For the ACR20 response at Week 12, a subject will be considered as a nonresponder if the subject discontinues prior to Week 12. Other imputation methods will be provided in the SAP as additional sensitivity analyses of the primary endpoint.

Missing data for all other secondary efficacy endpoints of binary data will be handled using a similar manner to ACR20. Further details for each endpoint will be provided in the SAP.

For the MRI analysis, a Missing At Random (MAR) pattern will be assumed for missing data in the Mixed Model for Repeated Measures.

Details of handling missing data for all other secondary efficacy endpoints of continuous data will be provided in the SAP.

Multiplicity Adjustment:

A family-wise Type I error rate (FWER) at the primary analysis will be controlled at the 2-sided 0.05 significance level for the 3 pairwise comparisons of evobrutinib dose versus placebo, using the Hochberg procedure. Further details will be provided in the SAP.

8.5.2 Analysis of Primary Endpoint

8.5.2.1 Efficacy Endpoints

The primary analysis of ACR20 at Week 12 will be based on the mITT analysis set using Last Observation Carried Forward for imputation of missing values of each ACR component. A subject will be considered as a nonresponder if the subject discontinues prior to Week 12.

The estimate of the odds ratio (OR), together with the associated 2-sided 95% CI and p-value, comparing each evobrutinib dose group to placebo, will be provided based on a logistic regression model for the odds of ACR20 response, with evobrutinib dose group or placebo as a factor and adjustment for covariates based on randomization strata (region, MRI-substudy participation). In order to further characterize the dose-response, the proportion of ACR20 response at Week 12 will also be presented for each treatment group, along with the difference in ACR20 response proportion between evobrutinib and placebo, and the 95% CI for the difference. Details will be provided in the SAP.

The dose response will also be assessed via a modeling approach as additional supportive analyses. Details will be provided in the SAP.

Additional sensitivity analyses will be performed to assess the robustness of the primary missing data imputation method and will be described in detail in the SAP.

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Key Secondary Efficacy Endpoints

Analyses of all key secondary efficacy endpoints will be performed using the same approach as the ACR20, based on the mITT analysis set.

8.5.3.2 Key Secondary Safety Endpoints

Analysis of safety secondary endpoints is described in Section 8.5.4.1.

8.5.3.3 Imaging Data and Other Efficacy Endpoints

Analysis of the change from Baseline scores of the MRI data will be performed on the appropriate analysis sets (MRI analysis set for the RAMRIS and CARLOS scores) using a Mixed Model for Repeated Measures, with treatment arm as factors, and randomization strata, and Baseline as

covariates. Missing data will be handled as MAR. Other imputation methods will be provided in the SAP as additional sensitivity analyses.

Analyses of all other efficacy endpoints will be exploratory in nature and details will be further provided in the SAP.

8.5.3.4 Patient-reported Health Related Quality of Life (HRQoL)

Change in SF-36 Physical Component Summary and Mental Component Summary scores (and their components) over time and change in FACIT-Fatigue score over time will be summarized using descriptive statistics.

Further details will be presented in the SAP that will be finalized before database lock.

8.5.4 Analysis of Safety and Other Endpoints

8.5.4.1 Safety

Analyses of safety will be carried out as follows.

Adverse events will be summarized by treatment group, severity, and relationship to IMP. Serious AEs, AEs leading to treatment discontinuation (permanent, temporary), and AEs leading to study withdrawal will be summarized by treatment group.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing 1 or more treatment-emergent AEs (TEAEs) will be summarized according to the MedDRA system organ classes and preferred terms by treatment group, relationship to IMP, and severity. The severity of AEs will be graded using NCI-CTCAE v4.03 toxicity grades (US Department of Health and Human Services 2010).

Summary and analysis of AEs will be performed based on the 3-tier approach (Crowe 2009) as further detailed in the trial SAP.

Summary statistics will be used to present observed values and changes from Baseline in continuous laboratory parameters and vital signs. Shift tables will be used to present changes in categorical laboratory parameters. Figures may be generated to assist safety evaluation.

The 12-lead ECG data (RR [ms], PR [ms], QRS [ms], QT [ms], and QTcF [ms]) will be summarized for observed values and change from baseline values by treatment using descriptive statistics. Electrocardiogram outlier values will be summarized by treatment in frequency tables using number and percentage of subjects. Investigator reported overall interpretation results will be listed and tabulated by treatment using the number and percentage of subjects for each interpretation category (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Abnormal Overall). A concentration-QT analysis may be conducted.

Additional details of safety data analyses will be provided in the SAP.

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8.5.4.7 Subgroup Analyses

All subgroup analyses are descriptive in nature and primarily aim at assessing the consistency of the results.

Analysis of the MRI change from Baseline scores will be performed on the MRI analysis set.

In addition, the following subgroup analyses will be performed for the primary and key secondary efficacy endpoints:

- Region: US, Western Europe, Japan, the rest of world
- MRI substudy participation: Yes/No
- Ethnicity: Japanese/Non-Japanese
- Gender: Male/Female.

Other subgroup analyses may also be performed. Details will be provided in the SAP.

8.6 Planned Analysis

There is 1 planned analysis from this study. The final analysis will be triggered when 100% of subjects randomized complete the safety follow-up or discontinue prematurely from the study, the protocol violations are determined, and the database is locked. All data collected up to and including the Safety Follow-up Visit will be included in this analysis. A consistency analysis is also planned to be performed as part of the final analysis to evaluate the consistency of efficacy at Week 12 between the Japan and non-Japan subjects. If the Japanese cohort enrollment is too slow to have n = 32 to 36 evaluable subjects included in the consistency analysis, then the consistency analysis will not occur.

All data collected will be included for statistical analyses. Further details will be provided in the SAP.

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 subjects who have given informed consent are included in the trial. For Japan only: The Investigator is also responsible for the standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Act in Japan, and the “Ministerial Ordinance on Good Clinical Practice for Drugs” (GCP) in Japan.

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 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. In Japan when a subject is < 20 years of age, the written informed consent must be obtained from the subject's parent or guardian in addition to the subject's voluntary written consent. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A Subject Information Sheet must be prepared in the local language in accordance with Note for Guidance on GCP (ICH Topic E6, 1996) and will be provided by the Sponsor for the purpose of obtaining informed consent. In Japan, a subject information sheet in the local language and prepared in accordance with Japan's GCP and the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject 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 subject about the trial and sign the ICF, as above.

Where the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator. In Japan, where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and/or the subject's legal representative as applicable, 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 sheet and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the Subject Information Sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised Subject Information Sheet and other written information, the Investigator will explain the

changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. In Japan, the Investigator will explain the changes to the previous version to each study subject and/or the subject's legal representative as applicable and obtain new written consent for continued participation in the study. The subject 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.

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9.3 Subject Identification and Privacy

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

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

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9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects 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 subject. 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 subject. 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, he or she will answer any questions. Any subsequent action (eg, 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 subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

In Japan, the Sponsor is entirely responsible for AEs that are associated with this trial and impair the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the trial site, and/or the subject. The Sponsor will provide insurance to fulfill this responsibility.

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 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.

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 were present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject 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.

In Japan, the person installing an IEC/IRB must retain all records, including documents that relate to the clinical trial for the required period in accordance with Japan's GCP.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (eg, IMP Dossier, Subject Information Sheet, 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 eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF 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 eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

For subject-reported outcome data such as HRQoL, physical functioning and pain assessments, an electronic patient-reported outcome system (ePRO) will be used.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. Portable document files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

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

- Subject's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, ie, the Sponsor trial number for this clinical trial, and subject 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 subject 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 subject 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.

For data that may be recorded directly in the eCRF such as a questionnaire or diary, there will be no record in the original subject file and therefore the data entered in the eCRF will be considered source data. The clinical trial protocol or the Manual of Operations should clearly and completely specify all subject data in the eCRF to be considered source data.

Electronic subject files will be printed whenever the Medical Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Medical Monitor, and kept in a safe place at the site.

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 Medical 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 Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject 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.

In Japan, a record retainer designated by the head of the trial site must retain all records, including documents and data, which relate to the clinical trial in accordance with GCP. The head of the trial site must retain the records at the site (hospital, research institute, or practice) for the longest possible time permitted by Japan's GCP, and/or as per ICH GCP guidelines, whichever is longer. In any case, the head of the trial site 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, the Japanese ministerial ordinance on GCP (for Japan only), and any other applicable regulations. The site Medical 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 CTR, will be subject 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 eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

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 (or through the head of the trial site, in Japan only) for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained (or only after written approval from the head of the trial site has been obtained, in Japan only).

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 subject'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 CTR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 within the legally required period of the participating countries.

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10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoint and will include data from all trial sites. 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 eudract.ema.europa.eu is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

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12 Appendices

Appendix I: 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 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel'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 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial 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[b]
  • oral
  • intravaginal[c]
  • transdermal[c]

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • injectable[c]

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b,c] • 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 trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.)
Barrier Methods
• Male or female condom with or without spermicide[c] • Cap[c], diaphragm or sponge with spermicide[c]
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. b) Hormonal contraception may be susceptible to interaction with the trial treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the Treatment Period and for at least 90 days after the last dose of trial treatment. c) Not approved in Japan apart from male condom.

Appendix II: 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

[a] For replaced, ankylosed, or arthrodesed joints, please record as 9 (not applicable) and record details of replaced, ankylosed, arthrodesed joints in sections of the eCRF that relate to medical history and physical examination.

Appendix III: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase IIb, Randomized, Double-blind Study in Subjects with Rheumatoid Arthritis Evaluating the Safety and Efficacy of Evobrutinib Compared with Placebo in Subjects with an Inadequate Response to Methotrexate
IND Number:	CCI
EudraCT Number:	2017-000384-32
Clinical Trial Protocol Date/Version:	12 July 2018/Version 3.0

Protocol Lead:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	EMD Serono Research & Development Institute
Address:	45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number:	PPD
E-mail address:	PPD

Signature Page – Coordinating Investigator

Trial Title	A Phase IIb, Randomized, Double-blind Study in Subjects with Rheumatoid Arthritis Evaluating the Safety and Efficacy of Evobrutinib Compared with Placebo in Subjects with an Inadequate Response to Methotrexate
IND Number	CCI
EudraCT Number	2017-000384-32
Clinical Trial Protocol Date/Version	12 July 2018/Version 3.0

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.

_____ _____

Signature Date of Signature

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

Signature Page – Principal Investigator

Trial Title	A Phase IIb, Randomized, Double-blind Study in Subjects with Rheumatoid Arthritis Evaluating the Safety and Efficacy of Evobrutinib Compared with Placebo in Subjects with an Inadequate Response to Methotrexate
IND Number	CCI [redacted]
EudraCT Number	2017-000384-32
Clinical Trial Protocol Date/Version	12 July 2018/Version 3.0
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, academic degree:	PPD
Function/Title:	
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	45A Middlesex Turnpike, Billerica MA 01821, USA
Telephone number:	PPD
E-mail address:	

Name, academic degree:	PPD
Function/Title:	Project Biostatistician
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number:	PPD
E-mail address:	

Appendix IV: Protocol Amendment History

The information for the current amendment is on the title page.

The original Protocol version 1.0 was issued on 11 May 2017.

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)	Version
Amendment 1	N	03 July 2017	United States	N	1.1
Amendment 2	Y	13 December 2017	Global	Y	2.0
Amendment 3	Y	16 November 2017	United States	N	2.1

Amendment 2

Protocol Version 1.0 (11 May 2017) was the original global protocol. A global amendment was issued on 13 December 2017.

Rationale and Major Scientific Changes

Major scientific changes to the protocol were made to add a Japanese cohort, to align the protocol with Japan GCP and local regulatory requirements in Japan, to add fasting requirements, to reduce the Treatment Period from 24 weeks to 12 weeks and remove rescue therapy, to increase safety monitoring by adding visits at Week 6 and Week 10 during the Treatment Period, and to reduce the length of the OLE Period from 24 months to 12 months.

Administrative and Editorial Changes

Minor editorial changes were made to correct typos, formatting, and stylistic consistency.