Clinical Trial Protocol

Clinical Trial Protocol Number	MS200527-0081
Title	A Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of M2951 in Subjects with Rheumatoid Arthritis on Stable Methotrexate Therapy
Phase	IIa
IND Number	CCI
EudraCT Number	2016-000064-42
Coordinating Investigator	PPD PPD PPD PPD Phone PPD Fax PPD PPD
Sponsor	Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany Medical Responsible: PPD EMD Serono Research & Development Institute 45A Middlesex Turnpike, Billerica, MA 01821, USA Telephone: PPD
Clinical Trial Protocol Version	02 September 2016/Version 3.0
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List of Abbreviations

Δ	Difference
ACR	American College of Rheumatology
AE	adverse event
AIID	autoimmune and inflammatory disorders
ALT	alanine aminotransferase
Anti-CCP	anti-cyclic citrullinated peptide
AST	aspartate aminotransferase
AUC_{0-6h}	area under the concentration-time curve from time zero to 6 hours
β-hCG	beta human chorionic gonadotropin
BTK	Bruton's tyrosine kinase
C	Collect
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{pre}	plasma concentration observed immediately before next dosing
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest X-ray
CYP	cytochrome P450
D	Dispense
DAS28	Disease Activity Score-28 joints
DMARD	disease-modifying antirheumatic drug
ECG	electrocardiogram
eCRF	Case Report Form, electronic
ESR	erythrocyte sedimentation rate
EULAR	The European League Against Rheumatism
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein

IA	interim analysis
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LFT	liver function test(s)
LLN	lower limit of normal
LLOQ	lower limit of quantification
LTBI	latent tuberculosis infection
MAD	multiple ascending doses
mITT	modified intent-to-treat
MOP	Manual of Procedures
MS	multiple sclerosis
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drugs
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PiC	powder-in-capsule
PK	pharmacokinetics
R	Review
RA	rheumatoid arthritis
$R_{acc(AUC0-6h)}$	accumulation ratio for AUC_{0-6h}
$R_{acc(Cmax)}$	accumulation ratio for C_{max}
RF	rheumatoid factor
RNA	ribonucleic acid
SAD	single ascending doses

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SJC	swollen joint count
SLE	systemic lupus erythematosus
SOCs	system organ classes
$t_{½}$	terminal half-life
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
t_{max}	time to reach maximum observed concentration
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VAS	visual analogue scale

1 Synopsis

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Trial Phase	IIa
IND Number	CCI
FDA covered trial	No
EudraCT Number	2016-000064-42
Coordinating Investigator	PPD PPD PPD PPD Phone PPD Fax PPD PPD
Sponsor	Merck KGaA Darmstadt, Germany Medical Responsible: PPD 45A Middlesex Turnpike Billerica, MA 01821, USA Telephone: PPD
Trial centers/countries	Approximately 50 sites in 10 countries
Planned trial period (first subject in-last subject out)	July 2016 to March 2017
Trial Registry	Clinicaltrials.gov

Objectives:

Primary objective: To assess the efficacy of M2951 in subjects with active rheumatoid arthritis (RA) on stable methotrexate (MTX) therapy, as measured by the American College of Rheumatology (ACR) 20% (ACR20) response rate over a duration of 84 days.

Key secondary objective: To assess the level of disease activity at 4 weeks in subjects with active RA as assessed by the percent change in high-sensitivity C-reactive protein (hsCRP) from Baseline to Day 29.

Other secondary objectives: To assess the safety and tolerability of M2951 and to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of M2951 in subjects with RA on stable MTX therapy.

Exploratory objectives: CCI [redacted]

Open-label extension objectives:

To evaluate the on-going safety and efficacy of M2951 in an open-label extension with treatment at 50 mg bid for an additional 6 months.

Methodology: This is a Phase IIa randomized, double-blind, placebo-controlled trial in approximately 64 modified intent-to-treat (mITT) subjects 18 to 75 years of age with RA on stable MTX therapy.

Total duration of subject participation is approximately between 5 months (20 weeks) to 11 months (46 weeks), which includes:

- Screening: 28 days (4 weeks)
- Treatment: 84 days (12 weeks)
- Optional 6-month open-label extension period (26 weeks)
- Safety Follow-Up: 28 days (4 weeks)

Screening will occur over Day -28 to -1 (Visit 1), during which time all Screening assessments must be completed and reviewed.

On Day 1 (Visit 2), after confirmation of eligibility, assessment of RA disease activity and vital signs, and obtaining of required blood and urine samples, subjects will be randomly assigned 1:1 to receive M2951 or placebo in combinations with MTX.

Blood and urine samples will be obtained for safety, markers of disease activity, PK, and PD following the schedule detailed in the Schedule of Assessments.

CCI [redacted]

Subjects will self-administer the Investigational Medical Product (IMP) at a set time each day (± 2 hours). Subjects must take their daily dose more than 1 hour prior to a meal or snack or more than 2 hours after a meal or snack. Clear fluids are allowed at any time. On trial visit days, the IMP will be administered during the trial visit, after trial visit procedures (other than PK/PD sampling) are completed.

Subjects will have trial visits weekly for the first 3 weeks of treatment; bi-weekly up until 8 weeks of treatment; a final On-Treatment Visit on Day 85, and then return for 1 Follow-Up Visit approximately 28 days (4 weeks) after the last dose of IMP.

After completing the 12-week treatment period, subjects will be offered the opportunity to participate in an optional 6-month open-label extension period where all subjects will receive M2951. For subjects who choose to participate in the optional extension period, the duration of participation will last a total of approximately 11 months.

Subjects who continue to receive M2951 during the extension period will also be required to undergo the Safety Follow-up Visit scheduled for approximately 28 days after the last treatment visit.

Planned number of subjects: A total of 64 subjects with RA.

Primary endpoint: The primary endpoint is the ACR20 response at Day 85.

Key secondary endpoints:

The key secondary endpoint is the percent change in hsCRP from Baseline to Day 29.

Other secondary endpoints (during the double-blind treatment period):

Safety endpoints (from signing ICF until Safety Follow-Up Visit):

- Nature, incidence, and severity of treatment-emergent adverse events
- Changes from Baseline in vital signs and 12-lead electrocardiogram (ECG) results
- Changes from Baseline in standard hematology and chemistry laboratory parameters including liver function tests, amylase/lipase, and urinalysis.

Efficacy endpoints:

- ACR50/ACR70 response at each time point assessed
- Percent change in hsCRP from Baseline to Day 85
- Change from Baseline in Disease Activity Score based on 28 joints (DAS28-hsCRP) score at Day 29
- Change from Baseline in DAS28-hsCRP score at Day 85
- Percentage of subjects with DAS28-hsCRP < 3.2 (well-controlled disease) at Day 85
- Percentage of subjects with DAS28-hsCRP < 2.6 at Day 85
- Change from Baseline in erythrocyte sedimentation rate (ESR), anti- cyclic citrullinated peptide (CCP), and rheumatoid factor ([RF] at Days 29 and 85)
- Change from Baseline to Day 85 in subject's self-assessments including:
  - Global assessment of disease activity
  - Self-assessment of pain
  - Self-assessment of disability (Health Assessment Questionnaire – Disability Index; HAQ-DI)
- Change from Baseline to Day 85 in Physician's Global Assessment of Disease Activity.

Pharmacokinetics: Pharmacokinetic parameters calculated for Days 1 and 29 include: plasma concentrations of M2951, area under the plasma concentration-time curve from time zero to 6 hours ($AUC_{0\text{-}6h}$) after administration, maximum observed plasma concentration (C_{max}), concentration observed immediately before next dosing (C_{pre}) (Day 29), time to reach

maximum plasma concentration (t_{max}), accumulation ratio for AUC_{0-6h} ($R_{acc[AUC0-6h]}$), and accumulation ratio for C_{max} ($R_{acc[Cmax]}$).

Other assessments:

Pharmacodynamics:

- Absolute concentrations and change from Baseline in immunoglobulin (Ig) levels (IgA, IgM, and IgG, and subclasses) on Days 29 and 85
- Absolute numbers and change from Baseline in B cell numbers and subsets on Day 85.

Exploratory:

CCI [redacted]

Endpoints for open-label extension:

Safety:

- Nature, incidence and severity of TEAEs
- Change from Baseline in vital signs and 12-lead ECG data
- Change from Baseline in standard hematology and chemistry laboratory parameters including liver function tests, amylase/lipase, and urinalysis.

Efficacy:

- ACR50/ACR70 response at Month 6
- Percent change in hsCRP from Baseline to Month 6
- Change from Baseline in DAS28-hsCRP score at Month 6
- Percentage of subjects with DAS28-hsCRP < 3.2 (well-controlled disease) at Month 6
- Percentage of subjects with DAS28-hsCRP < 2.6 at Month 6
- Change from Baseline in ESR, anti-CCP, rheumatoid factor (at Month 6)
- Change from Baseline to Month 6 in subject's self-assessments including:
  - Global assessment of disease activity (VAS)
  - Self-assessment of pain (VAS)
  - Self-assessment of disability (HAQ-DI)

Change from Baseline to Month 6 in Physician's Global Assessment of Disease Activity (VAS).

Diagnosis and key inclusion and exclusion criteria:

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

- Men or women 18 to 75 years of age at the time of informed consent signature
- Confirmed diagnosis of RA according to 2010 American College of Rheumatology (ACR)/ The European League Against Rheumatism (EULAR) RA classification criteria of at least 6 months duration
- Positive RF and/or anti-CCP (anti-cyclic citrullinated peptide)
- Persistently active disease defined as ≥ 6 swollen joints (of 66 counted) and ≥ 6 tender joints (of 68 counted)
- hsCRP ≥ 3.6 mg/L
- Treatment for ≥ 12 weeks with 10 to 25 mg/week MTX at a stable dose for at least 4 weeks prior to dosing with the IMP and maintained throughout the trial
- Women of childbearing potential must use a highly effective method of contraception combined with one supplementary barrier method for 4 weeks prior to randomization, throughout the trial, and for 90 days after the last dose of IMP. For the purposes of this trial:
    - 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
    - The definition of highly effective contraception includes:
        - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; oral, intravaginal or transdermal
        - progestogen-only hormonal contraception associated with inhibition of ovulation; oral, injectable, implantable
        - intrauterine device (IUD)
        - intrauterine hormone-releasing system (IUS)
        - bilateral tubal occlusion
        - vasectomized partner
        - sexual abstinence
    - Supplementary barrier methods include:
        - male or female condom with or without spermicide
        - cap, diaphragm or sponge with spermicide

- Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Day 1/randomization before dosing.

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

- Use of oral corticosteroids > 10 mg daily prednisone equivalent, use of injectable corticosteroids, or change in dose of corticosteroids within 2 weeks prior to Screening or during Screening
- Initiation or change in dose for nonsteroidal anti-inflammatory drugs (NSAIDs) within 2 weeks prior to Screening
- Treatment with tofacitinib, other BTK inhibitors, or a biologic disease-modifying antirheumatic drug (DMARD; eg, anti-tumor necrosis factor alpha [anti-TNF-α], tocilizumab [anti-interleukin-6 receptor], abatacept [CTLA4-Fc]), or other immunosuppressive drugs (sulfasalazine would be acceptable at a stable dose) other than methotrexate within 3 months prior to Screening or during Screening
- Treatment with anti-CD20 therapy (eg, rituximab) within 12 months prior to Screening or during Screening
- Immunologic disorder other than RA, with the exception of secondary Sjogren's syndrome associated with RA, and well-controlled diabetes or thyroid disorder, or any other condition requiring oral, intravenous, intramuscular, or intra-articular corticosteroid therapy
- Vaccination with live or live-attenuated virus vaccine within 1 month prior to Screening
- 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.
- History of or positive testing for human immunodeficiency virus (HIV), hepatitis C antibody and/or polymerase chain reaction, hepatitis B surface antigen (HBsAg) (+) and/or hepatitis B core total, and/or IgM antibody (+) at Screening.
- History of or current diagnosis of active tuberculosis (TB); undergoing treatment for latent TB infection (LTBI); untreated LTBI (as determined by documented results within 3 months of the Screening Visit of a positive TB skin test with purified protein derivative with induration ≥ 5 mm, a positive QuantiFERON®-TB test or positive or borderline T-SPOT [Elispot] test); or positive QuantiFERON-TB test at Screening. Subjects with documented completed appropriate LTBI treatment would not be excluded and are not required to be tested.
- Subjects with current household contacts with active TB will also be excluded.

- Indeterminate QuantiFERON-TB or T-SPOT tests may be repeated once, and will be considered positive if retest results are positive or indeterminate.
- History of cancer, except adequately treated basal cell or squamous cell carcinomas 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.
- Clinically significant abnormality on ECG, or an active infective process or any other clinically significant abnormality on Screening chest X-ray (CXR) taken within 4 weeks of the first dose, per Investigator opinion. If a CXR has been taken within the previous 3 months and results are available and normal, the CXR does not need to be carried out
- B cell (CD19) count < 50% of the lower limit of normal at Screening
- Significant cytopenia including absolute neutrophil count < 1,500/ mm^3, platelet count < 100,000/mm^3, or absolute lymphocyte count < 1,000/mm^3

Investigational Medicinal Product: dose/mode of administration/dosing schedule: M2951 (50 mg twice daily [bid]) will be administered as 2 x 25 mg capsules bid during the 12-week treatment period. Identical capsules filled with mannitol for placebo will be provided. M2951 will be administered as 2 x 25 mg tablets bid during the optional extension period.

Reference therapy: dose/mode of administration/dosing schedule: Not applicable.

Planned trial and treatment duration per subject: Total duration of subject participation is approximately between 5 months (20 weeks) to 11 months (46 weeks), which includes:

- Screening: 28 days (4 weeks)
- Treatment: 84 days (12 weeks)
- Optional 6-month open-label extension period (26 weeks)
- Safety Follow-Up: 28 days (4 weeks)

After completing the 12-week treatment period, subjects will be offered the opportunity to participate in an optional 6-month open-label extension period with M2951. For subjects who choose to participate in the optional extension period, the duration of participation will last a total of approximately 11 months.

Statistical methods:

The sample size of 60 evaluable subjects was chosen to provide 80% power to demonstrate superiority of M2951+MTX to placebo + MTX for the primary endpoint at the 1-sided 10% level. Eligible subjects will be randomized 1:1 to treatment with M2951 or placebo through a central randomization process by an Interactive Web Response System (IWRS). Approximately 64 subjects will be randomized under the assumption of a 6.25% drop-out rate.

There will be 3 analyses: (1) an interim analysis (IA), triggered when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data, or have discontinued treatment prior to Day 29, (2) a primary analysis, triggered when 100% of subjects enrolled have reached Day 85 of treatment or have discontinued

treatment prior to Day 85, and (3) a final analysis, triggered when 100% of subjects enrolled complete all study parts, or discontinue prematurely from study.

The percent change in hsCRP from Baseline to Day 29 will be the key endpoint evaluated at the IA. Point estimate and confidence interval (CI) estimates of the Day 29 hsCRP change from Baseline difference, comparing the 2 treatment groups, will be estimated for use in internal decision making. In addition, the change in DAS28-hsCRP from Baseline to Day 29 will be evaluated using the same approach as used for change in hsCRP. The IA will not be used to alter the design of the trial. No adjustment will be made to the 1-sided α of 10% to be used in the primary analysis at the end of the first treatment period (12 weeks).

The Day 85 ACR20 proportion and a 2-sided 80% CI will be provided for each treatment group. The difference (Δ) in 12-week ACR20 proportions between M2951+MTX and placebo + MTX, and a 2 sided 80% CI for Δ, based on the "corrected Miettinen-Nurminen" method will be provided. The primary analysis will be based on the mITT Analysis Set using Last Observation Carried Forward for imputation of missing values and will reject the null hypothesis (H0): $\Delta \leq 0$ if the lower limit of the CI exceeds zero.

The Day 85 ACR50 and ACR70 proportions will be analyzed in the same way as the Day 85 ACR20 proportions.

Safety data will be listed and summarized using descriptive statistics.

In addition, efficacy and safety data collected during the open-label extension period will be summarized.

Pharmacokinetics

M2951 concentrations and PK parameters will be listed and summarized by trial day.

Pharmacodynamics

Data on immunoglobulin levels, CCI [redacted], and B cell numbers and subsets will be summarized in tabular and/or graphic format, as appropriate to the data. Potential PK/PD correlations may be explored and reported separately.

Table 1 Schedule of Assessments

Trial Period	Screening	Treatment Period							Optional Open-Label Extension Period				Safety Follow-Up/ End of Trial Visit[a]
Trial Visit #	1	2	3	4	5	6	7	8/End of Treatment[b]	9	10	11	12	
Trial Week		W1	W2	W3	W5	W7	W9	W13					
Trial Day	-28 to -1	1	8	15	29	43	57	85/Day 1 OLE	Day 14	Month 1	Month 3	Month 6	~28 days post last dose
Visit Window (days)	-	-	±2	±2	±2	±4	±4		±2	±7	±7	±7	
Informed consent	X							(X)[b]					
Demographics	X												
RA and other medical history, medications history	X												
Inclusion/exclusion criteria	X	X											
Complete physical examination[c]	X				X			X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X		X		X	
Chest X-ray[e]	X												
Concomitant medications[f] and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, chemistry (incl. LFTs)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation[h]	X												
Urinalysis, microscopy, urine protein/creatinine ratio	X			X	X		X	X	X	X	X	X	X
Immunoglobulins[i]	X						X	X			X	X	
RF and anti-CCP[j]	X			X	X		X	X				X	X
ESR[j]	X			X	X		X	X				X	X
hsCRP[k]	X	X		X	X		X	X				X	X
B cell numbers and subtypes[l]	X	X			X			X			X	X	X
Viral serology[m]	X												

Trial Period	Screening	Treatment Period							Optional Open-Label Extension Period				Safety Follow-Up/ End of Trial Visit[a]
Trial Visit #	1	2	3	4	5	6	7	8/End of Treatment[b]	9	10	11	12	
Trial Week		W1	W2	W3	W5	W7	W9	W13					
Trial Day	-28 to -1	1	8	15	29	43	57	85/Day 1 OLE	Day 14	Month 1	Month 3	Month 6	~28 days post last dose
Visit Window (days)	-	-	±2	±2	±2	±4	±4		±2	±7	±7	±7	
Tuberculosis test[m]	X												
TSH	X												
Pregnancy test (serum β-hCG)[n]	X												
Urine pregnancy test[n]		X			X		X	X	X	X	X	X	X
Pharmacokinetic sampling[o]		X			X								
CCI [redacted]													
RA disease activity assessment[r]	X	X			X		X	X				X	X
Randomization		X											
Dispense/review/collect subject diary		D	R	R	R	R	R	R/C					
IMP dispensation[s]		X	X	X	X	X	X	(X)	X	X	X		
IMP administration[t]		Daily oral administration											
IMP compliance[u]			X	X	X	X	X	X	X	X	X	X	
AE evaluation[v]	X	X	X	X	X	X	X	X	X	X	X	X	X

ACR=American College of Rheumatology, AE=adverse event, anti-CCP=anti-cyclic citrullinated peptide, β-hCG=beta human chorionic gonadotropin, CCI [redacted] C=collect, D=dispense, DAS28=Disease Activity Score, ECG=electrocardiogram, ESR=erythrocyte sedimentation rate, hsCRP=high sensitivity C-reactive protein, Ig=immunoglobulin, IMP=investigational medicinal product, LFT=liver function test, OLE=open-label extension, PD=pharmacodynamics, PK=pharmacokinetics, R=review, RA=rheumatoid arthritis, RF=rheumatoid factor, RNA=ribonucleic acid, TSH=thyroid stimulating hormone.

[a] All subjects, whether not continuing to the optional extension period, continuing to the optional extension period, or early terminating from the study will undergo the Safety Follow-Up/End of Trial Visit approximately 28 days after last dose.

[b] Subjects who participate in the optional extension period will sign an ICF at Visit 8. The End of Treatment Visit during the treatment period (Visit 8) will be considered Day 1 of the optional extension period.

[c] A complete physical examination will be performed at Screening, and repeated on Days 29, 85, at each visit during the optional extension period, and the Safety Follow-up visit.

[d] Vital signs including height, weight, oral temperature, seated blood pressure, pulse rate, and respiratory rate will be assessed predose at every trial visit (height measured only at Screening), including visits during the optional extension period and Safety Follow-up visit.

[e] Subjects who have previously had a normal chest X-ray for clinical reasons within 3 months prior to Day 1 do not need to have the chest X-ray repeated. See Section 7.4.4.3 for details.

[f] Concomitant medications will be recorded at Screening and Day 1, and any changes solicited/recorded at every trial visit (including visits during the optional extension period), and with any ad hoc telephone contacts.

[g] Blood samples for hematology and chemistry will be obtained at Screening, predose at Visits 2 through 8, at each visit during the optional extension period, and at the Safety Follow-Up Visit. See Table 4 for detailed assessments.

[h] Samples for coagulation tests (partial thromboplastin time and international normalized ratio) will be obtained at Screening only.

[i] Blood samples for immunoglobulin levels will include IgM, IgA, and IgG and its subclasses.

[j] Samples for rheumatoid factors (IgG-RF, IgM-RF, IgA-RF) and anti-CCP antibodies will be obtained at Screening, predose at Visits 4, 5, 7, 8, (at Visit 12 during OLE), and at Safety Follow-Up Visit. ESR will also be collected separately at these same time points.

[k] Samples for hsCRP will be obtained at Screening, predose at Visits 2, 4, 5, 7, 8, (at Visit 12 during OLE), and at Safety Follow-Up Visit.

[l] B cell subtypes will include as examples but not limited to IgD, CD27, and CD20.

[m] Blood samples to test for viral serology (ie, human immunodeficiency virus, hepatitis B and C) and for tuberculosis (QuantiFERON®-TB) will be obtained at Screening.

[n] For female subjects only, a serum pregnancy test will be collected at Screening, and a urine pregnancy test will be collected predose at Visits 2, 5, 7, 8, at Safety Follow-Up Visit, and at every visit during the optional extension period.

[o] Subjects must be fasting 8 hours prior to visits with PK sampling. Subjects must also fast for 1 hour postdose at these visits. Blood samples for PK analysis will be collected predose and 0.25, 0.5, 1.0, 2.0, 4.0, and 6.0 hours postdose at Day 1 (Visit 2) and Day 29 (Visit 5). Subjects who discontinue IMP prior to PK sampling visit days will not have blood obtained for PK.

[p] CCI [redacted]

[r] Assessments for RA disease activity will include: ACR response criteria, DAS28, hsCRP, subject and physician visual analog scales, and Health Assessment Questionnaire Disability Index (see Sections 7.3.1 and 7.3.1.2 for details).

[s] The IMP (capsule formulation) will be dispensed after randomization on Day 1 and thereafter at each planned trial visit during the Treatment Period. Patients participating in the OLE will be dispensed IMP (tablet formulation) at Visit 8/Day1 of OLE and at Visits 9, 10, and 11 during the OLE. Patients participating in the OLE will be administered IMP (tablet formulation) at Visit 8/Day 1 OLE. All remaining IMP capsules will be collected at Visit 8 for all patients. Remaining IMP tablets will be collected at Visit 12 for those participating in OLE.

[t] On trial visit days, the IMP will be administered during the trial visit after trial visit procedures are completed (other than postdose PK/PD sampling); otherwise, the IMP will be self-administered at a set time each day (± 2 hours).

[u] On trial visit days after Visit 2, IMP compliance for the intervals since the previous visit will be documented using pill counts.

[v] Any AEs occurring during the Screening Period will be recorded, and AEs will be solicited/recorded at every trial visit and with any ad hoc telephone contacts

2 Sponsor, Investigators, and Trial Administrative Structure

The administrative structure of the trial is described in the following:

This clinical trial will be sponsored by Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany. The trial will be conducted at approximately 50 sites in 10 countries.

Sites to be used will include clinical centers, Phase I units, academic centers, inpatient or outpatient, etc.

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

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

The trial will appear in the following clinical trial registries: Clinicaltrials.gov.

PPD will be responsible for the clinical trial documents to be submitted to regulatory authorities, the conduct of the clinical trial, the central laboratory including coordination and distribution of laboratory supplies, drug supply and distribution, data management, statistical analysis, and clinical trial reporting. Further details will be provided in a separate document and updated as necessary. Clinical quality assurance will be performed under the responsibility of the Development Quality Assurance department at Merck KGaA Darmstadt.

An Independent Data Monitoring Committee (IDMC) will be established to continually review available safety and tolerability data. The IDMC will be composed of independent physicians with expertise in rheumatoid arthritis (RA) and an independent biostatistician who will serve as a voting member. Ad hoc members will be consulted as needed. IDMC meetings will take place every 4 months and at the interim analysis (IA). The full list of IDMC members and IDMC responsibilities will be included in the IDMC charter.

The Investigational medicinal products (IMP) will be supplied by the Clinical Trial Supply Department at Merck and packaged and labeled by PPD.

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

3 Background Information

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase expressed in cells of hematopoietic origin, and participates in both innate and adaptive immunity. BTK is involved in a variety of B cell functions, including proliferation, antigen presentation, and production of

cytokines and antibodies, and is also involved in the activation of innate immune cells (macrophages, neutrophils, and mast cells/basophils) by immune complexes via Fc receptors.

M2951, is a highly selective irreversible inhibitor of BTK. The mechanism of action of BTK suggests a use for BTK inhibitors in the treatment of autoimmune and inflammatory disorders (AIID) (1). BTK inhibitors are expected to impact both B cell- and T cell-mediated autoimmune disorders, given the direct effect on B cells (which have a dual role in autoimmunity including auto-antibody production and influencing T cell responses) as well as by blocking Fc receptor-mediated activation of innate immune cells (1, 2). The effects of BTK inhibitors have been demonstrated in preclinical models of autoimmune disease. Reduction of disease activity with BTK inhibitors was demonstrated in mouse models of lupus, collagen-induced arthritis, and anti-glomerular basement membrane glomerulonephritis (3-5). Likewise, M2951 was active in murine lupus models, with reduction in disease activity comparable with reference treatment, as well as in animal models of collagen-induced arthritis and passive cutaneous anaphylaxis. Reduction in disease activity in animal models was correlated with the extent of B cell inhibition and BTK occupancy.

B cell modulators have shown efficacy in several AIID. Belimumab, approved in 2011 for the treatment of lupus, inhibits B cell survival and differentiation into plasma cells (6). In addition, the efficacy of anti-CD20 B cell depleting therapy (eg, rituximab) provides indirect clinical evidence for the likely efficacy of the B cell modulatory effects of BTK inhibition in the AIID setting. Rituximab is approved in the US and EU for the treatment of RA and granulomatosis with polyangiitis/microscopic polyangiitis (7). Furthermore, efficacy has been reported in a broad range of AIIDs including multiple sclerosis (MS) (8-13). In addition, other agents targeting B cells are in late stage development for systemic lupus erythematosus (SLE)(14).

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

Refer to the current Investigator's Brochure (IB) for detailed results.

Rheumatoid arthritis is a systemic, inflammatory, autoimmune disease with characteristic autoantibody profiles and distinct patterns of organ involvement, including articular and extra-articular manifestations. The clinical features of RA include chronic joint inflammation and swelling that typically involves small joints of the hands and feet. RA can result in progressive destruction of cartilage and juxtaarticular bone with resultant joint space narrowing. Joint

inflammation and subsequent joint destruction can lead to progressive functional impairment with increasing disability (15).

Conventional RA therapy consists of treatments with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease modifying anti rheumatic drugs (DMARDs). Methotrexate (MTX) represents one of the most widely used DMARDs for RA, yet less than half of patients with RA show substantial and sustained clinical improvement in disease signs and symptoms (16). The emergence of biologic therapies for RA, such as tumor necrosis factor-alpha (TNF-α) inhibitors, represent treatment options that mitigate the clinical manifestations of RA by selectively targeting key inflammatory molecules. However, approximately 30% of patients with RA, usually those with more severe disease, will not experience satisfactory clinical improvement with use of currently available therapies (17). Accordingly, a significant unmet need remains for more effective treatments for RA.

This Phase IIa, 12-week trial with M2951 will be performed to assess: 1) the efficacy, safety, and tolerability of M2951 in subjects with RA, 2) the pharmacokinetics (PK) and pharmacodynamics (PD) profile in subjects with RA to compare the PK/PD relationship to that seen in healthy volunteers for use in the future development in this population, and 3) the early effects of M2951 on markers of RA disease activity.

3.1 Potential Risks and Benefits

The safety assessments of M2951 rely on data accumulated during product development and from data on other BTK inhibitors. Based on the nonclinical and clinical data available to date, the conduct of the trial is regarded as justifiable at the planned dose.

M2951, is being considered for the treatment of autoimmune diseases, including RA, SLE, and MS. To date, no efficacy data are available. However, because its mechanism of action directly targets both the production of autoantibodies and cellular effectors of end-organ injury, it is reasonable to anticipate that M2951 may represent a significant advance in the treatment of RA and other autoimmune diseases.

No identified risks or new potential risks have emerged from the first-in-human trial, Trial EMR200527-001. M2951 was well tolerated[redacted]

Important potential risks to subjects are based on nonclinical safety data of M2951 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, drug-drug interactions, and embryofetal toxicity. It is unknown whether there are additive risks of cytopenias and elevated transaminases when M2951 is given with MTX; however, these potential risks will be readily monitored.

Risk minimization measures inherent to early phase clinical trials are considered adequate for the proposed clinical trial in RA patients. An IDMC will be set up to continually review available safety and tolerability data and will be mandated to make immediate decisions regarding the conduct of the trial; no additional risk minimization measures are proposed.

The dose of M2951 (50 mg bid) selected for the proposed trial is well within the dose ranges studied in Trial EMR200527-001 and showed high levels of target occupancy in healthy volunteers.

Taking the above information into account, benefit-risk considerations support conduct of the proposed clinical trial EMR200527-0081 in patients with RA.

For full details, refer to the latest 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 guidelines, and any additional applicable regulatory requirements.

4 Trial Objectives

4.1 Primary Objective

To assess the efficacy of M2951 in subjects with active RA on stable MTX therapy, as measured by the American College of Rheumatology (ACR) 20% (ACR20) response rate over a duration of 84 days.

4.2 Key Secondary Objective

To assess the level of disease activity at 4 weeks in subjects with active RA as assessed by the percent change in high-sensitivity C-reactive protein (hsCRP) from Baseline to Day 29.

4.3 Other Secondary Objectives (during the double-blind period)

4.3.1 Safety

To assess the safety and tolerability of M2951 in subjects with active RA on stable MTX therapy from signing ICF until Safety Follow-up Visit, as assessed by the:

- Nature, incidence, and severity of TEAEs
- Changes from Baseline in vital signs and 12-lead electrocardiogram (ECG) data
- Changes from Baseline in standard hematology and chemistry laboratory parameters including liver function tests, amylase/lipase, and urinalysis.

4.3.2 Pharmacokinetics and Pharmacodynamics

To evaluate the PK and PD of M2951 in subjects with RA on stable MTX therapy, as assessed by:

- Pharmacokinetic parameters will include:
  - C_{max}, t_{max}, plasma concentration observed immediately before next dosing (C_{pre} [Day 29]), area under the concentration-time curve from time zero to 6 hours (AUC_{0-6h}),accumulation ratio for AUC_{0-6h} ($R_{acc[AUC0-6h]}$), and accumulation ratio for C_{max} ($R_{acc[Cmax]}$)

- Pharmacodynamic parameters will include:
  - Absolute concentrations and change from Baseline in immunoglobulin levels (IgA, IgM, IgG, and subclasses) at Days 29 and 85
  - Absolute numbers and change from Baseline in B cell numbers and subtypes at Day 85.

4.3.3 Other Secondary Efficacy Objectives

To further assess the level of disease activity in subjects with active RA as assessed by:

- ACR 50% and 70% (ACR50 and ACR70) response at each time point
- Percent change in hsCRP from Baseline to Day 85
- Change from Baseline in Disease Activity Score based on a 28 joint count (DAS28) and hsCRP (DAS28-hsCRP) at Days 29 and 85
- Percentage of subjects with DAS28-hsCRP < 3.2 (well controlled disease) at Day 85
- Percentage of subjects with DAS28-hsCRP < 2.6 at Day 85
- Change from Baseline in erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide (anti-CCP) antibody, and rheumatoid factor (RF) at Days 29 and 85
- Change from Baseline to Day 85 in a subject's self-assessments including:
  - Global assessment of disease activity
  - Self-assessment of pain
  - Self-assessment of disability (Health Assessment Questionnaire – Disability Index; HAQ-DI)
- Change from Baseline to Day 85 in Physician's Global Assessment of Disease Activity.

4.4 Exploratory Objectives

CCI [redacted]

4.5 Open-label Extension Objectives

To evaluate the on-going safety and efficacy of M2951 in a an open- label extension with treatment at 50 mg bid for an additional 6 months.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase IIa randomized, double-blind, placebo-controlled trial in approximately 64 subjects 18 to 75 years of age with RA on stable MTX background therapy.

Total duration of subject participation is approximately between 5 months (20 weeks) to 11 months (46 weeks), which includes:

- Screening: 28 days (4 weeks)
- Treatment: 84 days (12 weeks)
- Optional 6-month open-label extension period (26 weeks)
- Safety Follow-Up: 28 days (4 weeks)

After completing the 12-week treatment period, subjects will be offered the opportunity to participate in an optional 6-month open-label extension period where all subjects will receive M2951. For subjects who choose to participate in the optional extension period, the duration of participation will last a total of approximately 11 months.

Subjects who continue to receive M2951 during the extension period will also be required to undergo the Safety Follow-up Visit scheduled for approximately 28 days after the last treatment visit.

Screening will occur over Day -28 to -1 (Visit 1), during which time all Screening assessments must be completed and reviewed.

On Day 1 (Visit 2), after confirmation of eligibility, assessment of RA disease activity and vital signs, and obtaining of required blood and urine samples, subjects will be randomly assigned 1:1 to receive M2951 or placebo in combinations with MTX. CCI [redacted]

Blood and urine samples will be obtained for safety (hematology, biochemistry, coagulation, and urinalysis), markers of disease activity (hsCRP, ESR, anti-CCP, and RF), PK (M2951 concentration), and PD (immunoglobulin levels, CCI [redacted], and B cell numbers) following the schedule detailed in the Schedule of Assessments (Table 1).

CCI [redacted]

Subjects will self-administer the IMP at a set time each day (± 2 hours). Subjects must take their daily dose more than 1 hour prior to a meal or snack or more than 2 hours after a meal or snack. Clear fluids are allowed at any time. On trial visit days, the IMP will be administered during the trial visit after the trial visit procedures (other than PK/PD sampling) are completed.

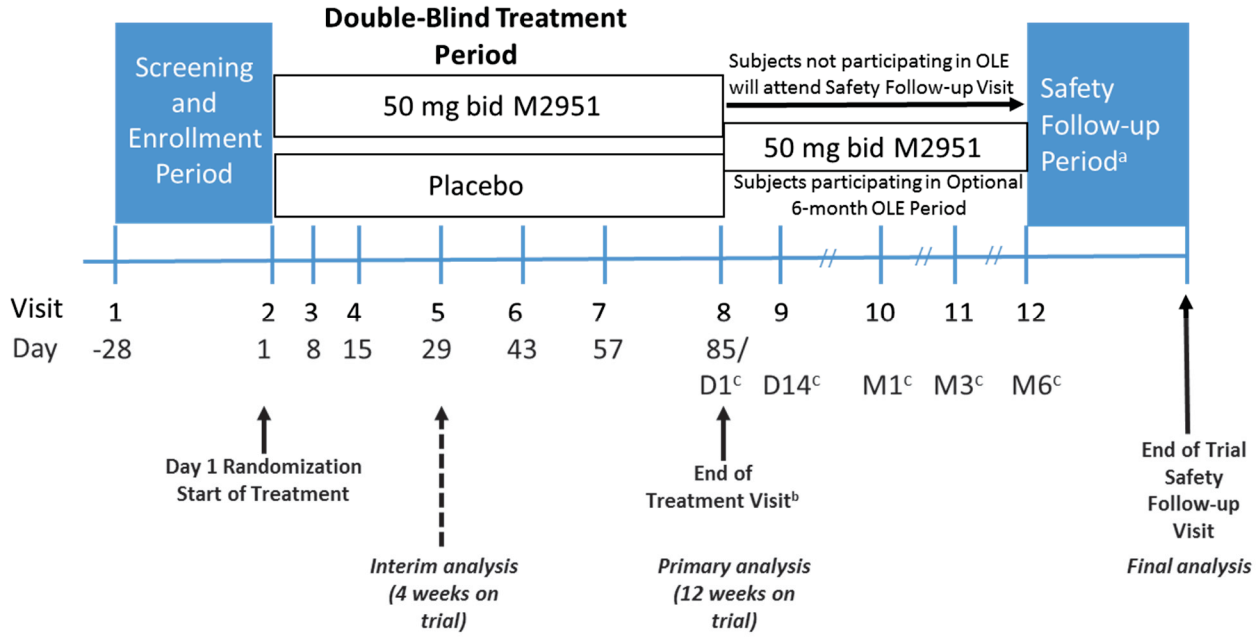
Subjects will have trial visits weekly for the first 3 weeks of treatment; bi-weekly up until 8 weeks of treatment; a final On-Treatment Visit on Day 85 (12 weeks), and then return for 1 Follow-Up Visit approximately 28 days (4 weeks) after the last dose of IMP.

The optional Extension Period includes four scheduled visits (Visits 9, 10, 11, and 12), which correspond with Day 14, and the end of Months 1, 3, and 6. Subjects will also attend a Safety Follow-Up Visit approximately 28 days after the last dose of IMP.

The IDMC will meet at times to be laid out in the IDMC charter during the trial to monitor the safety of participants throughout the trial.

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

Figure 1 Schematic of the Trial Design



[a] All subjects, whether not entering the optional open-label extension period, continuing on to the open-label extension period, on early terminating from the study will attend a Safety Follow-up Visit approximately 28 days after the last dose of IMP.
[b] Subjects who decide to participate in the optional open-label extension period will sign a consent form at Visit 8, which will be considered Day 1 of the optional extension period.
[c] Corresponds to the days (D) or months (M) during open-label extension period.
Bid=twice daily, OLE=open-label extension.

5.2 Discussion of Trial Design

This will be a double-blind trial. Eligible subjects will be randomized to treatment with M2951 or placebo. The 50 mg bid dose of M2951 was selected for this trial based on the results from the first-in-man trial in healthy subjects.

The primary objective of this trial is to assess the efficacy of M2951 in subjects with active RA on stable MTX background therapy as measured by the ACR20 over Day 85 of treatment. The key secondary objective is to evaluate the level of disease activity at Day 29 in subjects with active RA as assessed by percent change in hsCRP from Baseline to Day 29.

An open-label extension of 6 months duration will be offered to subjects completing the initial 12-week treatment period. The purpose is to allow all subjects the opportunity to be on active treatment with M2951 and to collect longer term safety data.

Other secondary objectives are to assess the safety and tolerability of M2951 and to evaluate the PK and PD of M2951 in subjects with RA on stable MTX background therapy.

CCI [redacted]

CCI [redacted]

[redacted]

The results of this trial will provide additional information to support dose range selection for relevant BTK occupancy for use in the future development in the RA population.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Only subjects meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial. 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

The current trial will enroll subjects who fulfill the following:

1. Men or women 18 to 75 years of age at the time of informed consent signature
2. Confirmed diagnosis of RA according to 2010 American College of Rheumatology (ACR)/The European League Against Rheumatism (EULAR) RA classification criteria of at least 6 months duration

3. Positive RF and/or anti-CCP
4. Persistently active disease defined as ≥ 6 swollen joints (of 66 counted) and ≥ 6 tender joints (of 68 counted)
5. hsCRP ≥3.6 mg/L
6. Treatment for ≥ 12 weeks with 10 to 25 mg/week MTX at a stable dose for at least 4 weeks prior to dosing with the IMP and maintained throughout the trial
7. Women of childbearing potential must use a highly effective method of contraception combined with one supplementary barrier method for 4 weeks prior to randomization, throughout the trial, and for 90 days after the last dose of IMP. For the purposes of this trial:
    - 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
    - The definition of highly effective contraception includes:
        - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; oral, intravaginal or transdermal
        - progestogen-only hormonal contraception associated with inhibition of ovulation; oral, injectable or implantable
        - intrauterine device (IUD)
        - intrauterine hormone-releasing system (IUS)
        - bilateral tubal occlusion
        - vasectomized partner
        - sexual abstinence
    - Supplementary barrier methods include:
        - male or female condom with or without spermicide
        - cap, diaphragm or sponge with spermicide
8. Men must agree to use and to have their female partners use a highly effective method of contraception combined with one supplementary barrier method as defined above for at least 90 days after the last IMP administration.
9. Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Day 1/randomization before dosing
10. History of vaccinations as follows: 1) against Streptococcus pneumoniae with PPSV23 or PCV13 with repeat administration as necessary to be up to date as per local guidelines; and 2) against influenza virus (as seasonally required); or vaccination against these pathogens during Screening. Subjects receiving 1 or more of these vaccinations during Screening must have at least 2 weeks between the vaccination(s) and the date of randomization

11. Signed and dated informed consent indicating that the subject has been informed of all the pertinent aspects of the trial prior to enrollment and will comply with the requirements of the protocol.

5.3.2 Exclusion Criteria

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

1. Use of oral corticosteroids > 10 mg daily prednisone equivalent, use of injectable corticosteroids, or change in dose of corticosteroids within 2 weeks prior to Screening or during Screening
2. Initiation or change in dose for nonsteroidal anti-inflammatory drugs (NSAIDs) within 2 weeks prior to Screening
3. Treatment with tofacitinib, other BTK inhibitors, or a biologic DMARD (eg, anti-TNF-α, tocilizumab [anti-interleukin-6 receptor], abatacept [CTLA4-Fc]), or other immunosuppressive drugs (sulfasalazine would be acceptable at a stable dose) other than MTX within 3 months prior to Screening or during Screening
4. Treatment with anti-CD20 therapy (eg, rituximab) within 12 months prior to Screening or during Screening
5. Immunologic disorder other than RA, with the exception of secondary Sjogren's syndrome associated with RA, and well-controlled diabetes or thyroid disorder, or any other condition requiring oral, intravenous, intramuscular, or intra-articular corticosteroid therapy
6. Vaccination with live or live-attenuated virus vaccine within 1 month prior to Screening
7. Severe drug allergy or history of anaphylaxis, or allergy to the IMP or any of its excipients
8. 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
9. History of or positive testing for human immunodeficiency virus (HIV), hepatitis C antibody and/or polymerase chain reaction, hepatitis B surface antigen (HBsAg) (+) and/or hepatitis B core total, and/or IgM antibody (+) at Screening
10. History of or current diagnosis of active tuberculosis (TB); undergoing treatment for latent TB infection (LTBI); untreated LTBI (as determined by documented results within 3 months of the Screening Visit of a positive TB skin test with purified protein derivative with induration ≥ 5 mm, a positive QuantiFERON®-TB test or positive or borderline T-SPOT [Elispot] test); or positive QuantiFERON-TB test at Screening. Subjects with documented completed appropriate LTBI treatment would not be excluded and are not required to be tested.
    - Subjects with current household contacts with active TB will also be excluded.

- Indeterminate QuantiFERON-TB or T-SPOT tests may be repeated once, and will be considered positive if retest results are positive or indeterminate.

11. History of splenectomy at any time, or any major surgery within 2 months prior to Screening
12. History of myocardial infarction or cerebrovascular event within 6 months prior to Screening, or current active angina pectoris, symptomatic heart failure, uncontrolled seizures, untreated hypertension, GI bleeding, or any other significant active medical condition in the Investigator's opinion
13. On anticoagulation or antiplatelet therapy other than daily aspirin for cardioprotection
14. On fish oil (unless discontinued prior to first dose)
15. 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
16. Breastfeeding/lactating or pregnant women
17. Clinically significant abnormality on ECG, or an active infective process or any other clinically significant abnormality on Screening chest X-ray (CXR) taken within 4 weeks of the first dose, per Investigator opinion. If a CXR has been taken within the previous 3 months and results are available and normal, the CXR does not need to be carried out
18. Estimated glomerular filtration rate by the 4-variable Modification of Diet in Renal Disease equation (19) of < 45 mL/min/1.73 m^2
19. TSH < 0.01 or ≥ 7.1 mIU/L at Screening
20. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, or lipase > 2X above upper limit of normal (ULN) of laboratory reference range, total bilirubin > 1.5X ULN, any other clinically significant laboratory abnormality
21. B cell (CD19) count < 50% of the lower limit of normal at Screening
22. Significant cytopenia, including absolute neutrophil count < 1,500/mm^3, platelet count < 100,000/mm^3, or absolute lymphocyte count < 1,000/mm^3
23. Has taken an investigational drug within 1 month or 5 half-lives of the investigational drug, whichever is longer, prior to Screening
24. Subjects currently receiving (or unable to stop using prior to receiving the first dose of IMP) medications or herbal supplements known to be potent inhibitors of cytochrome (CYP)3A (must stop at least 1 week prior), potent inducers of CYP3A (must stop at least 3 weeks prior), or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least 1 day prior).

5.4 Criteria for Randomization and Initiation of Trial Treatment

Randomization should occur on Day 1 (Visit 2) 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 with M2951 (50 mg bid) or placebo through a central randomization process by an Interactive Web Response System (IWRS). This will be a double-blind trial. CCI [redacted]

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 electronic case report form (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 immediately return for an End of Treatment Visit followed by the Safety Follow-Up/End of Trial Visit 4 weeks later. A subject must be withdrawn from M2951 or placebo if any of the following occur:

- Adverse events, if discontinuation of 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 that are considered necessary for the subject's well-being may be given at the discretion of the Investigator.
- Pregnancy
- Protocol noncompliance judged as significant by the Investigator and/or the Sponsor
- Subject withdrew consent
- Subject lost to follow-up
- Lack of efficacy
- Death
- Participation in another investigational clinical trial.

Withdrawal due to special precautions are described in Section 6.5.4.

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. Subjects who withdraw from the trial while still on the IMP should return immediately for an End of Treatment Visit upon discontinuation of the IMP and a Safety Follow-Up Visit 4 weeks after the last administered dose of IMP. Subjects who

withdraw and are no longer on the IMP must complete the Safety Follow-Up/End of Trial Visit assessments described in Section 7.1.4.

A subject must be withdrawn if any of the following occurs during the trial:

- Pregnancy (for further details in case of pregnancy, see Section 7.4.2)
- Subject withdrew consent
- Participation in another investigational clinical trial
- Lost to follow-up
- Death
- Any events that endanger the safety of the subject.

If a subject fails to return for the post-treatment Safety Visit, all attempts 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).

If 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).

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

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.

Participation in any other trial during the duration of this trial will not be allowed.

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 comparator from the market for safety reasons.

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

5.7 Definition of End of Trial

The end of the trial is defined as the last contact date with the last subject who participates in this trial (last subject’s last visit).

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

- Any subject is still receiving any IMP
- 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

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

6.1 Description of the Investigational Medicinal Product

During the 12-week treatment period, the active IMP is M2951 (2 x 25 mg bid), which is supplied as a capsule (size 0, color Swedish Orange) formulation for oral administration. No other excipients are used.

Identical capsules for placebo are filled with mannitol.

During the optional extension period, M2951 (2 x 25 mg bid) will be supplied as tablet formulation for oral administration.

The Sponsor, Merck KGaA, will provide IMP (M2951 and placebo) to the trial site, manufactured and tested according to applicable current Good Manufacturing Practice requirements for clinical trial supplies and a confirmation the IMPs are released for human use in clinical trials.

6.2 Dosage and Administration

During the 12-week treatment period, subjects will receive 50 mg bid M2951 or placebo administered as 2 matching oral capsules twice daily for 84 days. Subjects will self-administer the IMP at a set time each day (± 2 hours). Subjects must take their daily 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. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures (other than post-treatment PK/PD sampling and post-treatment ECGs) are completed.

After completing the treatment period, subjects will be offered the opportunity to participate in an optional 6-month M2951 extension period on Day 85 (Visit 8). Subjects who received M2951 during the treatment period will continue with the same dose of M2951 (in tablet formulation). All subjects in the placebo group during the treatment period will discontinue placebo and start

treatment with 50 mg bid M2951 tablets on Day 85/Day 1 of OLE. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures are completed. Subjects will take 2 matching oral tablets twice daily for 6 months. Subjects will self-administer the IMP at a set time each day (± 2 hours). Subjects must take their daily 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. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures are completed.

If a dose is missed, the subject can take the missed dose up to 6 hours after the scheduled time. If more than 6 hours have elapsed since the dose was missed, the subject should skip the dose for that period, make note of the missed dose, and take the next dose at the regularly scheduled time.

6.3 Assignment to Treatment Groups

Eligible subjects will be randomized through a central stratified randomization process by the IWRS to receive 50 mg bid M2951 or placebo in a 1:1 ratio prior to dosing on Visit 2/Day 1.

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.

Subjects continuing to the open-label extension period will be dispensed additional treatment kits for 6 months of treatment.

6.4 Noninvestigational Medicinal Products to be Used

Throughout the study, patients will remain on their chronic stable doses of MTX at the time of Screening (refer to Section 5.3.1) 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 (including those participating in and during the extension period) are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the 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.

The standard of care therapies for RA that are allowed to be continued during the trial include the following immunosuppressive or immunomodulating therapies:

- MTX (up to 25 mg/week) background therapy is required
- Sulfasalazine (up to 3 g/day)
- Oral corticosteroids (up to 10 mg/day prednisone equivalent)

Other permitted therapies that are allowed to be continued during the trial include antimalarials, such as hydroxychloroquine, quinacrine, and chloroquine.

With the exception of corticosteroids, the dose of which can be decreased, the dose of these medications must remain stable during the Screening Period and throughout the subject's participation in the trial, unless changes are required for safety issues.

The following additional treatments commonly given to subjects with RA are permitted to be continued during the trial and should be maintained at a stable dose during the trial unless a dose change is required for safety reasons:

- Nonsteroidal anti-inflammatory medications
- Opioids and other analgesics.

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.

6.5.2 Prohibited Medicines

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

- Initiation of an immunosuppressant or immunomodulator, or increase in immunosuppressant beyond the maximum allowable dose
- Oral corticosteroid dose > 10 mg/day or use of intramuscular or intravenous steroids
- Intra-articular steroids
- Biologic therapies
- Intravenous Ig therapy and/or plasmapheresis
- Live and live-attenuated vaccines
- Herbal supplements including, but not limited to, St. John's wort, grapefruit, Seville oranges, cranberries, or juices of these fruits
- Moderate or strong inhibitors or inducers of CYP3A or drugs mainly metabolized by CYP3A with a narrow therapeutic index (see Table 2). The additive effects of weak inhibitors taken in combination must also be taken into account.

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 2 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] matinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, soniazid, 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]		

[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.

Note: 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

Note: 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%.

Note: 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%-80%, and a strong inducer decreases AUC by 50%-80%.

Note: 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%-50%, and a weak inducer decreases AUC by 20%-50%.

Note: 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

Not applicable.

6.5.4 Special Precautions

The IMP should be temporarily withheld or permanently withdrawn if the following abnormalities occur or re-occur, as relevant, and only 1 re-initiation is allowed if the IMP is temporarily withheld:

- For a neutrophil count < 500/mm^3 or platelet count < 25,000/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 within 24 hours of receipt. If the value is still Grade 3, permanently discontinue the IMP. For a decrease from normal to Grade 1, or Grade 1 to Grade 2, temporarily hold the IMP and recheck the value within 24 hours of receipt. 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 AST or ALT to > 3X ULN or increase in bilirubin to > 1.5X ULN (Grade 2 or higher), the IMP should be permanently withdrawn.
- For an increase in amylase or lipase to > 5X ULN (Grade 4), the IMP should be permanently withdrawn.
  - For an increase in amylase or lipase to > 2 to 5X ULN (Grade 3), temporarily hold the IMP and recheck the value within 24 hours of receipt. If the value is still Grade 3, permanently discontinue the IMP. For any other increase from Baseline to another grade, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease, or re-initiate the IMP if a downward trend is observed.
- For an increase in serum creatinine to > 3X from Baseline (Grade 3 or higher), the IMP should be permanently withdrawn.
  - For any other increase in serum creatinine > 1.5X from Baseline, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease, or re-initiate the IMP if a downward trend is observed.
- For any other laboratory abnormality of Grade 4 severity, the IMP should be permanently withdrawn.
  - For any other laboratory increase/decrease (as relevant) from Baseline to a higher severity grade, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not improve, or re-initiate the IMP if an improving trend is observed.

Duplicate blood samples will be collected for selected safety laboratories to be processed by both the central laboratory and local laboratories. 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.

Laboratory values corresponding to Common Terminology Criteria for AEs (CTCAE) Grades 1 to 4 are presented for selected laboratory parameters in Table 3. For all other laboratory abnormalities, refer to the CTCAE, version 4.03 (20).

Table 3 CTCAE Grades for Relevant Laboratory Parameters

Laboratory Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil (/mm^3)	< LLN to 1,500	< 1,500 to 1,000	< 1,000 to 500	< 500
Platelets (/mm^3)	< LLN to 75,000	< 75,000 to 50,000	< 50,000 to 25,000	< 25,000
AST and ALT	< ULN to 3X ULN	> 3 to 5X ULN	> 5 to 20X ULN	> 20X ULN
Bilirubin	< ULN to 1.5X ULN	> 1.5 to 3X ULN	> 3 to 10X ULN	> 10X ULN
Amylase and lipase	< ULN to 1.5X ULN	> 1.5 to 2X ULN	> 2 to 5X ULN	> 5X ULN
Creatinine	> Baseline to ≤ 1.5X Baseline, or > ULN to 1.5X ULN	> 1.5 to 3X Baseline or > 1.5 to 3X ULN	> 3X Baseline, or > 3 to 6X ULN	> 6X ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CTCAE=Common Terminology Criteria for Adverse Events, LLN=lower limit of normal, ULN=upper limit of normal.

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.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

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

M2951 and matching placebo is supplied by the Sponsor. A description of the pharmaceutical properties and composition of the formulation of M2951 is provided in the IB. 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

Because the Investigator is blinded to trial treatment, subjects will be instructed on the proper handling and storage of the IMP by the trial nurse or pharmacist. Storage at or below 25°C is recommended.

Any unused product should be returned to the trial site.

6.8 Investigational Medicinal Product Accountability

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

- Upon receipt of the IMP, the responsible person 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 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, expiry dates, and the individual subject trial numbers.

The Investigator site should maintain records, which adequately document the 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 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. Subjects will be asked to record the date and time of dosing and food intake around dosing in a subject diary. 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.

6.10 Blinding

This will be a double-blind trial. After Day 1, the study site staff, the Sponsor, and the PPD study team will be blinded to:

- Results that can reveal the PD effects of M2951 in an individual subject (ie, immunoglobulins [IgA, IgM, IgG, and its subclasses], CCI , and B cell numbers and subtypes) and
- Results that can reveal the efficacy of M2951 in an individual subject (ie, hsCRP, ESR, anti-CCP, and RF).

Blinding to treatment codes or laboratory results capable of revealing treatment will be maintained throughout the trial duration, except for the unblinded IDMC, limited unblinding for the purposes

of the IA, partial unblinding to support early analysis of PK/PD data, or in the event that emergency unblinding is necessary (see Section 6.11). The blind may also be broken in the case of a pregnancy should the subject desire this information. Randomization data will be kept strictly confidential, accessible only to authorized staff, until the limited unblinding for the IA and full unblinding for the analysis at the end of 12 weeks of treatment for all randomized patients.

In order to maintain the blinded nature of the study, only the randomization statistician, an independent person at the study site responsible for receiving local laboratory ESR results and conveying those results to the central laboratory, and an independent statistician team (independent of the PPD study team) responsible for production of the IA outputs, will be fully unblinded during study conduct. The bioanalytical laboratory(ies) responsible for the analysis of the PK and PD samples will be allowed to be partially unblinded during study conduct using masked subject identifiers, to support association of PK/PD data with treatment codes for timely decision making, but prevent association of treatment codes with any other clinical data, such as safety data. A subteam of the Sponsor study team tasked with review of the IA data (medical responsible, Drug Safety representative, and biostatistician) will be unblinded to the IA results, which will be presented in the form of summary tables on a limited set of endpoints for subjects enrolled at the time of the IA: 4-week hsCRP, 4-week DAS28-hsCRP, safety, baseline characteristics, and disposition. The IDMC will also be unblinded to treatment, as described in the IDMC charter.

All other trial-related individuals, ancillary site staff, other clinical research associates/monitors, investigators, Sponsor staff other than those identified above, and PPD staff other than those identified above, will remain blinded to treatment codes or laboratory results capable of revealing treatment. Results from PK and PD testing or the IA will not be reported back to the sites or the PPD study team, with the exception of ESR results. The ESR results will be analyzed at a laboratory local to the site, received by a person at the site independent of study staff at the site, and conveyed to the central laboratory without sharing with study staff at the study site, the Sponsor, or the PPD study team. There will be no communication of results between the PPD study team tasked with conduct of the study and the independent statistician team responsible for the production of IA outputs.

Only when the 12-week Treatment Period is completed for all patients, the data file verified, protocol violations determined, statistical analysis plan (SAP) signed and database partially locked for the 12-week treatment period, will the drug codes be broken and made available, along with laboratory results capable of revealing treatment, for the primary data analysis. The final analysis will be performed after all subjects have completed the Safety Follow-up or discontinued from study early, with assessment of some safety and key efficacy variables.

All breaks of the trial blind must be adequately documented.

Processes to maintain blinding during the IA are described in Section 8.6.

6.11 Emergency Unblinding

There is no known antidote to M2951, so symptomatic and supportive treatment of any suspected and related AE, if necessary, is to be undertaken as clinically indicated.

The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of the subject. Contact information for breaking the blind in an emergency is given on the subject emergency card provided to each subject (see Section 9.4).

The Investigator will have the ability to break the blind with regard to IMP for any subject 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. The Investigator 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). The Investigator must record the date and reason for unblinding in the subject's eCRF and source documents.

Under certain circumstances, Drug Safety may be required to unblind the treatment assignment for an individual subject following an SAE or other serious event, eg, 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 Visit, followed 4 weeks later by the Safety Follow-Up/End of Trial Visit.

6.12 Treatment of Overdose

For purposes of this protocol, an overdose is defined as any dose greater than twice the highest daily dose included in the clinical trial protocol or planned for an individual subject enrolled in the trial, administered on 3 or more consecutive days. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section and AE section of the eCRF and reported to Drug Safety in an expedited manner using the paper SAE Report Form, and following the same timelines in Section 7.4.

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 physician.

7 Trial Procedures and Assessments

During the Screening Visit, 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. The maximum amount of blood to be obtained during the trial is within the commonly accepted maximum of 275 mL over 4 weeks and 550 mL over 8 weeks. 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:

- Urine testing for beta-human chorionic gonadotropin (β-HCG) will be conducted at the local laboratories
- PK samples and CCI samples will be analyzed by the analytical laboratories specified by the Sponsor
- 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.
- ESR will be analyzed by 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, and Section 7.1.4 for the Follow-Up Period.

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 Manual of Procedures (MOP) and in the SAP. 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. Patient reported outcome questionnaires must be performed prior to any other assessments at all visits. For volumes of blood collected, see Appendix C.

7.1.1 Screening Period

At the Screening Visit (Visit 1), 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 within 28 days prior to the first administration of the IMP according to assessments in Table 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 trial visits, patient reported outcome questionnaires must be performed prior to any other assessments. At the Day 1 Visit (Visit 2), assessments should be performed prior to randomization and the administration of trial treatment. Scheduled assessments will be performed according to Table 1 before administration of the IMP, with the exception of relevant postdose blood draws (eg, PK and CCI).

At subsequent visits (Visit 3 through 7), 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 Visit.

Subjects must be fasted for 8 hours prior to PK sampling as specified in Table 1. Subjects must also fast for 1 hour postdose at these visits with PK sampling.

7.1.2.1 End of Treatment Visit

The End of Treatment Visit (Visit 8) will be performed on Day 85 or within 5 days after early discontinuation of treatment with the IMP. Subjects will undergo the assessments as described in the Schedule of Assessments (Table 1).

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.

Subjects opting to participate in the optional extension period will sign a new ICF at this visit. The Investigator will discuss the benefits with the subject and the subject well-being. Subjects are free not to sign the new ICF for the extension period.

7.1.3 Optional Extension Period

After completing the treatment period (Visits 2 through 8), subjects will be offered the opportunity to participate in an optional 6-month M2951 extension period. Subjects electing to participate in the Extension Period will sign an ICF at Visit 8. Subjects who received M2951 during the treatment period will continue with M2951. Subjects who received placebo during the treatment period will discontinue placebo and start treatment with M2951 on Day 85/Day 1 of OLE. The End of Treatment Visit during the treatment period (Visit 8) will be considered Day 1 of the optional extension period.

The Optional Extension Period includes four scheduled visits (Visits 9, 10, 11, and 12), which correspond with Day 14, and the end of Months 1, 3, and 6. Subjects who signed the additional ICF at Visit 8 will undergo the Optional Extension Period assessments as described in the Schedule of Assessments (Table 1).

If a subject discontinues early from the optional extension period, he/she should complete the Safety Follow-Up Visit.

7.1.4 Safety Follow-Up Visit

For subjects who complete the first treatment period of 12 weeks, but do not continue to the optional extension period, assessments during the Safety Follow-Up/End of Trial Visit will be performed approximately 28 days after the last dose of IMP.

Subjects who withdraw from trial treatment or 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.

All subjects discontinuing the Optional Extension Period prematurely, or completing the Optional Extension Period, will have a Safety Follow-up visit.

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, and ethnicity.

7.2.2 Medical History

Information regarding previous medications (as part of medical history) and concomitant medications and procedures will also be recorded.

Medical and RA history data will be recorded, and a complete physical examination, will be performed. Vital signs, including oral temperature, heart rate, respiratory rate, blood pressure, and height will be obtained. All other Baseline measurements, such as safety laboratory parameters, ECG, and CXR, will be assessed.

7.3 Efficacy Assessments

The following tests and procedures have been selected to evaluate the efficacy of M2951 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, ESR, and subject and physician visual analog scales, which are described below.

7.3.1.1 American College of Rheumatology Response Rates

The primary efficacy endpoint is ACR20 at Day 85 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.

ACR Core Set

a. Tender Joint Count (TJC)

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

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The 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 the Screening Visit and will be excluded from evaluation during the trial. The locations (or a listing) of surgical procedures should be documented in the subject's source documents/eCRF pages.

b. Swollen Joint Count (SJC)

For ACR measures, the number of swollen joints will be determined by examination of 66 joints (33 joints on each side of the 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 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 knee joints, 2 ankle joints, 2 tarsus, 10 metatarsophalangeal joints of the feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet.

Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthrosis will be assessed as not swollen, unless there is unmistakable fluctuation. Joint assessments of 1 particular 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 the Screening Visit and will be excluded from evaluation during the trial. The locations (or a listing) of surgical procedures should be documented in the 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 M2951 on the subject's RA.

ACR20

The ACR20 is a primary efficacy measure for which, at Day 85, 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:
  - Subject's Global Assessment of Disease Activity
  - Subject's Assessment of Pain
  - Subject'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

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

7.3.1.2 Visual Analog Scales

Visual analog scales will include the subject's assessment of disease activity and pain, and the HAQ-DI and physician's assessment of disease activity. Patient reported outcome questionnaires (including global assessment of disease activity, self-assessment of pain, and HAQ-DI) must be performed prior to any other assessments at all visits.

Subject'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 the 100 mm horizontal visual analog scales (VAS) where the left end represents no disease activity (symptom free and no arthritis symptoms) and the right end represents maximum disease activity (maximum arthritis disease activity).

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

Subject's Assessment of Pain

The subject will be asked to assess his or her current level of pain by marking a vertical tick on a 100 mm horizontal VAS with the left end marked as "no pain" and the right end marked as "worst possible pain." The scale should be administered prior to the tender and swollen joint count examination.

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

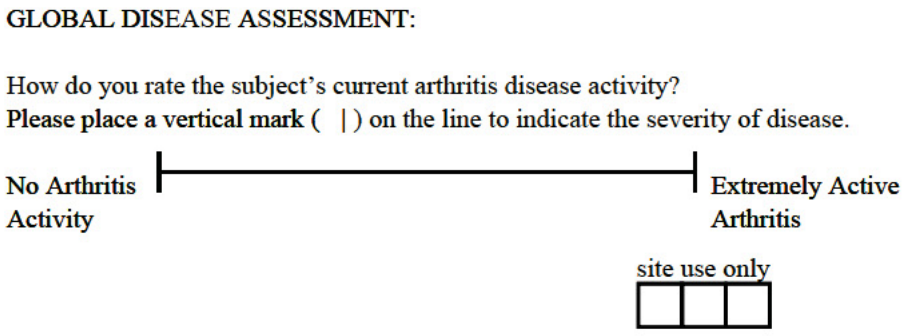
Subject's Assessment of Physical Function

The subject will be asked to complete the HAQ-DI to measure the impact of arthritis on their ability to function in daily life (see Section 7.3.1.4).

Physician's Global Assessment of Disease Activity

The Physician's Global Assessment is used to quantify disease activity. The Physician's Global Assessment will be determined on a continuous VAS on a validated ruler measuring exactly 100-mm (Figure 2). It is based upon the Investigator's assessment of the subject's current disease activity based on the 100-mm horizontal VAS.

Figure 2 Physician Global Assessment Scale



7.3.1.3 Disease Activity Score-C-Reactive Protein (DAS28-hsCRP)

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 Subject's Global Assessment of Disease Activity (21).

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 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints, and 2 knees (22).

DAS28-hsCRP will be derived using the following formula from the DAS28 website (23):

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

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 DAS (ie, patient's global assessment of disease activity).

7.3.1.4 Health Assessment Questionnaire – Disability Index (HAQ-DI)

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 (24-26).

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.

7.3.2 Rheumatoid Factor, anti-CCP, and hsCRP

Samples for RF, anti-CCP, and hsCRP will be collected at visits indicated in Table 1.

Samples will be analyzed by the central laboratory. Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the Laboratory Manual.

7.3.3 Erythrocyte Sedimentation Rate

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

Samples will be analyzed by the local laboratory. Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the Laboratory Manual.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting, and analysis of Baseline medical conditions, adverse events (AEs), and physical examination findings including vital signs 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 Event

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 National Cancer Institute CTCAE, version 4.03 (publication date: 14 June 2010); a descriptive terminology that will be provided in the Manual of Procedures 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 a 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 IMP(s)/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 the IMP, medical history, concomitant medication, course of the underlying disease, trial procedures.

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

Related: Reasonably related to the IMP/trial treatment. The AE could medically (pharmacologically/clinically) be attributed to the IMP/trial treatment 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 one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4.

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 chemotherapy and related hydration therapy application) 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.

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/date of first signature of first informed consent) and continues until the Safety Follow-Up/End of Trial Visit.

Any SAE occurring within 30 days after the last dose of IMP must be reported, even if the subject has discontinued from the trial. Any SAE assessed as related to the IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of the IMP.

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, the eCRF must be completed.

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, 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 the ICH GCP guidelines, 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.

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/End of Trial Visit. All SAEs ongoing at the Safety Follow-Up Visit/End of Trial 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 paper Pregnancy Report Form, which must be transmitted according to the same timelines 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 Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, 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 4, following the timing noted in the Schedule of Assessments (Table 1). All samples should be clearly identified. Sample collection, preparation, and handling/shipment procedures are described in the Laboratory Manual.

For women of childbearing potential, including those who are postmenopausal for less than 12 months, serum pregnancy tests will be performed at initial screening, and urine pregnancy tests will be performed at the visits specified in Table 1.

Additional laboratory tests may be performed after abnormal findings.

Table 4 Clinical Safety Laboratory Evaluations

Screening virology[a]	• Human immunodeficiency virus I and II 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		
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
Hematology	• Hematocrit • Hemoglobin • 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	• International normalized ratio • Partial thromboplastin time		
Urinalysis/microscopy	• pH • Nitrite • Protein • Blood	• Glucose • Ketone bodies • Urobilinogen	• Bilirubin • Specific gravity • Microscopy (white blood cells, red blood cells, casts)[d]
Spot Urine	• Protein	• Creatinine	
Other screening tests[a]	• Quantiferon tuberculosis test	• Thyroid-stimulating hormone	• Serum β-hCG (women only)
Urine	• Urine β-hCG		

β-hCG=beta-human chorionic gonadotropin, IgM=immunoglobulin M.

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 > 2X upper limit of normal.

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

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 (Table 1).

A semi-automated 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 in the semi-supine position with the subject's arm unconstrained by clothing or other material. The blood pressure should be assessed 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 findings during the trial as AEs.

7.4.4.3 12-Lead ECG and Chest X-Ray

A 12-lead ECG will be performed during Screening, predose on Day 85, Month 1 of OLE, and Month 6 of OLE. The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semi-supine position.

The following ECG parameters will be obtained directly from the computerized 12-lead ECG recordings: rhythm, ventricular rate, PR interval, QRS duration, and QT interval. The corrected QT interval 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).

Posterioanterior CXRs will be performed during Screening according to local standard practice. Subjects who had a CXR performed for clinical reasons within 3 months prior to Day 1 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.

7.5 Pharmacokinetic Assessments

For the PK analysis, plasma levels of M2951 will be analyzed by the analytical laboratory selected under responsibility of the Sponsor, using an appropriate validated bioanalytical method.

Venous blood samples for PK analysis will be collected per the Schedule of Assessments (Table 1).

Subjects must be fasting 8 hours prior to visits with PK sampling. Subjects must also fast for 1 hour postdose at these visits. Blood samples for PK analysis will be collected predose and 0.25, 0.5,

1.0, 2.0, 4.0, and 6.0 hours postdose at Day 1 (Visit 2) and Day 29 (Visit 5). See Appendix C for PK blood sample volumes. Subjects who discontinue IMP prior to PK sampling visit days will not have blood obtained for PK.

The exact date/time of sample collections should be recorded in the eCRF. Although every effort should be made to collect PK blood samples according to the Schedule of Assessment, blood samples collected outside of the planned window are not to be considered protocol deviations as long as the actual collection time is recorded, with the exception of the predose sample, which will be considered a deviation if it is not collected predose.

Samples will be collected, labeled, processed, stored, and shipped as detailed in the Laboratory Manual.

7.6 Pharmacodynamic Immunoglobulin Levels Assessments

Blood samples for immunoglobulin levels (IgA, IgM, and IgG and subclasses) will be collected for PD 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.

CCI [redacted]

For blood sample volumes, see Appendix C.

7.7 Pharmacodynamic Biomarker Assessments

Blood samples for biomarkers will be collected at the time points specified in the Schedule of Assessments (Table 1) for biomarker analysis.

Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the Laboratory Manual. The actual date and time of each sample will be recorded. For blood sample volumes, see Appendix C and the Laboratory Manual.

7.7.1 B cell number and B cell Subtypes Assessment

B cell number and B cell subtypes level assessments will be collected from all patients according to the Schedule of Assessments in Table 1.

Blood samples for B cell number and B cell subtypes (eg, IgD, CD27, and CD20) numbers will be obtained predose on visits specified in Table 1. The actual date and time of each sample will be recorded in the eCRF.

7.7.2 Other Exploratory Assessments

CCI [redacted]

[redacted]

8 Statistics

8.1 Sample Size

The trial is powered to demonstrate superiority of M2951+MTX to placebo + MTX in ACR20 response proportion after 84 days of treatment, using a test of the null hypothesis H0: $\Delta \leq 0$ based on the 2-sided 80% confidence interval (CI) for Δ, where Δ is the difference in Day 85 ACR20 response proportion comparing the 2 treatment groups. The null hypothesis H0 will be rejected if the lower limit of the 2-sided 80% CI exceeds zero. It is assumed that the Day 85 ACR20 response proportion in the placebo + MTX treatment group is 0.21 (27), and that the difference in Day 85 ACR20 response proportions between the 2 treatment groups under the alternative hypothesis H1: $\Delta > 0$ is $\Delta = 0.25$ (27, 28).

If the response proportions in the 2 treatment groups are 0.46 and 0.21, respectively, under the alternative hypothesis, then a sample size of approximately 60 mITT subjects randomized 1:1, M2951+MTX:placebo+MTX, provides 80.2% power to demonstrate superiority at the 1-sided 10% significance level. The power calculation is based on a simulation of the 2-sided 80% CI for Δ estimated using the "corrected Miettinen-Nurminen" method (29), conducted in R Cran software version 2.15.2 using the function PropCIs::diffscoreci (version 0.2 5, 2015).

A total of approximately 64 subjects will be randomized to provide 60 mITT subjects in the presence of a 6.25% dropout rate.

An IA will be conducted when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data and DAS28-hsCRP data, or have discontinued treatment prior to Day 29. Point and CI estimates of the Day 29 hsCRP change from Baseline difference, comparing the 2 treatment groups, will be estimated for use in internal decision making. A similar analysis of Day 29 DAS28-hsCRP will be performed. The IA will not be used to alter the design of the trial. No adjustment will be made to the 1-sided α of 10% to be used in the primary analysis at the end of the 12-week blinded treatment period.

A final analysis will be conducted at the end of the trial when all subjects have completed the Safety Follow-up visit or prematurely discontinued from study.

8.2 Randomization

Eligible subjects will be randomized in a blinded fashion by the IWRS in a ratio of 1:1 to M2951 dose of 50 mg bid + MTX or placebo + MTX, CCI [redacted]

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoint is the ACR20 response rate at Day 85.

8.3.2 Secondary Endpoints

The key secondary endpoint is the percent change in hsCRP from Baseline to Day 29.

Other secondary endpoints (during the double-blind treatment period):

Efficacy:

- ACR50/ACR70 response at each time point assessed
- Percent change in hsCRP from Baseline to Day 85
- Change from Baseline in DAS28-hsCRP score at Day 29
- Change from Baseline in DAS28-hsCRP score at Day 85
- Percentage of subjects with DAS28-hsCRP < 3.2 (well-controlled disease) at Day 85
- Percentage of subjects with DAS28-hsCRP < 2.6 at Day 85
- Change from Baseline in ESR, anti-CCP, rheumatoid factor (at Days 29 and 85)
- Change from Baseline to Day 85 in subject's self-assessments including:
  - Global assessment of disease activity (VAS, see Section 7.3.1.1)

- Self-assessment of pain (VAS)
- Self-assessment of disability (HAQ-DI)

- Change from Baseline to Day 85 in Physician's Global Assessment of Disease Activity (VAS).

Safety:

- Nature, incidence and severity of TEAEs
- Change from Baseline in vital signs and 12-lead ECG data
- Change from Baseline in standard hematology and chemistry laboratory parameters including liver function tests, amylase/lipase, and urinalysis.

Pharmacokinetics and pharmacodynamics:

- Plasma concentrations of M2951 after administration on Day 1 and Day 29, PK parameters calculated for Day 1 and Day 29: $AUC_{0\text{-}6h}$, C_{max}, C_{pre} (Day 29), t_{max}, $R_{acc(AUC0\text{-}6h)}$, and $R_{acc(Cmax)}$. Further endpoints may be defined in the SAP.
- Absolute concentrations and change from Baseline in immunoglobulin levels (IgA, IgM, and IgG, and subclasses) on Day 29 and Day 85
- Absolute numbers and change from Baseline in B cell numbers and subsets on Day 85.

8.3.3 Other Endpoints

CCI [redacted]

8.3.4 Endpoints for Open-label Extension

The endpoints for the open-label extension are as follows:

Safety:

- Nature, incidence and severity of TEAEs
- Change from Baseline in vital signs and 12-lead ECG data
- Change from Baseline in standard hematology and chemistry laboratory parameters including liver function tests, amylase/lipase, and urinalysis.

Efficacy:

- ACR50/ACR70 response at Month 6
- Percent change in hsCRP from Baseline to Month 6

- Change from Baseline in DAS28-hsCRP score at Month 6
- Percentage of subjects with DAS28-hsCRP < 3.2 (well-controlled disease) at Month 6
- Percentage of subjects with DAS28-hsCRP < 2.6 at Month 6
- Change from Baseline in ESR, anti-CCP, rheumatoid factor (at Month 6)
- Change from Baseline to Month 6 in subject's self-assessments including:
  - Global assessment of disease activity (VAS, see Section 7.3.1.2)
  - Self-assessment of pain (VAS)
  - Self-assessment of disability (HAQ-DI)
- Change from Baseline to Month 6 in Physician's Global Assessment of Disease Activity (VAS).

8.4 Analysis Sets

Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo. The Safety Analysis Set will be used for all demographic/baseline characteristics and safety analyses.

The open-label extension (OLE) Safety Analysis Set will include all subjects who received at least 1 dose of M2951 during the open-label extension period. The OLE Safety Analysis Set will be used for all safety analyses at time of final analysis.

Modified Intent to Treat Analysis Set

The Modified Intent-to-Treat (mITT) Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point postdose. The mITT Analysis Set will be used for the analysis of all efficacy endpoints. For the IA, the mITT Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo and have at least 1 available hsCRP evaluation at a time point postdose.

The OLE Modified Intent-to-Treat (OLE mITT) Analysis Set will include all subjects who received at least 1 dose of M2951 during open-label extension period and have at least 1 available ACR20 evaluation at a time point after first dose in open-label extension period. The OLE mITT Analysis Set will be used for the analysis of all efficacy endpoints at time of final analysis.

Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point postdose without any important deviations or events that may impact the quality of the data or alter the evaluation of the PK. The PK Analysis Set will be used for all PK analyses. Subjects who receive placebo will not be included.

Pharmacodynamic Analysis Set

The PD Analysis Set will include all subjects who receive at least 1 dose of M2951 or placebo and have at least 1 measured PD endpoint, not including CCI [redacted] at a scheduled PD time point postdose without deviations or important events affecting PD, and who provide evaluable PD data. All PD analyses, not including CCI [redacted], will be based on this analysis set.

CCI [redacted]

[redacted]

The "as-treated" principle will be applied to all evaluations, except those based on the mITT Analysis Set, ie, subjects who receive a treatment other than the one assigned by randomization will be analyzed by the actual treatment received.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

The following descriptive statistics will be used as applicable to summarize the trial data by treatment group and overall unless otherwise specified:

- Continuous variables: number of non-missing and missing observations, mean, standard deviation (SD), median, first and third quartiles, minimum, and maximum
- Categorical variables: frequencies and percentages.

In general, missing data will not be imputed (see Section 8.5.2). A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

All subjects will be included in individual subject data listings. All derived data will also be listed.

Statistical analysis will be performed using the computer program package SAS® System for Windows (version 9.4 or higher; PPD [redacted]).

The Baseline measurement is defined as the predose value reported on Day 1 or the screening value as relevant in accordance with the Schedule of Assessments (Table 1). Further details on all statistical analyses will be presented in the SAP that will be finalized before database lock.

Changes in the conduct of the trial or planned analyses will be reported in the corresponding section of the SAP, if applicable, and in the clinical trial report.

Significance levels will not be adjusted for multiplicity. Specifically, the 2-sided 80% CI for Δ in Day 85 ACR20 proportions, estimated at the time of the final analysis, will not be adjusted to

account for the 2-sided 80% CI for the difference Δ in Day 29 hsCRP change from Baseline between M2951 + MTX and placebo + MTX, estimated at the time of the IA. Indeed, the IA will not be used to alter the design of the trial; it will be conducted only for internal decision making.

8.5.2 Analysis of Primary Endpoints

The hypotheses tested are as follows:

- H0: Difference in ACR20 response rates at Day 85 (M2951 versus placebo) ≤ 0.
- H1: Difference in ACR20 response rates at Day 85 (M2951 versus placebo) > 0.

Tests will be based on the 2-sided 80% CI for Δ.

The Day 85 ACR20 proportion and a 2-sided 80% CI will be provided for each treatment group. The difference Δ in ACR20 proportions between M2951 + MTX and placebo + MTX, and a 2-sided 80% CI for Δ, based on the "corrected Miettinen-Nurminen" method (29) - method of Mee interval corrected with Miettinen and Nurminen factor n/(n+1), n being the total number of evaluable randomized subjects - will be provided. The primary analysis will be based on the mITT Analysis Set using Last Observation Carried Forward for imputation of missing values and will reject the null hypothesis H0: Δ ≤ 0 if the lower limit of the CI exceeds zero.

A sensitivity analysis will be performed based on non-responder imputation for missing values, ie, subjects without observed data at Day 85 are considered non-responders.

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Efficacy Endpoints

Descriptive statistics for the percent change in hsCRP from Baseline to Day 29 will be presented by treatment group. A point estimate and 2-sided 80% CI for the difference Δ in Day 29 hsCRP change from Baseline between subjects treated with M2951+MTX and subjects treated with placebo + MTX will be provided.

The Day 85 hsCRP change from Baseline will be analyzed in the same way as the Day 29 hsCRP change from Baseline. This analysis will also be applied to Day 85 DAS28-hsCRP score change from Baseline.

- The Day 85 ACR50 and ACR70 proportions will be analyzed in the same way as the Day 85 ACR20 proportions. This analysis will also be applied to Day 85 "DAS28-hsCRP < 3.2" proportion and Day 85 "DAS28-hsCRP < 2.6" proportion.

The ACR20/50/70 proportions and proportion of subjects achieving DAS28-hsCRP < 3.2 (well-controlled disease) or DAS28-hsCRP < 2.6 will be tabulated by treatment group and time point.

Descriptive statistics will be tabulated by treatment group and time point for the following continuous variables, both absolute value and change from baseline: DAS28-hsCRP score, hsCRP,

ESR, anti-CCP, and rheumatoid factor, subject's global assessment of disease activity, subject's assessment of pain, subject's self-assessment of disability (HAQ-DI), and Physician's Global Assessment of Disease Activity.

8.5.3.2 Safety Endpoints

Analysis of safety secondary endpoints is described in Section 8.5.5.

8.5.3.3 Pharmacokinetics

Pharmacokinetic calculations will be performed, if appropriate, using noncompartmental analysis, using commercial software such as Phoenix® WinNonlin® (Version 6.4 or higher). The actual elapsed time from dose will be used in the final PK parameter calculations. Data handling and analysis procedures will be detailed in the SAP.

Plasma concentrations and derived PK parameters of M2951 will be presented descriptively by time point for the PK analysis set. The PK variables will be summarized by the number of observations, mean, geometric mean, median, SD, standard error of mean, minimum, maximum, and coefficient of variation. Concentration values below the lower limit of quantification (LLOQ) will be taken as zero for descriptive statistics.

Individual plasma and mean (± SD) concentration time plots will be provided using a linear and semi-logarithmic scale.

For each subject with PK data, the following PK parameters will be calculated for M2951:

Day 1 and Day 29

- $AUC_{0\text{-}6h}$ Area under the plasma concentration-time curve from time zero to 6 hours after dosing
- C_{max} Maximum observed plasma concentration
- C_{pre} The concentration observed immediately before next dosing (Day 29 only)
- t_{max} Time to reach maximum plasma concentration
- $R_{acc(AUC0\text{-}6h)}$ Accumulation ratio for AUC, calculated as $AUC_{0\text{-}6h,Day29}/AUC_{0\text{-}6h,Day1}$
- $R_{acc(Cmax)}$ Accumulation ratio for C_{max}, calculated as $C_{max,Day29}/C_{max,Day1}$

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the SAP.

The concentrations of M2951 and PK parameters will be listed and summarized by trial day. In addition to standard descriptive statistics (mean, SD, median, minimum/maximum, and 25th and 75th percentile), analysis of PK data will include the geometric mean, the geometric coefficient of variation, and a 95% CI for the geometric mean. The PK concentration values below the LLOQ will be set to zero prior to computing descriptive statistics of PK concentrations. An additional descriptive statistics table will be created with values below the LLOQ set to missing.

8.5.3.4 Pharmacodynamics

The analysis set for the PD analyses will be the relevant PD Analysis Set.

Data on immunoglobulin levels and B cell numbers and subtypes (observed values, change, and percent change from Baseline, with Baseline defined as the predose sample obtained on Day 1 or the screening sample, as relevant) will be descriptively summarized in tabular and/or graphic format, as appropriate to the data.

Potential PK/PD correlations may be explored and reported separately.

8.5.4 Analysis of Exploratory Endpoints

CCI [redacted]

8.5.5 Analysis of Safety and Other Endpoints

The analysis set for the safety assessments will be the Safety Analysis Set for the primary analysis and the OLE Safety Analysis Set for final analysis.

All safety endpoints will be summarized by treatment group unless otherwise specified. Analyses including both for the first 12-week treatment period and open-label extension period data will be summarized according to treatment groups 'M2951+MTX' and 'Placebo+MTX/M2951'.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded using NCI-CTCAE v4.03 toxicity grades (20). Adverse events with missing classification concerning IMP relationship will be considered related to the IMP.

The number and percentage of subjects experiencing 1 or more TEAEs will be summarized according to the MedDRA system organ classes and preferred terms by treatment group, relationship to IMP, and severity. Exposure-adjusted incidence rates of TEAEs will also be reported according to the MedDRA system organ class and preferred term.

Clinical laboratory parameters being monitored for safety will be summarized using descriptive statistics, by postdose shifts relative to Baseline for relevant parameters using relevant cutoffs as detailed in the SAP, box and whisker plots as relevant, and data listings of clinically significant abnormalities/outliers. Subject listings and summary statistics at each assessment time will be presented using the International System of Units (SI units).

Observed values and change from Baseline in vital signs and ECG data will be summarized for each treatment group using descriptive statistics. Clinically noteworthy physical examination, ECG, and CXR findings for individual subjects will be listed and summarized as appropriate.

At the end of the study, for final analysis, safety endpoints will be reported both for the first 12-week treatment period and for entire study, by treatment group, based on OLE Safety Analysis Set.

8.5.6 Analysis of Open-label Extension Endpoints

Efficacy data collected from the 6-month open-label extension period will be summarized. Details will be provided in the SAP.

Safety data collected from the 6-month open-label extension period will be analyzed as described in Section 8.5.5.

8.6 Interim and Additional Planned Analyses

There will be 3 analyses: (1) an interim analysis (IA), triggered when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data, or have discontinued treatment prior to Day 29, (2) a primary analysis, triggered when 100% of subjects enrolled have reached Day 85 of treatment or have discontinued treatment prior to Day 85, and (3) a final analysis, triggered when 100% of subjects enrolled complete all study parts, or discontinue prematurely from study.

Interim Analysis

The percent change in hsCRP from Baseline to Day 29 will be the key endpoint evaluated at the IA. Descriptive statistics will be presented by treatment group. A point estimate and 2-sided 80% CI for the difference Δ in Day 29 hsCRP change from Baseline between subjects treated with M2951+MTX and subjects treated with placebo + MTX will be provided. In addition, the change in DAS28-hsCRP from Baseline to Day 29 will be evaluated using the same approach as used for change in hsCRP. Some safety, baseline characteristics, and disposition data will also be summarized by treatment group at the time of IA.

The results of this IA will be used for internal decision making only and will not impact the conduct of the trial. See Section 6.10 for more details regarding limited unblinding.

Primary Analysis

When the last subject reaches Day 85 of treatment or discontinues from treatment prematurely prior to Day 85, the protocol violations are determined, the SAP is signed, the database is locked for the first 12-week treatment period for all randomized patients for the primary analysis, and the data file verified, the drug codes will be broken and made available for the primary data analysis. All endpoints, demographics and safety data will be analyzed at that time.

Final Analysis

The final analysis will occur only when the last subject completes all study parts, the protocol violations are determined, the database is locked for the final analysis, and the data file verified. Only some safety and key efficacy data will be summarized.

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

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the US 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 Food Drug Administration), the Investigator and all Subinvestigators are obliged to disclose any financial interest in which they, their spouses, or their dependent children may have in the Sponsor or the Sponsor's product under trial. 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. 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 the ICH GCP guidelines and 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 Informed Consent Form, as above.

After the information is provided by the Investigator, the Informed Consent Form must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing, and

inspection purposes. A copy of the signed and dated information and Informed Consent Form 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. 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.

A separate Subject Information Sheet and Informed Consent Form will be signed prior to collection of samples for biomarker analysis.

A separate ICF will be signed at the End of Treatment Visit by subjects wishing to participate in the optional extension period.

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 Medical Monitor, audits, and regulatory inspections, but patient confidentiality will be strictly maintained.

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

The duration of storage of blood samples for biomarkers after trial completion will be according to the ICF and according to country regulation. The samples may be reanalyzed for newly identified markers or with new or improved technology. The samples will be destroyed or fully anonymized according to ICF and according to country regulation.

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 the 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, they 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 in the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

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

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 the favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version, and the Subject Information Sheet and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (eg, IMP Dossier, Subject Information Sheet, and Informed Consent Form) 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 manner. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring 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 the eCRFs and any other associated documents forwarded to the Sponsor or its designated organization contain no mention of any subject names.

For subject-reported outcome data such as QoL and pain assessments, 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. Electronic PDF 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 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, 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 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 Informed Consent Forms. 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 the ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP guidelines 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 clinical trial report, 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 for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the 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 clinical trial report 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.

10.6.2 Publication

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 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 A Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of M2951 in Subjects with Rheumatoid Arthritis on Stable Methotrexate Therapy
EudraCT Number:	2016-000064-42
Clinical Trial Protocol Date / Version:	02 September 2016/Version 3.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD

_____ _____ September 2, 2016

Signature Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: EMD Serono Research & Development Institute, Inc.

Address: 45A Middlesex Turnpike, Billerica, MA 01821, USA

Telephone number: PPD

E-mail address: PPD

Signature Page – Coordinating Investigator

Trial Title:	A Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of M2951 in Subjects with Rheumatoid Arthritis on Stable Methotrexate Therapy
EudraCT Number:	2016-000064-42
Clinical Trial Protocol Date / Version:	02 September 2016/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.

PPD

Signature

PPD

Date of Signature

P
P

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

Signature Page – Principal Investigator

Trial Title:	A Phase IIa Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of M2951 in Subjects with Rheumatoid Arthritis on Stable Methotrexate Therapy
EudraCT Number:	2016-000064-42
Clinical Trial Protocol Date / Version:	02 September 2016/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:	PPD
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Address:	45A Middlesex Turnpike, Billerica MA 01821, USA
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Appendix B Joint Count Assessment Forms

66/68 JOINT EVALUATION												
	Subject Right						Subject 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 C Blood Volumes

Blood will be drawn on 9 separate days/occasions. On the day of PK/PD sampling, subjects will have an intravenous catheter inserted to facilitate obtaining the multiple samples required. The planned maximum volume of blood to be drawn in this trial is approximately 271.2 mL over the 4-week Screening Period, 12-week Treatment Period, and 4-week Follow-Up Period (20 weeks total) and 72 mL during the Extension Period.

Assay	Sample (mL)	Number of Samples during 12-week Treatment Period	Subtotal Volume (mL) during 12-week Treatment Period	Number of Samples during Extension Period	Subtotal Volume (mL) during Extension Period
Screening tests: hematology, chemistry (including LFTs), coagulation, β-hCG, viral serology (HBsAg, Anti-HCV, HIV)	17.2	1	17.2	n/a	n/a
Chemistry (including LFTs), hematology[a]	5.5	8	44	4	42
Immunoglobulins[b]	5	3	15	2	10
RF, anti-CCP	8	6	48	1	8
ESR	2	6	12	1	2
QuantiFERON-TB test	3	1	3	n/a	n/a
PK	1	14	28	n/a	n/a
CCI					
B cell count and subtypes	5	5	25	2	10
CCI					
		Total	**271.2**		**72**

Note: Blood volumes are estimated based on samples expected to be taken during scheduled visits.
ALT=Alanine aminotransferase, AST=Aspartate aminotransferease, β-hCG=beta human chorionic gonadotropin, CCI CCI CCP=cyclic citrullinated peptide, ESR=erythrocyte sedimentation rate, GGT=gamma-glutamyl transferase, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, hsCRP=high sensitivity C-reactive protein, LDH=lactate dehydrogenase, LFT=liver function tests, n/a=not applicable, RF=rheumatoid factor, PK=pharmacokinetics, TB=tuberculosis.

[a] Chemistry including LFTs will include: sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, total protein, albumin, amylase, lipase, AST, ALT, GGT, LDH, alkaline phosphatase, lactate dehydrogenase, bilirubin, uric acid as shown in Table 4.

[b] Immunoglobulins will include IgA, IgG, IgM, IgG1, IgG2, IgG3, and IgG4.

C

Appendix D Protocol Versions and List of Changes

Table of Protocol Versions

Protocol	Submission to Health Authority (Yes/No/ Notification only)	Date	Region or Country	Included in the current document (Y/N)
Version 2.0	Yes	11 May 2016	Global	Yes
Version 3.0	Yes	02 September 2016	Global	Yes

Protocol Version 2

Scope: Global

Effective date: 11 May 2016

Rationale

The purpose of this protocol amendment is to incorporate feedback from the Voluntary Harmonisation Procedure assessment:

- To modify the text for contraceptive measures to specify "highly effective" contraception, according to the definitions provided by the Clinical Trials Facilitation Group Guideline.

List of Changes

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

Comparison with Clinical Trial Protocol Version 1.0, 28 February 2016

Change	Section(s)	Previous Wording	New Wording
Modification of text to specify 'highly effective' contraceptive measures	Synopsis, Diagnosis and key inclusion and exclusion criteria 5.3.1 Inclusion Criteria	[…] • Women of childbearing potential must use acceptable methods of contraception for 4 weeks prior to randomization, throughout the trial, and for 90 days after the last dose of IMP. For the purposes of this trial: ○ 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 ○ Acceptable contraception is defined as use of either 2 barrier methods (eg, female diaphragm and male condom), or 1 barrier method in conjunction with one of the following: spermicide, an intrauterine device, or hormonal contraceptives (implant or oral) […]	[…] • Women of childbearing potential must use **a highly effective** ~~acceptable~~ method~~s~~ of contraception **combined with one supplementary barrier method** for 4 weeks prior to randomization, throughout the trial, and for 90 days after the last dose of IMP. For the purposes of this trial: ○ 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 ○ ~~Acceptable contraception is defined as use of either 2 barrier methods (eg, female diaphragm and male condom), or 1 barrier method in conjunction with one of the following: spermicide, an intrauterine device, or hormonal contraceptives (implant or oral)~~ **The definition of highly effective contraception includes:** ▪ **combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; oral, intravaginal or transdermal** ▪ **progestogen-only hormonal contraception associated with inhibition of ovulation; oral, injectable, implantable** ▪ **intrauterine device (IUD)** ▪ **intrauterine hormone-releasing system (IUS)** ▪ **bilateral tubal occlusion** ▪ **vasectomized partner** ▪ **sexual abstinence** ○ **Supplementary barrier methods include:** ▪ **male or female condom with or without spermicide** ▪ **cap, diaphragm or sponge with spermicide** […]

Change	Section(s)	Previous Wording	New Wording
Modification of text to specify 'highly effective' contraceptive measures	5.3.1 Inclusion Criteria	[…] Men must agree to use and to have their female partners use acceptable contraception as defined above for at least 90 days after the last IMP administration.	[…] Men must agree to use and to have their female partners use ~~acceptable~~ **a highly effective method of** contraception **combined with one supplementary barrier method** as defined above for at least 90 days after the last IMP administration.

Protocol Version 3

Scope: Global

Effective date: 02 September 2016

Rationale

The purpose of this protocol amendment is to include an optional open label extension period for subjects to continue receiving benefit from the IMP.

List of Changes

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

Comparison with Clinical Trial Protocol Version 2.0, 11 May 2016

Change	Section(s)	Previous Wording	New Wording
Insertion of IND number	Cover page	Not applicable	~~Not applicable~~**122,963**
Modification of text to change planned trial period	Synopsis	June 2016 to March 2017	~~June~~**July** 2016 to March 2017
Modification of text to include open-label extension period	Synopsis: Objectives	Exploratory objectives: CCI [redacted]	Exploratory objectives: CCI [redacted] **Open-label extension objectives:** **To evaluate the on-going safety and efficacy of M2951 in an open-label extension with treatment at 50 mg bid for an additional 6 months.**
	Synopsis: Investigational Medicinal Product: dose/mode of administration/dosing schedule	M2951 (50 mg twice daily [bid]) will be administered as 2 x 25 mg capsules bid for 12 weeks. Identical capsules filled with mannitol for placebo will be provided.	M2951 (50 mg twice daily [bid]) will be administered as 2 x 25 mg capsules bid **during the**~~for~~ 12**-** week~~s~~ **treatment period.** Identical capsules filled with mannitol for placebo will be provided. **M2951 will be administered as 2 x 25 mg tablets bid during the optional extension period.**
Modification of text to include open-label extension period	Synopsis: Methodology	Total duration of subject participation is approximately 140 days (20 weeks): • Screening: 28 days (4 weeks) • Treatment: 84 days (12 weeks) • Safety Follow-Up: 28 days (4 weeks). […] Subjects will have trial visits weekly for the first 3 weeks of treatment; bi-weekly up until 8 weeks of treatment; a final On-Treatment Visit on Day 85, and then return for 1 Follow-Up Visit approximately 28 days (4 weeks) after the last dose of IMP.	Total duration of subject participation is approximately ~~140 days (20 weeks~~ **between 5 months (20 weeks) to 11 months (46 weeks), which includes**: • Screening: 28 days (4 weeks) • Treatment: 84 days (12 weeks) • **Optional 6-month open-label extension period (26 weeks)** • Safety Follow-Up: 28 days (4 weeks). […] Subjects will have trial visits weekly for the first 3 weeks of treatment; bi-weekly up until 8 weeks of treatment; a final On-Treatment Visit on Day 85, and then return for 1 Follow-Up Visit approximately 28 days (4 weeks) after the last dose of IMP.

Change	Section(s)	Previous Wording	New Wording
			After completing the 12-week treatment period, subjects will be offered the opportunity to participate in an optional 6-month open-label extension period where all subjects will receive M2951. For subjects who choose to participate in the optional extension period, the duration of participation will last a total of approximately 11 months. **Subjects who continue to receive M2951 during the extension period will also be required to undergo the Safety Follow-up Visit scheduled for approximately 28 days after the last treatment visit.**
Modification of text to include open-label extension period	Synopsis: Endpoints	**Other secondary endpoints:** […] Exploratory: [redacted]	**Other secondary endpoints <u>(during the double-blind treatment period):</u>** […] Exploratory: [redacted] **<u>Endpoints for open-label extension:</u>** **Safety:** • **Nature, incidence, and severity of TEAEs** • **Change from Baseline in vital signs and 12-lead ECG data** • **Change from Baseline in standard hematology and chemistry laboratory parameters including liver function tests, amylase/lipase, and urinalysis.** **Efficacy:** • **ACR50/ACR70 response at Month 6** • **Percent change in hsCRP from Baseline to Month 6** • **Change from Baseline in DAS28-hsCRP score at Month 6** • **Percentage of subjects with DAS28-hsCRP < 3.2 (well-controlled disease) at Month 6** • **Percentage of subjects with DAS28-hsCRP < 2.6 at Month 6** • **Change from Baseline in ESR, anti-CCP, and rheumatoid factor (at Month 6)** • **Change from Baseline to Month 6 in subject's self-assessments including:** • **Global assessment of disease activity (VAS)**

Change	Section(s)	Previous Wording	New Wording
			• **Self-assessment of pain (VAS)** • **Self-assessment of disability (HAQ-DI)** • **Change from Baseline to Month 6 in Physician's Global Assessment of Disease Activity (VAS).**
Modification to align with main text	Synopsis: Inclusion/exclusion criteria	• hsCRP ≥ 3.0 mg/L […] • Subjects with current household contacts with active TB will also be excluded unless treated and evidence of household contacts being treated. […] • Significant cytopenia including neutrophil count < 1,500/ mm^3, or platelet count < 75,000/mm^3.	• hsCRP ≥ 3.**6** mg/L […] • Subjects with current household contacts with active TB will also be excluded ~~unless treated and evidence of household contacts being treated.~~ […] • Significant cytopenia including **absolute** neutrophil count < 1,500/mm^3, ~~or~~ platelet count < **100**~~75~~,000/mm^3.**, or absolute lymphocyte count < 1,000/mm^3**
Modification of text to include open-label extension period	Synopsis: Planned trial and treatment duration per subject	**Planned trial and treatment duration per subject:** Total duration of subject participation is approximately 140 days (20 weeks), which includes: • Screening: 28 days (4 weeks) • Treatment: 84 days (12 weeks) • Safety Follow-Up: 28 days (4 weeks)	**Planned trial and treatment duration per subject:** Total duration of subject participation is approximately **between 5 months (20 weeks) to 11 months (46 weeks)**~~140 days (20 weeks)~~, which includes: • Screening: 28 days (4 weeks) • Treatment: 84 days (12 weeks) • **Optional 6-month open-label extension period (26 weeks)** • Safety Follow-Up: 28 days (4 weeks) **After completing the 12-week treatment period, subjects will be offered the opportunity to participate in an optional 6-month open-label extension period with M2951. For subjects who choose to participate in the optional extension period, the duration of participation will last a total of approximately 11 months.**
Modification of text to include open-label extension period	Synopsis: Statistical methods	The sample size of 60 evaluable subjects was chosen to provide 80% power to demonstrate superiority of M2951+MTX to placebo + MTX for the primary endpoint at the 1-sided 10% level. Eligible subjects will be randomized 1:1 to treatment with M2951 or placebo through a central randomization process by an Interactive Web Response System (IWRS). Approximately 64 subjects will be randomized under the assumption of a 6.25% drop-out rate. An interim analysis (IA) will be conducted when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data, or have	The sample size of 60 evaluable subjects was chosen to provide 80% power to demonstrate superiority of M2951+MTX to placebo + MTX for the primary endpoint at the 1-sided 10% level. Eligible subjects will be randomized 1:1 to treatment with M2951 or placebo through a central randomization process by an Interactive Web Response System (IWRS). Approximately 64 subjects will be randomized under the assumption of a 6.25% drop-out rate. **There will be 3 analyses: (1) an interim analysis (IA), triggered when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data, or have discontinued treatment prior to Day 29, (2) a primary analysis, triggered when 100% of subjects enrolled have reached Day 85 of treatment or have discontinued treatment prior to Day 85, and (3) a**

<table>
<tr><th>Change</th><th>Section(s)</th><th>Previous Wording</th><th>New Wording</th></tr>
<tr><td></td><td></td><td>discontinued treatment prior to Day 29. Point estimate and confidence interval (CI) estimates of the Day 29 hsCRP change from Baseline difference, comparing the 2 treatment groups, will be estimated for use in internal decision making. In addition, the change in DAS28-hsCRP from Baseline to Day 29 will be evaluated using the same approach as used for change in hsCRP. The IA will not be used to alter the design of the trial. No adjustment will be made to the 1-sided α of 10% to be used in the final analysis at the end of the trial.</td><td>final analysis, triggered when 100% of subjects enrolled complete all study parts, or discontinue prematurely from study.
<s>An interim analysis (IA) will be conducted when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data, or have discontinued treatment prior to Day 29.</s> The percent change in hsCRP from Baseline to Day 29 will be the key endpoint evaluated at the IA. Point estimate and confidence interval (CI) estimates of the Day 29 hsCRP change from Baseline difference, comparing the 2 treatment groups, will be estimated for use in internal decision making. In addition, the change in DAS28-hsCRP from Baseline to Day 29 will be evaluated using the same approach as used for change in hsCRP. The IA will not be used to alter the design of the trial. No adjustment will be made to the 1-sided α of 10% to be used in the <s>final</s> primary analysis at the end of the first treatment period (12 weeks)<s>trial</s>.
[…]
In addition, efficacy and safety data collected during the open-label extension period will be summarized.</td></tr>
<tr><td>Modification of text to include open-label extension period</td><td>Table 1 - Schedule of Assessments</td><td>(Refer to Table 1 in previous version)

[a] A complete physical examination will be performed at Screening, and repeated on Days 29, 85, and 113.
[b] Vital signs including height, weight, oral temperature, seated blood pressure, pulse rate, and respiratory rate will be assessed predose at every trial visit (height measured only at Screening).
[…]

[d] Concomitant medications will be recorded at Screening and Day 1, and any changes solicited/recorded at every trial visit, and with any ad hoc telephone contacts.
[e] Blood samples for hematology and chemistry will be obtained at Screening, predose at Visits 2 through 8, and at Safety Follow-Up (Visit 9). See Table 4 for detailed assessments.
[…]
[h] Samples for rheumatoid factors (IgG-RF, IgM-RF, IgA-RF) and anti-CCP antibodies will be obtained at Screening, predose at Visits 4, 5, 7, 8, and at Safety Follow-Up (Visit 9). ESR will also be collected</td><td>(Trial week numbers were corrected as follows: W4 changed to W5, W6 to W7, W8 to W9, and W12 to W13. The Safety Follow-Up/End of Trial Visit was clarified to occur at approximately 28 days post last dose. At Visit 8, an “(X)” was added to the ICF row to indicate signature of a new ICF will be collected for those participating in the optional extension period. An “(X)” was also added to IMP dispensation to reflect the changes due to OLE. Columns for Visits 9-12 and assessments performed during the optional open-label extension period were inserted as shown below. Footnotes a and b were added to Table 1 and lettering of subsequent footnotes were updated sequentially.)
<table>
<tr><th>Trial Period</th><th colspan="4">Optional Open-Label Extension Period</th></tr>
<tr><th>Trial Visit #</th><th>9</th><th>10</th><th>11</th><th>12</th></tr>
<tr><th>Trial Week</th><th></th><th></th><th></th><th></th></tr>
<tr><th>Trial Day</th><th>Day 14</th><th>Month 1</th><th>Month 3</th><th>Month 6</th></tr>
<tr><th>Visit Window (days)</th><th>±2</th><th>±7</th><th>±7</th><th>±7</th></tr>
<tr><td>Informed consent</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Demographics</td><td></td><td></td><td></td><td></td></tr>
<tr><td>RA and other medical history, medications history</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Inclusion/exclusion criteria</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Complete physical examination[c]</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Vital signs[d]</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>12-lead ECG</td><td></td><td>X</td><td></td><td>X</td></tr>
<tr><td>Chest X-ray[e]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Concomitant medications[f] and procedures</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Hematology, chemistry (incl. LFTs)[g]</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table></td></tr>
</table>

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<tr><th>Change</th><th>Section(s)</th><th>Previous Wording</th><th>New Wording</th></tr>
<tr>
<td></td>
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<td>separately at these same time points.
[i] Samples for hsCRP will be obtained at Screening, predose at Visits 2, 4, 5, 7, 8, and at Safety Follow-Up (Visit 9).
[…]
[l] For female subjects only, a serum pregnancy test will be collected at Screening, and a urine pregnancy test will be collected predose at Visits 1, 5, 7, 8, and at Safety Follow-Up (Visit 9).
[m] Subjects should be fasting 8 hours prior to visits with PK sampling. Blood samples for PK analysis will be collected predose and 0.25, 0.5, 1.0, 2.0, 4.0, and 6.0 hours postdose at Day 1 (Visit 2) and Day 29 (Visit 5). Subjects who discontinue IMP prior to PK sampling visit days will not have blood obtained for PK.
[…]

[q] The IMP will be dispensed after randomization on Day 1 and thereafter at each planned trial visit. All remaining IMP will be collected at Visit 8.</td>
<td>
<table>
<tr><td>Coagulation[h]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Urinalysis, microscopy, urine protein/creatinine ratio</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Immunoglobulins[i]</td><td></td><td></td><td>X</td><td>X</td></tr>
<tr><td>RF and anti-CCP[j]</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>ESR[j]</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>hsCRP[k]</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>B cell numbers and subtypes[l]</td><td></td><td></td><td>X</td><td>X</td></tr>
<tr><td>Viral serology[m]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Tuberculosis test[m]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>TSH</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pregnancy test (serum β-hCG)[n]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Urine pregnancy test[n]</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Pharmacokinetic sampling[o]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CCI [redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>RA disease activity assessment[r]</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Randomization</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Dispense/review/collect subject diary</td><td></td><td></td><td></td><td></td></tr>
<tr><td>IMP dispensation[s]</td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>IMP administration[t]</td><td colspan="4">Daily oral administration</td></tr>
<tr><td>IMP compliance[u]</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>AE evaluation[v]</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table>
[a] All subjects, whether not continuing to the optional extension period, continuing to the optional extension period, or early terminating from the study will undergo the Safety Follow-Up/End of Trial Visit approximately 28 days after last dose.
[b] Subjects who participate in the optional extension period will sign an ICF at Visit 8. The End of Treatment Visit during the treatment period (Visit 8) will be considered Day 1 of the optional extension period.
[c] A complete physical examination will be performed at Screening, and repeated on Days 29, 85, <s>and 113</s>at each visit during the optional extension period, and the Safety Follow-up visit.
[d] Vital signs including height, weight, oral temperature, seated blood pressure, pulse rate, and respiratory rate will be assessed predose at every trial visit (height measured only at Screening), including visits during the optional extension period and Safety Follow-up visit.
[…]
[f] Concomitant medications will be recorded at Screening and Day 1, and any changes solicited/recorded at every trial visit (including visits during the optional extension period), and with any ad hoc telephone contacts.
[g] Blood samples for hematology and chemistry will be obtained at Screening, predose at Visits 2 through 8, at each visit during the optional
</td>
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</table>

Change	Section(s)	Previous Wording	New Wording
			extension period, and at **the** Safety Follow-Up ~~(~~Visit ~~9)~~. See Table 4 for detailed assessments. […] [j] Samples for rheumatoid factors (IgG-RF, IgM-RF, IgA-RF) and anti-CCP antibodies will be obtained at Screening, predose at Visits 4, 5, 7, 8, **(at Visit 12 during OLE),** and at Safety Follow-Up ~~(~~Visit ~~9)~~. ESR will also be collected separately at these same time points. [k] Samples for hsCRP will be obtained at Screening, predose at Visits 2, 4, 5, 7, 8, **(at Visit 12 during OLE),** and at Safety Follow-Up ~~(~~Visit ~~9)~~. […] [n] For female subjects only, a serum pregnancy test will be collected at Screening, and a urine pregnancy test will be collected predose at Visits ~~1~~**2**, 5, 7, 8, ~~and~~ at Safety Follow-Up ~~(~~Visit ~~9)~~.**, and at every visit during the optional extension period.** [o] Subjects ~~should~~**must** be fasting 8 hours prior to visits with PK sampling. **Subjects must also fast for 1 hour postdose at these visits.** Blood samples for PK analysis will be collected predose and 0.25, 0.5, 1.0, 2.0, 4.0, and 6.0 hours postdose at Day 1 (Visit 2) and Day 29 (Visit 5). Subjects who discontinue IMP prior to PK sampling visit days will not have blood obtained for PK. […] [s] The IMP **(capsule formulation)** will be dispensed after randomization on Day 1 and thereafter at each planned trial visit **during the Treatment Period. Patients participating in the OLE will be dispensed IMP (tablet formulation) at Visit 8/Day1 of OLE and at Visits 9, 10, and 11 during the OLE. Patients participating in the OLE will be administered IMP (tablet formulation) at Visit 8/Day 1 OLE.** All remaining IMP **capsules** will be collected at Visit 8 **for all patients. Remaining IMP tablets will be collected at Visit 12 for those participating in OLE**.
Modification of heading to clarify objectives during treatment period from open-label extension period	Section 4.3 - Other Secondary Objectives	4.3 Other Secondary Objectives	**4.3 Other Secondary Objectives <u>(during the double-blind period)</u>**

Change	Section(s)	Previous Wording	New Wording
Modification of text to include open-label extension period	Section 4.5 - Open-label Extension Objective	n/a	**Open-label Extension Objectives** **The open-label objective of this study is to evaluate the on-going safety and efficacy of M2951 in an open-label extension with treatment at 50 mg bid for an additional 6 months.**
Modification of text to include open-label extension period	Section 5.1 - Overall Trial Design and Plan	Total duration of subject participation is approximately 140 days (20 weeks): • Screening: 28 days (4 weeks) • Treatment: 84 days (12 weeks) • Safety Follow-Up: 28 days (4 weeks).	Total duration of subject participation is approximately **between 5 months (20 weeks) to 11 months (46 weeks), which includes**~~140 days (20 weeks)~~: • Screening: 28 days (4 weeks) • Treatment: 84 days (12 weeks) • **Optional 6-month open-label extension period (26 weeks)** • Safety Follow-Up: 28 days (4 weeks). **After completing the 12-week treatment period, subjects will be offered the opportunity to participate in an optional 6-month open-label extension period where all subjects will receive M2951. For subjects who choose to participate in the optional extension period, the duration of participation will last a total of approximately 11 months.** **Subjects who continue to receive M2951 during the extension period will also be required to undergo the Safety Follow-up Visit scheduled for approximately 28 days after the last treatment visit.** […] **The optional Extension Period includes four scheduled visits (Visits 9, 10, 11, and 12), which correspond with Day 14, and the end of Months 1, 3, and 6. Subjects will also attend a Safety Follow-Up Visit approximately 28 days after the last dose of IMP.**
Modification of text to include open-label extension period	Section 5.1 - Overall Trial Design and Plan	(Refer to previous Figure 1 in previous version.)	(Updated Figure 1 in Section 5.1 to include open-label extension period.)
Modification of text to include open-label extension period	Section 5.2 - Discussion of Trial Design	The primary objective of this trial is to assess the efficacy of M2951 in subjects with active RA on stable MTX background therapy as measured by the ACR20 over Day 85 of treatment. The key secondary objective is to evaluate the level of disease activity at Day 29 in subjects with active RA as assessed by percent change in hsCRP from Baseline to Day 29.	The primary objective of this trial is to assess the efficacy of M2951 in subjects with active RA on stable MTX background therapy as measured by the ACR20 over Day 85 of treatment. The key secondary objective is to evaluate the level of disease activity at Day 29 in subjects with active RA as assessed by percent change in hsCRP from Baseline to Day 29. **An open-label extension of 6 months duration will be offered to subjects completing the initial 12-week treatment period. The purpose**

Change	Section(s)	Previous Wording	New Wording
			is to allow all subjects the opportunity to be on active treatment with M2951 and to collect longer term safety data.
Modification of text to increase cutoff for hsCRP	Section 5.3.1 - Inclusion Criteria	5. hsCRP ≥3 mg/dL	5. hsCRP ≥~~3~~**3.6** mg/dL
Formatting change for consistency	Section 5.3.1 - Inclusion Criteria	n/a	(Formatting change only to change bullet points to numbers.)
Erratum	Section 5.3.2 - Exclusion Criteria	3. Treatment with tofacitinib, other BTK inhibitiors,	13. Treatment with tofacitinib, other BTK ~~inhibitiors~~**inhibitors**,
Modification of text to clarify definition of cytopenia	Section 5.3.2 - Exclusion Criteria	22. Significant cytopenia, including neutrophil count < 1,500/ mm^3, or platelet count < 75,000/mm^3	22. Significant cytopenia, including **absolute** neutrophil count < 1,500/mm^3, ~~or~~ platelet count < **100**~~75~~,000/mm^3**, or absolute lymphocyte count < 1,000/mm^3**
Modification of text to clarify exclusion criteria	Section 5.3.2 - Exclusion Criteria	23. Participation in any investigational drug trial within 1 month or 5 half-lives of the investigational drug, whichever is longest, prior to Screening	23. **Has taken an** investigational drug ~~trial~~ within 1 month or 5 half-lives of the investigational drug, whichever is longer ~~longest~~, prior to Screening
	Section 6.1 - Description of the Investigational Medicinal Product		~~In this trial~~**During the 12-week treatment period**, the active IMP is M2951 (2 x 25 mg bid), which is supplied as a ~~white to yellow powder in a gelatin~~ capsule (size 0, color Swedish Orange) formulation for oral administration. No other excipients are used. Identical capsules for placebo are filled with mannitol . **During the optional extension period, M2951 (2 x 25 mg bid) will be supplied as tablet formulation for oral administration.**
Modification of text to include open-label extension period	Section 6.2 - Dosage and Administration	Subjects will receive 50 mg bid M2951 or placebo administered as 2 matching oral capsules twice daily for 84 days. Subjects will self-administer the IMP at a set time each day (± 2 hours). Subjects must take their daily 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. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures (other than post-treatment PK/PD sampling and post-treatment ECGs) are completed.	**During the 12-week treatment period, s**~~S~~ubjects will receive 50 mg bid M2951 or placebo administered as 2 matching oral capsules twice daily for 84 days. Subjects will self-administer the IMP at a set time each day (± 2 hours). Subjects must take their daily 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. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures (other than post-treatment PK/PD sampling and post-treatment ECGs) are completed. **After completing the treatment period, subjects will be offered the opportunity to participate in an optional 6-month M2951 extension period on Day 85 (Visit 8). Subjects who received M2951 during the**

Change	Section(s)	Previous Wording	New Wording
			treatment period will continue with the same dose of M2951 (in tablet formulation). All subjects in the placebo group during the treatment period will discontinue placebo and start treatment with 50 mg bid M2951 tablets on Day 85/Day 1 of OLE. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures are completed. Subjects will take 2 matching oral tablets twice daily for 6 months. Subjects will self-administer the IMP at a set time each day (± 2 hours). Subjects must take their daily 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. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures are completed.
Modification of text to include open-label extension period	Section 6.3 - Assignment to Treatment Groups	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.	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. **Subjects continuing to the open-label extension period will be dispensed additional treatment kits for 6 months of treatment.**
Modification of text to include open-label extension period	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, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.	All concomitant medications taken by the subject during the trial from the date of signature of informed consent **(including those participating in and during the extension period)** are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.
Modification of text to clarify IMP packaging	Section 6.6 - Packaging and Labeling of the Investigational Medicinal Product	M2951 and placebo capsules will be packaged as alu/alu blister packs in cartons, protected from light.	~~M2951 and placebo capsules will be packaged as alu/alu blister packs in cartons, protected from light.~~ **M2951 and matching placebo is supplied by the Sponsor. A description of the pharmaceutical properties and composition of the formulation of M2951 is provided in the IB. Additional details of packaging and labeling of the IMP will be defined in a separate Operations Manual.**

Change	Section(s)	Previous Wording	New Wording
Modification of text to correct team members and to include open-label extension period	6.10 - Blinding	Blinding to treatment codes or laboratory results capable of revealing treatment will be maintained throughout the trial duration, except for the unblinded IDMC, limited unblinding for the purposes of the IA, partial unblinding to support early analysis of PK/PD data, or in the event that emergency unblinding is necessary (see Section 6.11). The blind may also be broken in the case of a pregnancy should the subject desire this information. Randomization data will be kept strictly confidential, accessible only to authorized staff, until the limited unblinding for the IA and full unblinding for the final analysis. In order to maintain the blinded nature of the study, only the randomization statistician, the site pharmacists, an independent person at the study site responsible for receiving local laboratory ESR results and conveying those results to the central laboratory, and an independent statistician team (independent of the PPD study team) responsible for production of the IA outputs, will be fully unblinded during study conduct. The bioanalytical laboratory(ies) responsible for the analysis of the PK and PD samples will be allowed to be partially unblinded during study conduct using masked subject identifiers, to support association of PK/PD data with treatment codes for timely decision making, but prevent association of treatment codes with any other clinical data, such as safety data. A subteam of the Sponsor study team tasked with review of the IA data (medical responsible, Drug Safety representative, and biostatistician) will be unblinded to the IA results, which will be presented in the form of summary tables (not subject listings) on a limited set of endpoints for subjects enrolled at the time of the IA: 4-week hsCRP, 4-week DAS28-hsCRP, safety, baseline characteristics, and disposition. The IDMC will also be unblinded to treatment, as described in the IDMC charter.	Blinding to treatment codes or laboratory results capable of revealing treatment will be maintained throughout the trial duration, except for the unblinded IDMC, limited unblinding for the purposes of the IA, partial unblinding to support early analysis of PK/PD data, or in the event that emergency unblinding is necessary (see Section 6.11). The blind may also be broken in the case of a pregnancy should the subject desire this information. Randomization data will be kept strictly confidential, accessible only to authorized staff, until the limited unblinding for the IA and full unblinding for the ~~final~~ analysis **at the end of 12 weeks of treatment for all randomized patients**. In order to maintain the blinded nature of the study, only the randomization statistician, ~~the site pharmacists,~~an independent person at the study site responsible for receiving local laboratory ESR results and conveying those results to the central laboratory, and an independent statistician team (independent of the PPD study team) responsible for production of the IA outputs, will be fully unblinded during study conduct. The bioanalytical laboratory(ies) responsible for the analysis of the PK and PD samples will be allowed to be partially unblinded during study conduct using masked subject identifiers, to support association of PK/PD data with treatment codes for timely decision making, but prevent association of treatment codes with any other clinical data, such as safety data. A subteam of the Sponsor study team tasked with review of the IA data (medical responsible, Drug Safety representative, and biostatistician) will be unblinded to the IA results, which will be presented in the form of summary tables ~~(not subject listings)~~ on a limited set of endpoints for subjects enrolled at the time of the IA: 4-week hsCRP, 4-week DAS28-hsCRP, safety, baseline characteristics, and disposition. The IDMC will also be unblinded to treatment, as described in the IDMC charter. […] Only when the **12-week Treatment Period** ~~**trial**~~ is completed **for all patients**, ~~database locked~~, the data file verified, ~~**and**~~ protocol violations determined**, statistical analysis plan (SAP) signed and database partially locked for the 12-week treatment period,** will the drug codes be broken and made available, along with laboratory results capable of revealing treatment, for the **primary**~~final~~ data analysis. **The final analysis will be performed after all subjects have completed the Safety Follow-up or**

Change	Section(s)	Previous Wording	New Wording
		[…] Only when the trial is completed, database locked, the data file verified, and protocol violations determined will the drug codes be broken and made available, along with laboratory results capable of revealing treatment, for the final data analysis.	**discontinued from study early, with assessment of some safety and key efficacy variables.**
Modification of text to clarify fasting for PK sampling	7.1.2 - Treatment Period	Subjects should be fasted for 8 hours prior to PK sampling as specified in Table 1.	Subjects **must**~~should~~ be fasted for 8 hours prior to PK sampling as specified in Table 1. **Subjects must also fast for 1 hour postdose at these visits with PK sampling.**
Modification of text to include open-label extension period	7.1.2.1 - End of Treatment Visit	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.	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. **Subjects opting to participate in the optional extension period will sign a new ICF at this visit. The Investigator will discuss the benefits with the subject and the subject well-being. Subjects are free not to sign the new ICF for the extension period.**
Modification of text to include open-label extension period	7.1.3 - Optional Extension Period	(new section)	**After completing the treatment period (Visits 2 through 8), subjects will be offered the opportunity to participate in an optional 6-month M2951 extension period. Subjects electing to participate in the Extension Period will sign an ICF at Visit 8. Subjects who received M2951 during the treatment period will continue with M2951. Subjects who received placebo during the treatment period will discontinue placebo and start treatment with M2951 on Day 85/Day 1 of OLE. The End of Treatment Visit during the treatment period (Visit 8) will be considered Day 1 of the optional extension period.** **The Optional Extension Period includes four scheduled visits (Visits 9, 10, 11, and 12), which correspond with Day 14, and the end of Months 1, 3, and 6. Subjects who signed the additional ICF at Visit 8 will undergo the Optional Extension Period assessments as described in the Schedule of Assessments (Table 1).** **If a subject discontinues early from the optional extension period, he/she should complete the Safety Follow-Up Visit.**
Modification of text to include open-label extension period	7.1.4 - Safety Follow-Up Visit (previously Section 7.1.3)	For subjects who complete treatment, assessments during the Safety Follow-Up/End of Trial Visit (Visit 9) will be performed on Day 113 ± 7 days according to Table 1.	For subjects who complete **the first** treatment **period of 12 weeks, but do not continue to the optional extension period,** assessments during the Safety Follow-Up/End of Trial Visit ~~(Visit 9)~~ will be performed approximately 28 days after last dose of IMP. [...]

Change	Section(s)	Previous Wording	New Wording
			All subjects discontinuing the Optional Extension Period prematurely, or completing the Optional Extension Period, will have a Safety Follow-up Visit.
Modification of in-figure text to clarify that the physician completes the assessment	7.3.1.2 - Visual Analog Scales	Figure 2 reads: "How do you assess your current arthritis disease activity?" […] Results should be recorded on the appropriate page of the eCRF.	Figure 2 now reads: "How do you ~~assess~~ **rate** ~~your~~ **the subject's** current arthritis disease activity?" […] ~~Results should be recorded on the appropriate page of the eCRF.~~
Erratum	7.3.1.3 - Disease Activity Score-C-Reactive Protein (DAS28-hsCRP)	DAS28-hsCRP will be derived using the following formula from the DAS28 website (23): DAS28-hsCRP = 0.56*√(TJC28) +0.28*√(SJC28)+0.014*GH+0.36*ln(hsCRP+1)+0.96 Where: • TJC28=28 joint count for tenderness • SJC28=28 joint count for swelling • ln(hsCRP)=natural logarithm of hsCRP • ln(ESR)=natural logarithm of ESR • GH=the general health component of the DAS (ie, patient's global assessment of disease activity).	DAS28-hsCRP will be derived using the following formula from the DAS28 website (23): DAS28-hsCRP = 0.56*√(TJC28) +0.28*√(SJC28)+0.014*GH+0.36*ln(hsCRP+1)+0.96 Where: • TJC28=28 joint count for tenderness • SJC28=28 joint count for swelling • ln(hsCRP)=natural logarithm of hsCRP • ~~ln(ESR)=natural logarithm of ESR~~ • GH=the general health component of the DAS (ie, patient's global assessment of disease activity).
Addition of blood to laboratory parameters assessed with urinalysis	Section 7.4.3 - Clinical Laboratory Assessments	(see Table 4)	(see Table 4 above) "Blood" was added to the list of parameters tested during urinalysis/microscopy assessments. Footnote d was modified to include "if urinalysis results are abnormal **for blood, protein, or nitrite**."
Addition of ECG analysis during OLE	Section 7.4.4.3 - 12-Lead ECG and Chest X-Ray	A 12-lead ECG will be performed during Screening and predose on Day 85. The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semi-supine position.	A 12-lead ECG will be performed during Screening ~~and~~, predose on Day 85, **Month 1 of OLE, and Month 6 of OLE**. The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semi-supine position.
Modification of text to clarify fasting for PK sampling	Section 7.5 - Pharmacokinetic Assessments	Subjects should be fasting 8 hours prior to visits with PK sampling. Blood samples for PK analysis will be collected predose and 0.25, 0.5, 1.0, 2.0, 4.0, and 6.0 hours postdose at Day 1 (Visit 2) and Day 29 (Visit 5). See Appendix C for PK blood sample volumes. Subjects who discontinue IMP prior to PK	Subjects **must**~~should~~ be fasting 8 hours prior to visits with PK sampling. **Subjects must also fast for 1 hour postdose at these visits.** Blood samples for PK analysis will be collected predose and 0.25, 0.5, 1.0, 2.0, 4.0, and 6.0 hours postdose at Day 1 (Visit 2) and Day 29 (Visit 5). See Appendix C for PK blood sample volumes. Subjects who discontinue IMP prior to PK sampling visit days will not have blood obtained for PK.

Change	Section(s)	Previous Wording	New Wording
		sampling visit days will not have blood obtained for PK.	
Errata and modification of text to include open-label extension period	Section 8.1 - Sample Size	The trial is powered to demonstrate superiority of M2951+MTX to placebo + MTX in ACR20 response proportion after 85 days of treatment, using a test of the null hypothesis H0: $\Delta \leq 0$ based on the 2-sided 80% confidence interval (CI) for Δ, where Δ is the difference in Day 85 ACR20 response proportion comparing the 2 treatment groups. The null hypothesis H0 will be rejected if the lower limit of the 2-sided 80% CI exceeds zero. It is assumed that the Day 85 ACR20 response proportion in the placebo + MTX treatment group is 0.21 (27), and that the difference in Day 85 ACR20 response proportions between the 2 treatment groups under the alternative hypothesis H1: $\Delta > 0$ is $\Delta = 0.25$ (27, 28). […] An IA will be conducted when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data and DAS28-hsCRP data, or have discontinued treatment prior to Day 29. Point and CI estimates of the Day 29 hsCRP change from Baseline difference, comparing the 2 treatment groups, will be estimated for use in internal decision making. A similar analysis of Day 29 DAS28 hsCRP will be performed. The IA will not be used to alter the design of the trial. No adjustment will be made to the 1-sided α of 10% to be used in the final analysis at the end of the trial.	The trial is powered to demonstrate superiority of M2951+MTX to placebo + MTX in ACR20 response proportion after **84~~85~~** days of treatment, using a test of the null hypothesis H0: $\Delta \leq 0$ based on the 2-sided 80% confidence interval (CI) for Δ, where Δ is the difference in Day 85 ACR20 response proportion comparing the 2 treatment groups. The null hypothesis H0 will be rejected if the lower limit of the 2-sided 80% CI exceeds zero. It is assumed that the Day 85 ACR20 response proportion in the placebo + MTX treatment group is 0.21 (27), and that the difference in Day 85 ACR20 response proportions between the 2 treatment groups under the alternative hypothesis H1: $\Delta > 0$ is $\Delta = 0.25$ (27, 28). […] An IA will be conducted when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data and DAS28-hsCRP data, or have discontinued treatment prior to Day 29. Point and CI estimates of the Day 29 hsCRP change from Baseline difference, comparing the 2 treatment groups, will be estimated for use in internal decision making. A similar analysis of Day 29 DAS28 hsCRP will be performed. The IA will not be used to alter the design of the trial. No adjustment will be made to the 1-sided α of 10% to be used in the **primary** ~~final~~ analysis at the end of the **12-week blinded treatment period** ~~trial~~. **A final analysis will be conducted at the end of the trial when all subjects have completed the Safety Follow-up Visit or prematurely discontinued from study.**
Modification of text to include open-label extension period	8.3 - Endpoints	**8.3.2 Secondary Endpoints** The key secondary endpoint is the percent change in hsCRP from Baseline to Day 29. **Other secondary endpoints:** […]	**8.3.2 Secondary Endpoints** The key secondary endpoint is the percent change in hsCRP from Baseline to Day 29. **Other secondary endpoints <u>(during the double-blind treatment period):</u>** […] **<u>8.3.4 Endpoints for Open-label Extension</u>** **The endpoints for the open-label extension are as follows:**

Change	Section(s)	Previous Wording	New Wording
			Safety: • **Nature, incidence, and severity of TEAEs** • **Change from Baseline in vital signs and 12-lead ECG data** • **Change from Baseline in standard hematology and chemistry laboratory parameters including liver function tests, amylase/lipase, and urinalysis.** **Efficacy:** • **ACR50/ACR70 response at Month 6** • **Percent change in hsCRP from Baseline to Month 6** • **Change from Baseline in DAS28-hsCRP score at Month 6** • **Percentage of subjects with DAS28-hsCRP < 3.2 (well-controlled disease) at Month 6** • **Percentage of subjects with DAS28-hsCRP < 2.6 at Month 6** • **Change from Baseline in ESR, anti-CCP, and rheumatoid factor (at Month 6)** • **Change from Baseline to Month 6 in subject's self-assessments including:** o **Global assessment of disease activity (VAS, see Section 7.3.1.1)** o **Self-assessment of pain (VAS)** o **Self-assessment of disability (HAQ-DI)** • **Change from Baseline to Month 6 in Physician's Global Assessment of Disease Activity (VAS).**
Modification of text to include open-label extension period	Section 8.4 - Analysis Sets	The Safety Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo. The Safety Analysis Set will be used for all demographic/baseline characteristics and safety analyses. […] The Modified Intent-to-Treat (mITT) Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point postdose. The mITT Analysis Set will be used for the analysis of all efficacy endpoints. For the IA, the mITT Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo and have at least 1 available hsCRP evaluation at a time point postdose.	The Safety Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo. The Safety Analysis Set will be used for all demographic/baseline characteristics and safety analyses. **The open-label extension (OLE) Safety Analysis Set will include all subjects who received at least 1 dose of M2951 during the open-label extension period. The OLE Safety Analysis Set will be used for all safety analyses at time of final analysis.** […] The Modified Intent-to-Treat (mITT) Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point postdose. The mITT Analysis Set will be used for the analysis of all efficacy endpoints. For the IA, the mITT Analysis Set will include all subjects who received at least 1 dose of M2951 or placebo and have at least 1 available hsCRP evaluation at a time point postdose. **The OLE Modified Intent-to-Treat (OLE mITT) Analysis Set will include all subjects who received at least 1 dose of M2951 during open-label**

Change	Section(s)	Previous Wording	New Wording
			extension period and have at least 1 available ACR20 evaluation at a time point after first dose in open-label extension period. The OLE mITT Analysis Set will be used for the analysis of all efficacy endpoints at time of final analysis.
Modification of text to include open-label extension period	Section 8.5.5 - Analysis of Safety and Other Endpoints	The analysis set for the safety assessments will be the Safety Analysis Set. All safety endpoints will be summarized by treatment group unless otherwise specified. […] The number and percentage of subjects experiencing 1 or more TEAEs will be summarized according to the MedDRA system organ classes and preferred terms by treatment group, relationship to IMP, and severity.	The analysis set for the safety assessments will be the Safety Analysis Set **for the primary analysis and the OLE Safety Analysis Set for final analysis**. All safety endpoints will be summarized by treatment group unless otherwise specified. **Analyses including both for the first 12-week treatment period and open-label extension period data will be summarized according to treatment groups 'M2951+MTX' and 'Placebo+MTX/M2951 '.** […] The number and percentage of subjects experiencing 1 or more TEAEs will be summarized according to the MedDRA system organ classes and preferred terms by treatment group, relationship to IMP, and severity. **Exposure-adjusted incidence rates of TEAEs will also be reported according to the MedDRA system organ class and preferred term**. […] **At the end of the study, for final analysis, safety endpoints will be reported both for the first 12 week treatment period and for entire study, by treatment group, based on OLE Safety Analysis Set.**
Modification of text to include open-label extension period	Section 8.5.6 - Analysis of Open-label Extension Endpoints	(new section)	**Efficacy data collected from the 6-month open-label extension period will be summarized. Details will be provided in the SAP.** **Safety data collected from the 6-month open-label extension period will be analyzed as described in Section 8.5.5.**
Modification of text to clarify interim analyses	8.6 - Interim and Additional Planned Analyses	An IA will be conducted when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have Day 29 data, or have discontinued treatment prior to Day 29. The percent change in hsCRP from Baseline to Day 29 will be the key endpoint evaluated at the IA. Descriptive statistics will be presented by treatment group. A point estimate and 2-sided 80% CI for the difference Δ in Day 29 hsCRP change from Baseline between subjects treated with M2951+MTX and subjects treated with placebo + MTX will be provided. In addition, the change in DAS28 hsCRP from Baseline to Day 29 will be evaluated using the same approach as used for change in hsCRP. Some	**There will be 3 analyses: (1) an interim analysis (IA), triggered when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have available Day 29 hsCRP data, or have discontinued treatment prior to Day 29, (2) a primary analysis, triggered when 100% of subjects enrolled have reached Day 85 of treatment or have discontinued treatment prior to Day 85, and (3) a final analysis, triggered when 100% of subjects enrolled complete all study parts, or discontinue prematurely from study.** **Interim Analysis** ~~An IA will be conducted when subjects from the first 50% of the planned enrollment have reached Day 29 of treatment and have Day 29 data, or have discontinued treatment prior to Day 29.~~ The percent change in hsCRP from Baseline to Day 29 will be the key endpoint evaluated at the IA. Descriptive

Change	Section(s)	Previous Wording	New Wording
		safety, baseline characteristics, and disposition data will also be summarized by treatment group at the time of IA. The results of this IA will be used for internal decision making only and will not impact the conduct of the trial. See Section 6.10 for more details regarding limited unblinding. The primary analysis will be performed by PPD staff when all subjects have either completed the Safety Follow-Up Visit or prematurely discontinued from the trial and the database is locked.	statistics will be presented by treatment group. A point estimate and 2-sided 80% CI for the difference Δ in Day 29 hsCRP change from Baseline between subjects treated with M2951+MTX and subjects treated with placebo + MTX will be provided. In addition, the change in DAS28-hsCRP from Baseline to Day 29 will be evaluated using the same approach as used for change in hsCRP. Some safety, baseline characteristics, and disposition data will also be summarized by treatment group at the time of IA. The results of this IA will be used for internal decision making only and will not impact the conduct of the trial. See Section 6.10 for more details regarding limited unblinding. ~~re-analyzed. The primary analysis will be performed by~~ PPD ~~staff when all subjects have either completed the Safety Follow-Up Visit or prematurely discontinued from the trial and the database is locked.~~ **Primary Analysis** **When the last subject reaches Day 85 of treatment or discontinues from treatment prematurely prior to Day 85, the protocol violations are determined, the SAP is signed, the database is~~partially locked~~ locked for the first 12-week treatment period for all randomized patients for the primary analysis, and the data file verified, the drug codes will be broken and made available for the primary data analysis. All endpoints, demographics and safety data will be analyzed at that time.** **Final Analysis** **The final analysis will occur only when the last subject completes all study parts, the protocol violations are determined, the database is locked for the final analysis, and the data file verified. Only some safety and key efficacy data will be summarized.**
Modification of text to include open-label extension period	Section 9.2 -Subject Information and Informed Consent	A separate Subject Information Sheet and Informed Consent Form will be signed prior to collection of samples for biomarker analysis.	A separate Subject Information Sheet and Informed Consent Form will be signed prior to collection of samples for biomarker analysis. **A separate ICF will be signed at the End of Treatment Visit by subjects wishing to participate in the optional extension period**.
Modification of text to clarify anonymization of samples	Section 9.3 -Subject Identification and Privacy	There is no time limit on the storage of blood samples for biomarkers after trial completion. The samples may be reanalyzed for newly identified markers or with new or improved technology. The samples will be destroyed or fully anonymized.	~~There is no time limit on the~~The **duration of** storage of blood samples for biomarkers after trial completion **will be according to the ICF and according to country regulation**. The samples may be reanalyzed for newly identified markers or with new or improved technology. The samples will be destroyed or fully anonymized **according to ICF and according to country regulation**.

Change	Section(s)	Previous Wording	New Wording
Modification of text to clarify the amount of blood drawn during the study	Appendix C - Blood Volumes	(see Appendix C in previous version)	(Blood samples/volumes for coagulation (only done at screening) was merged with Screening tests. Row for hsCRP was deleted as this is included in Chemistry. Volumes for Screening tests, Chemistry, Immunoglobulins, RF, anti-CCP, QuantiFERON-TB test, PK, and B cell count were corrected. Footnote specifying which immunoglobulins are tested was added. Additional columns for samples and volumes collected during Extension Period were added to reflect the additional samples collected during this period. Total volumes for Treatment Period and for Extension Period were updated in text.)
Modification of text to clarify versions of protocol	Appendix D - Protocol Versions and List of Changes	(see Appendix D in previous version)	Language was updated to “Protocol **Versions**” rather than Amendments for better clarity. Table of protocol versions and comparison tables were updated accordingly.