Title: A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

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Amendment 4	20 December 2016
Amendment 5	**17 October 2017**

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled "A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis", dated **17 October** 20**17** and agree to abide by all provisions set forth therein.

I agree to comply with the International **Council for** Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

Study Phase: Phase 3

Indication: Rheumatoid Arthritis (RA)

Primary Objective: To evaluate the efficacy of etanercept monotherapy compared to methotrexate monotherapy on maintenance of remission in subjects with RA who were on etanercept plus methotrexate therapy.

Secondary Objective(s):

- To evaluate the efficacy of etanercept plus methotrexate therapy compared to methotrexate monotherapy on maintenance of remission
- To evaluate the efficacy of 1) etanercept monotherapy compared to methotrexate monotherapy and 2) etanercept plus methotrexate therapy compared to methotrexate monotherapy on:
    - disease activity
    - disease worsening and time to disease worsening
    - remission and time to recapture remission after rescue treatment

Hypothesis: Etanercept monotherapy is superior to methotrexate monotherapy for maintaining remission in subjects with RA who were on etanercept plus methotrexate therapy.

Primary Endpoint: Simplified Disease Activity Index (SDAI) remission (≤ 3.3) at week 48

Secondary Endpoints:

- SDAI score and change from baseline at all measured timepoints
- Disease activity score (28 joint) calculated using the erythrocyte sedimentation rate formula (DAS-28-ESR) and change from baseline at all measured timepoints
- Disease activity score (28 joint) using the C-reactive protein formula (DAS-28-CRP) and change from baseline at all measured timepoints
- Clinical Disease Activity Index (CDAI) and change from baseline at all measured timepoints
- SDAI remission (≤ 3.3) at all measured timepoints
- Boolean remission at all measured timepoints
- Disease worsening defined as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization
- Time to disease worsening defined as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization

In subjects that receive rescue treatment:

- Time to recapture SDAI remission after starting rescue treatment
- SDAI remission at week 48

Study Design: This is a multicenter, randomized withdrawal, double-blind controlled study in subjects with RA on etanercept plus methotrexate therapy who are in very good disease control for 6 months prior to study entry. The study will consist of a 30-day screening period, a 24-week open-label run-in period, a 48-week double-blind treatment period and a 30-day safety follow-up period.

Approximately **358** subjects will be enrolled and approximately **250** subjects will be randomly assigned in a 2:2:1 ratio to one of three treatment groups: etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate (n = 1**0**0), oral methotrexate

10 to 25 mg weekly plus placebo for etanercept (n = 100) and etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly (n = **50**).

Sample Size: Approximately **358** subjects enrolled and approximately **250** subjects randomized.

Summary of Subject Eligibility Criteria: Subjects must be adults with a history of moderate to severe RA. Subjects must be in very good RA disease control for ≥ 6 months and be in remission as defined by an SDAI ≤ 3.3 at screening and at the end of the run-in period. Subjects must be on etanercept 50 mg per week plus methotrexate therapy for ≥ 6 months prior to the start of the run-in period. The methotrexate dose must be 10 to 25 mg per week for ≥ 6 months prior to the start of the run-in period and the dose must be stable for ≥ 8 weeks prior to the start of the run-in period. If a subject is taking subcutaneous methotrexate they must switch to an equivalent oral methotrexate dose of 10 mg to 25 mg weekly and remain on a stable oral dose ≥ 8 weeks prior to run-in visit 1. For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Etanercept dosing in the planned study follows the recommended label dosing for subjects with RA. During the run-in period open-label etanercept will be provided as a 50-mg pre-filled syringe for injection once weekly for 24 weeks. During the double-blind treatment period etanercept will be provided as a 50-mg pre-filled syringe or matching placebo for injection once weekly for 48 weeks.
See Section 6.2.1.

Non-Amgen Investigational Product Dosage and Administration: Methotrexate dosing will be 10 to 25 mg weekly. During the run-in period methotrexate will be provided as 2.5 mg tablets and will be taken once weekly by oral administration for 24 weeks. During the double-blind treatment period, methotrexate will be supplied as 2.5 mg methotrexate capsules, or as matching placebo capsules and will be taken once weekly by oral administration for 48 weeks.
See Section 6.2.2.

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration: Folic acid dosing will be 5 to 7 mg per investigator judgment or administration according to local standard of care.
See Section 6.3.

Procedures: Written informed consent must be obtained from all subjects before any screening procedures are performed. The following procedures will occur per the schedule of assessments: medical and medication history, physical examination, physical measures, vital signs, adverse event and concomitant medication assessment, tuberculosis testing, pregnancy testing, urinalysis, and blood draw for serum chemistry, hematology, hepatitis B and C testing, CRP and biomarkers, tender and swollen joint assessment and count and patient reported outcomes. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 1).

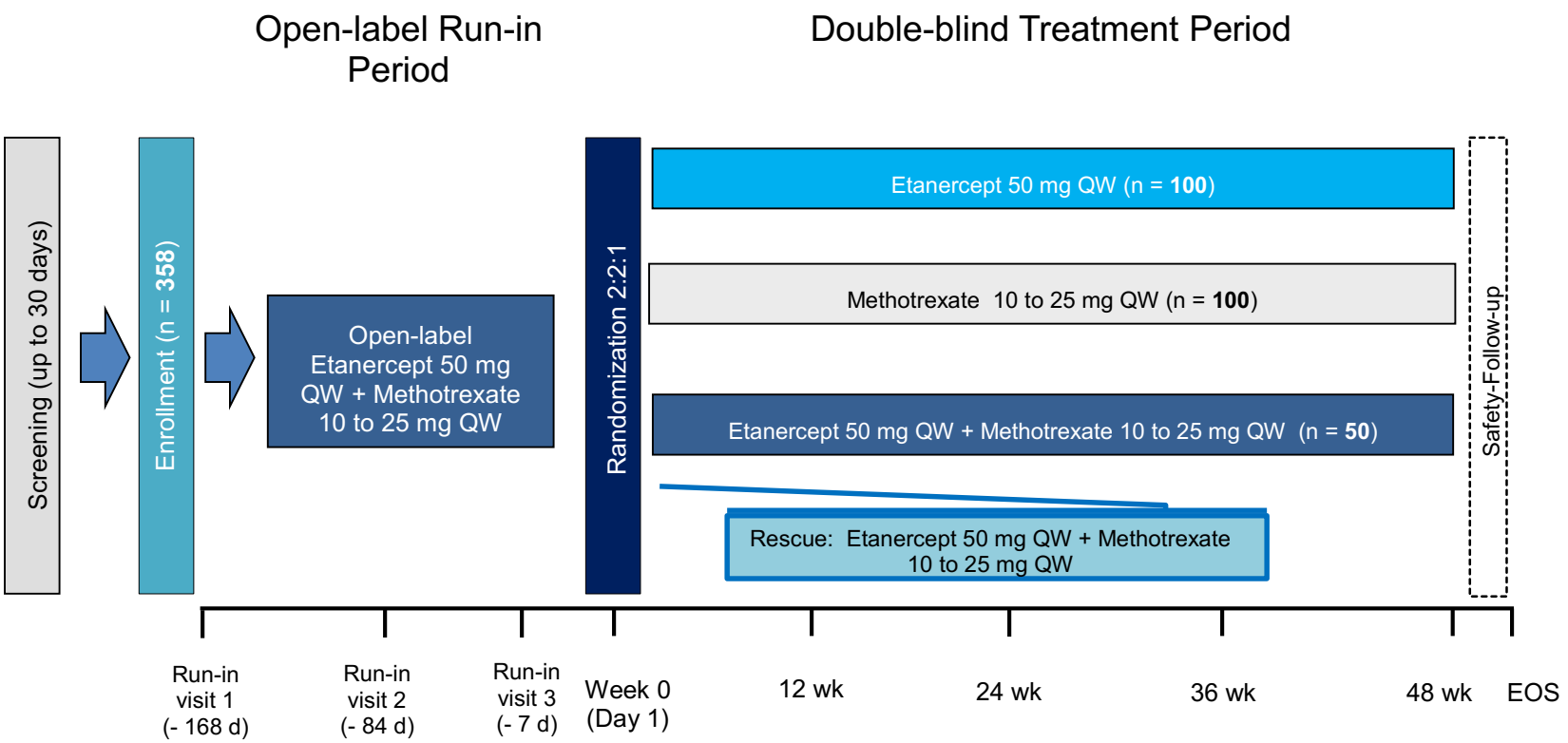
Statistical Considerations: The primary endpoint for this study is SDAI remission (SDAI ≤ 3.3) at week 48. The proportion of subjects achieving this endpoint will be compared across treatment arms using the chi-square test. The etanercept monotherapy treatment arm will be compared to the methotrexate monotherapy arm. Both subjects who drop out and subjects receiving rescue therapy due to disease worsening during the double-blind period will be considered non-responders. Furthermore, the randomized subjects who did not receive any dose of any of the investigational products will be considered non-responders in the primary analysis. As a sensitivity analysis, subjects who receive rescue therapy or drop out will have their post-rescue SDAI responses set to missing and a multiple imputation technique to impute these values will be employed.

Summary statistics will be provided for endpoints listed in this protocol. For categorical endpoints, the summary statistics contain the frequency and percentage. For continuous endpoints, the summary statistics contain number of observations, mean, standard deviation, standard error, median, minimum, maximum, and 95% confidence interval. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s):	Version 4.0 31 October 2013

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
eSAE contingency form	electronic serious adverse event contingency form
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
CDAI	Clinical disease activity index
eCRF	Electronic case report form
CRP	C-reactive protein
DA	Disease assessment visit
DAS-28-CRP	Disease activity score (28 joint) calculated using the C-reactive protein formula
DAS-28-ESR	Disease activity score (28 joint) calculated using the erythrocyte sedimentation rate formula
Disease Worsening	Simplified Disease Activity Index (SDAI) > 3.3 and ≤ 11 on two consecutive visits at least two weeks apart OR SDAI > 3.3 and ≤ 11 on three or more separate visits OR SDAI > 11 at any time after randomization
DILI	Drug-induced liver injury
DMARD	Disease modifying antirheumatic drug
DNA	Deoxyribonucleic acid
EDC	Electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study (for individual subject)	End of study for individual subject defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (end of trial)	The time when the last subject is assessed or receives an intervention for evaluation in the study.
ESR	Erythrocyte Sedimentation Rate
End of Treatment (EOT)	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
ET	Early termination
GCP	Good clinical practice
HAQ-DI	Disability Index of the Health Assessment Questionnaire
HBV	hepatitis B virus
ICF	Informed consent form
ICH	International **Council for** Harmonisation

Abbreviation or Term	Definition/Explanation
ICMJE	International Committee of Medical Journal Editors
IXRS	Interactive Voice and Web Response System
IPIM	Investigational product instruction manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LDA	Low disease activity
NSAID	Non-steroidal anti-inflammatory drug
PCR	polymerase chain reaction
PFS	Prefilled syringe
PI	principal investigator
PPD	Purified protein derivative
ePRO	electronic patient reported outcomes
PRO	Patient reported outcomes
QW	Once weekly
RA	Rheumatoid arthritis
RBC	Red blood cells
SAP	statistical analysis plan
SDAI	Simplified Disease Activity Index
SF-36	Medical Outcomes Short Form-36 Questionnaire
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
TBL	Total bilirubin
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cells

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1. OBJECTIVES

1.1 Primary

To evaluate the efficacy of etanercept monotherapy compared to methotrexate monotherapy on maintenance of remission in subjects with rheumatoid arthritis (RA) who were on etanercept plus methotrexate combination therapy.

1.2 Secondary

To evaluate the efficacy of etanercept plus methotrexate therapy compared to methotrexate monotherapy on maintenance of remission

To evaluate the efficacy of 1) etanercept monotherapy compared to methotrexate monotherapy and 2) etanercept plus methotrexate therapy compared to methotrexate monotherapy on:

- disease activity
- disease worsening and time to disease worsening
- remission and time to recapture remission after rescue treatment

1.3 Safety

To evaluate the safety of etanercept and methotrexate

1.4 Exploratory

- To evaluate Patient Reported Outcomes (PRO)
- To investigate potential biomarkers of disease activity and response to etanercept.
- To investigate the effects of genetic variation in disease genes and drug target genes on RA and/or subject response to etanercept.

2. BACKGROUND AND RATIONALE

2.1 Disease

RA is a chronic, systemic, autoimmune, inflammatory disease of unknown etiology that primarily affects the joints. Symptoms include joint stiffness, pain, and swelling that can progress to deformities and loss of function of both small and large joints. RA occurs in approximately 1% of adults worldwide in all races. Disease onset occurs most often between the ages of 20 and 60 years, with peak occurrence at 40 to 45 years. The prevalence of RA increases with age in both sexes, and prevalence is higher in women than men, with a ratio of approximately 2.5 to 1.0 (Alamanos et al, 2006).

2.2 Etanercept (Enbrel®) Background

Tumor Necrosis Factor (TNF) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays a role in the inflammatory process of

plaque psoriasis. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Two distinct receptors for TNF, a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNF receptor. Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, rendering TNF biologically inactive.

In many countries, etanercept is indicated for the treatment of: (1) moderately to severely active RA; (2) moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 and older; (3) psoriatic arthritis; (4) active ankylosing spondylitis; and (5) adult patients with chronic moderate to severe plaque psoriasis. Refer to the specific section of the investigational brochure or product label for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.3 Non-Amgen Medicinal Product Background: Methotrexate

Methotrexate inhibits dihydrofolic acid reductase and interferes with DNA synthesis, repair, and cellular replication. Its efficacy in RA is well-established and is traditionally used as a first line agent for RA treatment. Although methotrexate is effective, many patients continue to have active disease despite maximum dose therapy. Methotrexate can also be used in combination with other Disease Modifying Antirheumatic Drug (DMARD) including etanercept. The combination of methotrexate and etanercept for treatment of RA is well-established.

Refer to the regional manufacturer package insert for additional information.

2.4 Rationale

Etanercept has become a well-established agent in the management of RA. It can be used either as monotherapy or in combination with methotrexate to treat RA. Etanercept is commonly used in combination therapy after monotherapy with a first line agent such as methotrexate has failed. Patients report lower disease activity and improved quality of life with the incorporation of etanercept into their traditional DMARD therapies (Klareskog et al, 2004).

Recent studies including PRIZE (Emery et al, 2012), PRESERVE (Smolen et al, 2013), and DOSERA (van Vollenhoven et al, 2013a), have characterized the role of etanercept

on inducing and maintaining low disease activity in RA subjects. Importantly, these studies demonstrated that a significantly greater proportion of subjects taking combination etanercept plus methotrexate therapy are able to maintain low disease states compared to subjects taking methotrexate alone. The DOSERA study importantly demonstrated that most patients whose disease activity worsens after drug withdrawal are able to return to low disease activity (van Vollenhoven et al, 2013b).

Other studies provide insights regarding the role of etanercept as monotherapy in the maintenance of low disease states. In the COMET study (Emery et al, 2010) subjects who achieved DAS-28 remission on combination etanercept plus methotrexate were randomized to continue the combination therapy or to discontinue methotrexate and be treated with etanercept alone for one year. There was a numerically greater decrease in the percentage of subjects who maintained remission in the etanercept arm compared to the combination arm but the differences were relatively minor. In the CAMEO study, subjects with active RA were treated for 6 months with combination etanercept plus methotrexate (Pope et al, 2013). After 6 months the patients were randomized to continue on the combination or to be treated with etanercept monotherapy for the next 18 months. In patients who achieved low disease activity (DAS-28-ESR < 3.2) at month 6, the disease activity at 24 months was similar whether they discontinued methotrexate or remained on combination therapy. Combination treatment led to lower disease activity scores compared to etanercept monotherapy, however, in subjects with moderate to high disease activity at randomization (DAS-28-ESR > 3.2).

Collectively, these studies have shown that etanercept may be required to maintain disease control and that etanercept may be sufficient as monotherapy in maintaining good disease control. Sustained disease remission with etanercept alone could potentially lead to a reduction in polypharmacy and undesired side effects.

There are some caveats to these study results that merit consideration. In the clinical practice setting, drug reduction, whether etanercept or methotrexate, would most likely be considered in those patients who have been in good disease control for at least one year in duration. The clinical trials described above, with the exception of DOSERA which was limited by its small size, were designed to reduce or withdraw etanercept and/or methotrexate soon or just after inducing the target low disease state. Duration of good disease control may be a factor that contributes to the proportion of subjects who maintain low disease after drug reduction. Also, there were differences in the trials on the key low disease activity target for maintenance including DAS-28 Low Disease

Activity (LDA) and DAS-28 remission. Recently, the FDA released a draft guidance document for developing drug products for the treatment of RA (Guidance for Industry Rheumatoid Arthritis: Developing Drug Products for Treatment May 2013) which suggested the use of the American College of Rheumatology/European League Against Rheumatism criteria for remission. The criteria include Simplified Disease Activity Index (SDAI) remission (SDAI < 3.3) which is a more stringent measurement of remission compared to DAS-28 remission. SDAI is considered a clinically meaningful and an achievable target disease activity state for maintenance of disease control.

The present study will evaluate the effectiveness of three separate treatment regimens on maintaining remission of RA in patients who are well controlled and receiving etanercept plus methotrexate therapy for at least 12 months prior to randomization. The three treatment arms include, etanercept monotherapy, methotrexate monotherapy and combination etanercept plus methotrexate therapy. Subjects who fail to maintain remission and have a meaningful increase in the SDAI score during the randomized treatment period of the trial will be rescued in a blinded fashion with combination etanercept plus methotrexate therapy.

2.5 Clinical Hypothesis

Etanercept monotherapy is superior to methotrexate monotherapy for maintaining remission in subjects with RA who were on etanercept plus methotrexate therapy.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 3, multicenter, randomized withdrawal, double-blind controlled study in subjects with RA on etanercept plus methotrexate who are in very good disease control for 6 months prior to study entry. The study will consist of a 30-day screening period, a 24-week open-label run-in period, a 48-week double-blind treatment period and a 30-day safety follow-up period.

The study will enroll approximately **358** subjects. During the run-in period subjects will receive open-label etanercept and methotrexate at the same dose they were receiving during screening. It is expected that approximately 30% of subjects will early terminate the run-in period. Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately **250** subjects are randomized to treatment.

Approximately **250** subjects will be randomly assigned in a 2:2:1 ratio to one of three treatment groups:

- Etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate (n = 1**0**0)
- Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept (n = 1**0**0)
- Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly (n = **50**)

Subjects randomized to the etanercept plus methotrexate group and the methotrexate monotherapy group will receive methotrexate at the same dose they were receiving at screening and during the run-in period.

3.1.1 Rescue Therapy

After randomization, if a subject experiences disease worsening as defined below he/she will initiate rescue treatment with etanercept 50 mg once weekly (QW) plus methotrexate (10 to 25 mg). Those assigned to the etanercept plus methotrexate arm will continue on the assigned treatments. Subjects will receive methotrexate at the same dose that they were receiving at screening.

Original treatment assignments will remain blinded. Dispensing of etanercept plus methotrexate rescue therapy will be managed via the Interactive Voice and Web Response System (IXRS).

3.1.2 Disease Worsening

After randomization, disease worsening for the study is defined as:

- SDAI > 3.3 and ≤ 11 on two consecutive visits at least two weeks apart OR
- SDAI > 3.3 and ≤ 11 on three or more separate visits OR
- SDAI > 11 at anytime

Disease worsening may be assessed at a regularly scheduled visit or at a Disease Assessment visit as described in Section 7.2.7. If subject meets the criteria for disease worsening then new investigational product will be re-dispensed in a blinded fashion. Subjects will remain on study and complete all study visits as per the Schedule of Assessments (Table 1).

The overall study design is described by a study schema at the end of the protocol synopsis section. The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 105 sites globally will participate in the study. Additional regions and sites may be added if necessary. Sites that do not enroll subjects within 3 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

The number of subjects expected to be enrolled in the study is approximately **358** of which approximately **250** will be randomized to the double-blind treatment period.

Amgen may choose to alter the sample size of enrolled subjects to ensure that approximately **250** subjects are randomized to the double-blind treatment period.

Sample size considerations are provided in Section 10.2.

3.4 Replacement of Subjects

During the double blind-treatment period, subjects who are removed from treatment or from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The study will consist of up to a 30-day screening, a 24-week open label run-in period, a 48-week double-blind treatment period, and a 30-day safety follow-up period. The maximal duration of trial participation for an individual subject is approximately 82 weeks including the screening, run-in period, treatment period and safety follow-up.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: **The end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study

(ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). Part 1 eligibility criteria will be evaluated during screening. Part 2 eligibility criteria will be evaluated during the run-in period in subjects that successfully meet Part 1 eligibility criteria (see Section 5. Subject Enrollment).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria – Part 1

4.1.1 Inclusion Criteria – Part 1

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures.

102 ≥ 18 years of age at screening

103 A history of RA consistent with the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria

104 History of moderate to severe RA in the opinion of the investigator

105 In very good RA disease control for ≥ 6 months in the opinion of the investigator

106 SDAI ≤ 3.3 at screening

107 Receiving treatment with etanercept 50 mg per week for RA for ≥ 6 months prior to run-in visit 1

108 Receiving treatment with methotrexate dose of 10 mg to 25 mg weekly for ≥ 6 months AND on a stable dose of oral methotrexate for ≥ 8 weeks prior to run-in visit 1. If subject is taking subcutaneous methotrexate they must switch to an equivalent oral methotrexate dose of 10 mg to 25 mg weekly and remain on a stable oral dose ≥ 8 weeks prior to run-in visit 1.

109 May be receiving a stable dose of ≤ 5 mg oral prednisone or prednisone equivalent per day and the dose must be stable for ≥ 4 weeks prior to run-in visit 1

110 May be receiving a stable dose of sulfasalazine, hydroxychloroquine, minocycline and the dose must be stable for ≥ 8 weeks prior to run-in visit 1

111 If subject is receiving continuous treatment with acetaminophen, non-steroidal anti-inflammatory drug (NSAID) or tramadol, hydrocodone, oxycodone, codeine, and/or propoxyphene the dose must be stable for ≥ 4 weeks prior to run-in visit 1

112 Negative test for hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody at screening

113 Subject if female and not at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, has a negative serum pregnancy test ≤ 4-weeks prior to run-in visit 1.

114 No known history of active tuberculosis

115 National guidelines should be followed for appropriate tuberculosis screening in the setting of anti-TNF therapy, including a minimum of:

- Subject has a negative test for tuberculosis during screening defined as either:
  - negative purified protein derivative (PPD) (< 5 mm of induration at 48 to 72 hours after test is placed) OR
  - negative Quantiferon test

Subjects with a positive PPD and a history of bacillus Calmette-Guérin vaccination are allowed with a negative Quantiferon test.

Subjects with a positive PPD test (without a history of bacillus Calmette-Guérin vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have all of the following:

- no symptoms, per tuberculosis worksheet provided by Amgen
- documented history of a completed course of adequate treatment or prophylaxis (per local standard of care) prior to the start of investigational product
- no known exposure to a case of active tuberculosis after most recent prophylaxis
- no evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of investigational product

4.1.2 Exclusion Criteria – Part 1

RA Related

201 Subject is diagnosed with Felty's syndrome (RA, splenomegaly and granulocytopenia)

Other Medical Conditions

202 Subject has known history of alcoholic hepatitis, nonalcoholic steatohepatitis or immunodeficiency syndromes, including Human Immunodeficiency Virus infection.

203 Subject has any active infection (including chronic or localized infections) for which anti-infectives were indicated within 4 weeks prior to run-in visit 1.

204 Subject has a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to run-in visit 1.

205 Subject had prosthetic joint infection within 5 years of screening or native joint infection within 1 year of screening.

206 Subject has known alcohol addiction or dependency, uses alcohol daily, or has current substance use or abuse.

207 Subject has one or more significant concurrent medical conditions per investigator judgment, including the following:

- poorly controlled diabetes
- chronic kidney disease stage IIIb, IV, or V
- symptomatic heart failure (New York Heart Association class II, III, or IV)
- myocardial infarction or unstable angina pectoris within the past 12 months prior to randomization
- uncontrolled hypertension
- severe chronic pulmonary disease (eg, requiring oxygen therapy)
- multiple sclerosis or any other demyelinating disease
- major chronic inflammatory disease or connective tissue disease other than RA (eg, systemic lupus erythematosus with the exception of secondary Sjögren's syndrome)

Excluded Medications

208 Subject is currently receiving or had treatment ≤ 6 months with cyclophosphamide, chlorambucil, nitrogen mustard, or any other alkylating agent.

209 Subject has used biologic DMARD (including anakinra and abatacept) other than etanercept OR has used an oral janus kinase inhibitor ≤ 6 months prior to run-in visit 1

210 Subject has used any of the following ≤ 6 months prior to run-in visit 1:

- azathioprine
- cyclosporine
- gold
- mycophenolate mofetil
- Prosorba column
- Systemic tacrolimus

211 Subject has used leflunomide ≤ 8 weeks prior to run-in visit 1

212 Subject has used any of the following ≤ 4 weeks prior to run-in visit 1:

- intraarticular, intramuscular or intravenous corticosteroids, including adrenocorticotropic hormone
- intraarticular hyaluronic acid injections
- live vaccines

213 For subjects not on continuous analgesics, subject has taken the following within 12 hours prior to screening: acetaminophen, NSAIDs, hydrocodone, codeine, tramadol, propoxyphene and/or oxycodone (unless in the form of oxycontin). For subjects not on continuous analgesics, subject has taken oxycontin within 24 hours prior to screening.

Laboratory Abnormalities

215 Subject has any other laboratory abnormality, which, in the opinion of the investigator poses a safety risk, will prevent the subject from completing the study, or will interfere with the interpretation of the study results.

230 Subject has laboratory abnormalities during screening, including the following:

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 x the upper limit of normal (ULN). If the AST and/or ALT value is between 1.5 and 2 x the ULN without a documented etiology of aminotransferase elevation or without a history of stable elevated aminotransferase for at least 3 months prior to screening.
- Platelet count < 125,000/mm^3
- White blood cell count < 3,000 cells/mm^3
- Absolute neutrophil count < 1500/mm^3
- Estimated creatinine clearance < 30 mL/min (Cockroft-Gault formula, calculated value to be provided to sites. If the estimated creatinine clearance is between 30 and 50 mL/min (Cockroft-Gault formula, calculated value to be provided to sites) without a documented etiology for reduced creatinine clearance or without a 3-month history of stable creatinine clearance prior to screening.

Other

217 Other investigational procedures while participating in this study are excluded.

218 Female subject is not willing to use highly-effective methods of birth control during treatment and for 6 months after the end of treatment (except if at least 2 years postmenopausal or surgically sterile [hysterectomy, bilateral oophorectomy, or bilateral salpingectomy] or has had a bilateral tubal ligation**)**.

219 Male subject with a partner of child-bearing potential is not willing to use a condom during treatment and for 6 months after the end of treatment (except for men who are surgically sterile).

220 Male subject with a pregnant partner, who is not willing to use a condom to prevent exposure of the fetus to semen during treatment and for 6 months after the end of treatment.

221 Subject is pregnant or breastfeeding, or planning to become pregnant or breastfeed while enrolled in the study, up to the subject's last visit and for 6 months after the end of treatment.

222 Malignancy, except adequately treated non-melanoma skin cancers, cervical or breast ductal carcinoma in situ with no evidence of disease within the last 5 years.

223 Subject has known sensitivity to any of the products or components to be administered during dosing.

224 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Patient Reported Outcomes [PROs]) to the best of the subject's and investigator's knowledge.

225 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

226 Subject previously has enrolled in this study

231 Currently receiving treatment with an investigational device or drug product, or < 30 days since ending treatment with an investigational device or drug product that is not commercially available.

4.2 Inclusion and Exclusion Criteria – Part 2

4.2.1 Inclusion Criteria – Part 2

116 SDAI ≤ 3.3 at run-in visit 3

117 Subject if female and not at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, has a negative urine pregnancy test at baseline (day 1).

4.2.2 Exclusion Criteria – Part 2

227 Any clinically significant change in the Part 1 eligibility criteria during the run-in period

228 SDAI > 3.3 and ≤ 11 on two consecutive visits at least two weeks apart OR SDAI > 3.3 and ≤ 11 on two or more separate visits OR SDAI > 11 at any time during the run-in period

229 Subject has a clinically significant laboratory abnormality during run-in period which in the opinion of the investigator poses a safety risk, will prevent the subject from completing the study, or will interfere with the interpretation of the study results during the run-in period.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All

subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all Part 1 eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and register enrollment in the IXRS. Additionally, it is the responsibility of the investigator to record the current protocol version each subject enrolled under.

Upon completion of run-in period procedures the subject is evaluated by the investigator, and if the subject meets all Part 2 eligibility criteria he/she is subsequently randomized to a treatment regimen. Subjects who do not meet Part 2 eligibility criteria will complete an early termination run-in visit.

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent form*)* receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number, assigned by IXRS, will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

Subjects not meeting Part 1 eligibility criteria are permitted to re-screen up to 2 additional times after failing the first screening.

5.1 Randomization/Treatment Assignment

Subjects who meet Part 2 eligibility criteria will be randomized to receive etanercept plus placebo for methotrexate, methotrexate plus placebo for etanercept or etanercept plus methotrexate in a 2:2:1 ratio via IXRS.

Assignment to the treatment arms will be based on a computer-generated randomization schedule prepared by Amgen before the start of the study. Each randomized subject will receive a single, unique randomization number via IXRS at randomization. The randomization date is to be documented in the subject's medical record as registered in the IXRS.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. In the event that a subject's treatment assignment must be unblinded by the investigator the subject will not be allowed to receive any further investigational product. Refer to the Investigational Product Instruction Manual (IPIM) for a description regarding how responsible pharmacists and investigators will access treatment information via IXRS in the event that there is a need to break the treatment blind.

Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Global Clinical Trial Manager before unblinding any subject's treatment assignment. If not possible, the investigator must inform the Amgen Global Clinical Trial Manager within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Products

The Amgen Investigational Product(s) (except if required by local regulation) used in this study include(s): etanercept or placebo for etanercept

The Non-Amgen Investigational product(s) used in this study include(s): methotrexate or placebo for methotrexate.

The non-Amgen non-investigational product used in this study includes: folic acid.

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of etanercept, methotrexate, and folic acid.

6.2 Investigational Product

6.2.1 Amgen Investigational Product Etanercept

Etanercept will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Etanercept will be supplied in a single-use pre-filled 1mL syringe as a sterile, preservative-free solution for subcutaneous injection. The solution of etanercept is clear and colorless and is formulated at pH 6.3 ± 0.2. Each single-use prefilled syringe (PFS) contains 0.98 mL of 50 mg/mL etanercept in a formulation consisting of 100 mM sodium chloride, 25 mM sodium phosphate, 25 mM L-arginine-HCl, and 1% sucrose. Etanercept will be provided with 4-syringes to a pack. Placebo will be presented in identical containers and stored/packaged the same as etanercept.

6.2.1.1 Dosage, Administration, and Schedule

Etanercept dosing in the study will follow the recommended label dosing for subjects with RA (subcutaneous injection, 50 mg once weekly). Etanercept will be provided as a 50-mg PFS (0.98 mL of a 50- mg/mL solution of etanercept). Each dose of investigational product will consist of the complete contents of 1 syringe. The injection site should be rotated with each dose. During the open-label run-in period subjects will receive 1 dose of etanercept per week (scheduled approximately 7 days apart) for 24 weeks. During the double-blind treatment period, subjects will receive 1 dose of etanercept or matching placebo per week (scheduled approximately 7 days apart) for 48 weeks. Throughout the entire trial, administration of etanercept should occur on the scheduled dose day; however, if unavoidable, it may be given earlier or later as long as the dose is not within 2 days of the next scheduled dose. If the dosing window is missed, that dose should be skipped and the reason for the missed dose must be reported on the case report form. Subsequent doses of investigational product should resume on the original schedule, calculated from the run-in visit 1 for the open label run-in period of the study and from Day 1 for the double-blind treatment period. If etanercept is to be taken the day of a study visit, it must be taken after the study visit has occurred (ie, at the subject's location on the scheduled dose day). Injections of etanercept will be administered by the subject or a caregiver. The individual administering the dose must demonstrate to the site staff that he or she is competent to correctly administer the subcutaneous doses. The first dose of etanercept in the open label run-in period and Day 1 in the double-blind treatment period must be administered at the study site. All subsequent doses will be administered at the subject's location on the scheduled dose day. Supplies of etanercept will be dispensed to subjects for administration at home. The site will instruct the subject in appropriate handling and storage of used and unused syringes and documentation of dosing in the subject diary. The dose date, quantity administered and box number of investigational product are to be recorded in each subject's diary/ electronic case report form (eCRF). Please refer to the Investigator's Brochure for the most recent safety information. A link to the United States Prescribing Information can be found in the Investigator's Brochure.

6.2.2 Non-Amgen Investigational Product: Methotrexate

Non-Amgen investigational product methotrexate will also be used in this study. Methotrexate will be distributed using Amgen clinical trial drug distribution procedures. Methotrexate will be supplied as 2.5 mg methotrexate tablets, capsules, or as matching placebo capsules.

Additional details regarding the product(s) are provided in the IPIM.

6.2.2.1 Dosage, Administration, and Schedule

Methotrexate dosing in the study will be 10 to 25 mg weekly, consistent with the subject's dosing prior to screening.

During the open-label run-in period, methotrexate will be provided as 2.5 mg tablets and will be taken once weekly by oral administration. Subjects will receive 1 dose of open-label methotrexate per week (scheduled approximately 7 days apart) for 24 weeks. Subjects will remain on the same dose of methotrexate that they were receiving at screening.

During the double-blind treatment period, methotrexate will be provided as 2.5 mg capsules, or as placebo capsules, and will be taken once weekly by oral administration. Subjects will receive 1 dose of methotrexate or placebo per week (scheduled approximately 7 days apart) for 48 weeks. Subjects randomized to etanercept plus methotrexate therapy or methotrexate monotherapy arm will remain on the same dose that they were receiving at screening/run-in.

Throughout the entire trial, administration of methotrexate or matching placebo should occur on the scheduled dose day; however, if unavoidable, it may be given earlier or later as long as the dose is not within 4 days of the next scheduled dose. If the dosing window is missed, that dose should be skipped and the next dose should be resumed at the scheduled time. The reason for the missed dose must be reported on the case report form. Double or extra doses should not be taken. The dose date, quantity administered and bottle number of methotrexate is to be recorded on the subject's diary and entered into the eCRF.

6.3 Non-investigational Product

6.3.1 Non-Amgen Non-investigational Product: Folic Acid

Folic acid will be sourced by the site. Additional details regarding the product are provided in the IPIM.

6.3.1.1 Dosage, Administration, and Schedule

The dose of folic acid will be 5 to 7 mg per week as per investigator judgment or according to local standard of care. The dose of folic acid may be adjusted in response to methotrexate-related toxicity.

6.4 Hepatotoxicity Stopping and Rechallenge Rules, Reporting, and Monitoring

A United States Food and Drug Administration Guidance exists for drug-induced liver injury (Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009). This guidance is general for all investigational products, and its recommendations can be found in Appendix A.

6.4.1 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, and total bilirubin [TBL]) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding of Amgen investigational product or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. Criteria for permanent or conditional withholding of investigational product in the event that a subject develops signs or symptoms of hepatitis during a clinical trial is provided in Appendix A. Criteria for rechallenge of Amgen investigational product and other protocol required therapies after potential hepatotoxicity is provided in Appendix A.

6.4.2 Hepatotoxicity Reporting and Monitoring

Subjects with abnormal hepatic laboratory values (eg, ALP, AST, ALT, TBL, or signs/symptoms of hepatitis) may require follow-up, depending upon the clinical circumstances discussed below (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

6.4.3 Criteria for Reporting Hepatotoxicity as a Serious Adverse Event

Subjects who have TBL > 2 x ULN and AST or ALT > 3 x ULN must have the event submitted to Amgen as a serious adverse event within 24 hours following the investigator's knowledge of the event (ie, before additional etiologic investigations have been concluded).

Additional clinical assessments and observations in subjects who experience AST or ALT elevations > 3 x ULN will be performed until abnormalities return to normal or to the subject's baseline levels. Assessments to be performed during this period are outlined in Appendix A.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

Concomitant therapies are to be collected in the eCRF from signing of the informed consent through the end of study. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.5.1 Analgesics and NSAIDs

If the study subject enters the study taking acetaminophen, narcotic analgesics, or NSAIDs on a scheduled basis or as needed, the dose can be reduced or discontinued during the study if necessary for safety reasons or standard of care.

If the study subject is not taking acetaminophen, narcotic analgesics, or NSAIDs prior to entering the study and they take any of these agents for reasons related to RA, they may take these agents but must be seen at a regularly scheduled visit or a Disease Assessment visit (Section 7.2.7) no later than 1 week after commencing treatment. Analgesics and NSAIDs should not be taken for more than 2 weeks at a time.

If at any time the subject is taking acetaminophen, narcotic analgesics or NSAIDs these must not be used within 12 hours before a scheduled study visit, with the exception of oxycontin which may not be used within 24 hours of a scheduled study visit.

6.5.2 Corticosteroids

Subjects entering the study while taking oral corticosteroids cannot exceed the dose of 5 mg of prednisone or equivalent daily. The investigator may prescribe corticosteroids at a regularly scheduled visit or Disease Assessment visit (Section 7.2.7) if the subject is experiencing increased disease activity. However, any increase in dose or treatment with corticosteroids for increased disease activity must not exceed 2-weeks.

6.5.3 DMARDS

Subjects taking sulfasalazine (not to exceed 3 g/day) and/or hydroxychloroquine (not to exceed 400 mg/day) must remain on a stable dose throughout the study.

6.6 Medical Devices

Medical devices (eg, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.8 Excluded Treatments and/or Procedures During Study Period

Proscribed medications during this study include the following:

- Anakinra
- Abatacept
- Any other investigational agents or commercially available biologics
- Azathioprine
- Leflunomide
- Cyclosporine
- Cytotoxic agents including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
- Gold
- Intraarticular, intramuscular, or intravenous corticosteroids, including adrenocorticotropic hormone
- Intraarticular hyaluronic acid injections
- Mycophenolate mofetil
- Prosorba Column
- Systemic tacrolimus
- Live vaccines

6.9 Contraceptive Requirements

Female Subjects

Female subjects of child-bearing potential must agree to practice true sexual abstinence (refrain from heterosexual intercourse) or use a highly effective method of contraception during treatment and for an additional 6 months after the last dose of protocol required therapies.

Contraceptive methods that achieve a failure rate less of less than 1% per year when used consistently and correctly are considered highly effective and may include: hormonal (combined estrogen and progestogen or progestogen only), contraception associated with inhibition of ovulation (oral, injectable, implantable, intravaginal, or transdermal route), intrauterine device, intrauterine hormonal-releasing system, bilateral tubal occlusion, vasectomized partner (provided that partner is the sole sexual partner of the female participant and the vasectomized partner has received medical assessment of the surgical success), true sexual abstinence when this is in line with the preferred

and usual lifestyle of the subject. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

Females not of child-bearing potential are defined as: any female who has had a hysterectomy, OR bilateral salpingectomy, OR bilateral oophorectomy, OR are postmenopausal. Postmenopausal women are those who have had no spontaneous menses for at least 2 years.

Male Subjects

Male subjects who have had a vasectomy and received medical assessment of surgical success or whose female partner has had a bilateral tubal occlusion are not required to use additional forms of contraception.

Otherwise, male subjects with a partner of child-bearing potential must agree to practice true sexual abstinence (refrain from heterosexual intercourse) or use a condom with spermicide (if spermicide is commercially available) during treatment and for an additional 6 months after the last dose of protocol required therapies. The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

The female partner should also consider using an acceptable method of effective contraction such as: hormonal, intrauterine device, intrauterine hormonal-releasing system, female barrier method (diaphragm, cervical cap, contraceptive sponge; a female condom is not an option because there is a risk of tearing when both partners use a condom).

Male subjects with a pregnant partner must practice sexual abstinence or wear a condom to prevent exposure of the unborn child to methotrexate through semen.

Unacceptable methods of birth control for male and female subjects include birth control methods that are considered unacceptable in clinical trials and include: periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 1 can only be performed after obtaining informed consent. This includes any discontinuation of the subject's medication for the purpose of participation in this study.

All on-study visits during the run-in period should be scheduled from run-in visit 1. All on-study visits during the treatment period should be scheduled from day 1 (date of the first dose of investigational product) on the study. It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated below. When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit window as defined in the visit-specific section below.

With the exception of the screening and re-screen visits, all study procedures for a visit should be completed on the same day. Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

Any blood sample collected according to the Schedule of Assessments (Table 1) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analysis for method transfer and comparability. Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

	30-day Screening	Open-Label Run-in Period[h]				Double Blind Treatment Period[g]						Follow-Up
Weeks		Run-in Visit 1	Run-in visit 2	Run-in visit 3	Run-in ET	0[g]	12	24	36	48/ET	Disease Assessment[e]	Safety (EOS)[i]
Days	-198 (from Day 1)	-168 (from Day 1)	-84 (from Day 1)	-7 (from Day 1)		Day 1						30
GENERAL & SAFETY ASSESSMENTS												
Informed consent	X											
Part 1 Eligibility Criteria	X											
Part 2 Eligibility Criteria		X	X	X		X						
Medical/Medication history	X											
Concomitant medications		X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[a]	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Weight	X					X				X		
Height	X											
LABORATORY ASSESSMENTS												
Pregnancy test (serum)[b]	X											
Pregnancy test (urine)[b, c]		X				X	X	X	X	X		
Tuberculosis testing[d]	X											
Hematology and chemistry profile	X		X	X				X		X	X	
Rheumatoid Factor and anti CCP antibody						X						
Hepatitis B surface antigen/core antibody & hepatitis C virus antibody[j]	X											
Erythrocyte Sedimentation Rate	X	X	X	X		X	X	X	X	X	X	
C-reactive Protein	X	X	X	X		X	X	X	X	X	X	
Urinalysis	X			X								
Blood for biomarker analysis						X		X		X		

Footnotes defined on the next page of the table

Table 1. Schedule of Assessments

	30-day Screening	Open-Label Run-in Period[h]				Double Blind Treatment Period[g]						Follow-Up
Weeks		Run-in Visit 1	Run-in visit 2	Run-in visit 3	Run-in ET	0[g]	12	24	36	48/ET	Disease Assessment[e]	Safety (EOS)[i]
Days	-198 (from Day 1)	-168 (from Day 1)	-84 (from Day 1)	-7 (from Day 1)		Day 1						30
DOSING												
Etanercept/placebo for etanercept dispensation		X	X			X	X	X	X		X[f]	
Methotrexate/placebo for methotrexate dispensation		X	X			X	X	X	X		X[f]	
Dispense dosing diary		X	X			X	X	X	X			
Review dosing diary			X	X	X	X	X	X	X	X	X	
DISEASE ASSESSMENTS												
66 Swollen joint count	X	X	X	X		X	X	X	X	X	X	
68 Tender joint count	X	X	X	X		X	X	X	X	X	X	
Physician global assessment of disease activity	X	X	X	X		X	X	X	X	X	X	
SUBJECT ASSESSMENTS (PRO)												
Patient global assessment of joint pain	X	X	X	X		X	X	X	X	X	X	
Patient global assessment of disease activity	X	X	X	X		X	X	X	X	X	X	
Disability Index of the Health Assessment Questionnaire (HAQ-DI)						X		X		X		
Medical Outcomes Short Form-36 Questionnaire (SF-36)						X		X		X		

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ET = early termination; ESR = erythrocyte sedimentation rate; EOS = end of study; HBV = hepatitis B virus; PCR = polymerase chain reaction.

[a] Screening physical exam will be a full exam; subsequent exams per standard of care to monitor for any changes

[b] For all women, unless at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

[c] Additional pregnancy testing may be completed at the discretion of the investigator

[d] Subjects will receive either a PPD test or Quantiferon test at screening. National guidelines should be followed for appropriate tuberculosis screening in the setting of anti-TNF therapy.

[e] Disease Assessment Visit - disease activity may be assessed at a regularly scheduled visit or at a Disease Assessment visit as described in Section 7.2.7

[f] If subjects meet the criteria for disease worsening then etanercept plus methotrexate will be dispensed at the same dose they were receiving at screening

[g] Baseline (Day 1) visit must be scheduled ≤7 days from the run-in visit 3

[h] Visit window is +/- 7 days for all visits after screening

[i] Subjects will be contacted by phone by the site staff to collect any serious adverse events

[j] At screening, if the subject is positive for hepatitis B core antibody, the confirmatory reflex testing will be performed using HBV DNA PCR.

7.2 General Study Procedures

The procedures performed at each study visit are outlined in Table 1. Details regarding each type of procedure are provided in subsequent sub-sections.

Refer to the applicable supplemental central laboratory, IXRS, IPIM, and study manuals for detailed collection and handling procedures.

7.2.1 Screening

Informed consent must be obtained before completing any other screening procedure. After written informed consent is signed by the subject, the subject will be screened in order to assess eligibility for study participation. The screening window is 30 days. If a subject has not met all Part 1 eligibility criteria at the end of the 30-day window, the subject will be registered as a screen fail. At screening, if the subject is positive for hepatitis B core antibody, the confirmatory reflex testing will be performed using hepatitis B virus (HBV) DNA polymerase chain reaction (PCR). Subjects who screen fail may be eligible to rescreen two additional times per Section 7.2.2.

7.2.2 Re-screening

Subjects who are unable to complete or meet Part 1 eligibility criteria on initial screening will be permitted to re-screen two additional times after the first screening visit failure. Re-screen subjects must first be registered as screen failed in IXRS and subsequently registered as a re-screen subject with the same subject identification number. Once the subject is registered as re-screened, a new 30-day screening window will begin.

If the re-screening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent must be repeated. If the re-screening occurs within 30 days after the original signing of the informed consent, only those criteria that were originally not met would be required to be repeated. Tuberculosis testing will not need to be repeated for re-screen subjects if negative at the original screening. Subjects who fail screening for not meeting inclusion criterion 114 are not permitted to re-screen. Subjects screen failing for not meeting inclusion criteria 106 are permitted to re-screen 1 additional time if their initial SDAI screening score is < 6.0. If a subject does not meet inclusion criteria 106 after 2 screening attempts no additional rescreening is permitted. Rescreening for failure to meet inclusion criteria 106 must occur at least 2 weeks after the initial screening.

7.2.3 Open Label Run-in Period

Once a subject has met the Part 1 eligibility criteria evaluated during screening, the subject will enter the 24-week open-label run-in period. During the run-in period, Part 2 eligibility criteria will be evaluated at the regularly scheduled run-in visits or at a Disease Assessment visit (see Section 7.2.7) if required. If the subject does not meet the Part 2 eligibility criteria they must complete a run-in early termination visit.

Subjects will initiate treatment with open-label etanercept and methotrexate at the same dose they were receiving at screening. Investigational products, subject diaries, and related supplies will be dispensed to the subject at every regularly scheduled visit for self-administration.

All procedures during run-in visit 3 (see Table 1) must be completed within 7 days of the baseline (day 1) visit in order to confirm the subject's eligibility.

7.2.4 Early Termination Run-in

Subjects not meeting Part 2 eligibility criteria will complete a run-in early termination visit and will complete the procedures described in Table 1.

7.2.5 Baseline Visit (Day 1)

Subjects meeting Part 1 and Part 2 eligibility criteria will be randomized by IXRS as described in Section 5. The date of first dose of blinded investigational product is defined as Day 1 Week 0. All subsequent doses and study visits will be scheduled based on the Day 1 date. Following the first blinded dose, investigational products and related supplies will be dispensed to the subject for 12 weeks of self-administration.

7.2.6 Treatment

Visits will occur per the Schedule of Assessments (Table 1) during the treatment period from day 1 until week 48. On-study visits may be completed within ± 7 days of the target visit date. The procedures completed during the 48-week treatment period are those listed in the Schedule of Assessments (Table 1). Administration of investigational product is to be administered after all other study procedures, as applicable, during each visit that is required.

7.2.7 Disease Assessment Visit

Subjects can be seen at a regularly scheduled visit or at a disease assessment visit any time after screening to assess disease activity to either:

- establish Part 2 eligibility criteria during the run-in period OR
- to determine if subject can receive rescue treatment after randomization

During the double-blind randomized treatment period, if the subject meets the criteria for disease worsening as defined in Section 3.1.2 subjects will initiate treatment with etanercept and methotrexate at the same dose they were receiving during the run-in period. Subjects will continue to receive etanercept plus methotrexate for the remaining study visits per Table 1.

7.2.8 Subject End of Treatment/Early Termination

Subjects will complete an end of treatment (EOT) visit at week 48 within a window of ± 7 days of the target visit date (see Table 1). Subjects ending the study prior to week 48 will be asked to complete an Early Termination visit.

7.2.9 Safety Follow-up/End of Study

Approximately 30 days, within a window of + 7 days of the target visit date, after the last dose of investigational products, subjects will be contacted by phone by the site staff to collect any serious adverse events (refer to Section 9).

7.3 Description of Study Assessments and Procedures

Assessment and procedures are further detailed in this section. See Table 1 for required timepoints.

7.3.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IEC/IRB approved informed consent before any study-specific procedures are performed. See Section 11.1 for further details.

7.3.2 Demographic Data

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact on biomarker variability of the protocol required therapies.

7.3.3 Medical History

The subject's relevant medical and surgical history that started within 5 years or as necessary for chronic co-morbid conditions prior to enrollment through the start of the adverse event reporting period will be collected. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF. In addition to the medical history above, RA history should date back to the original diagnosis.

7.3.4 Medication History

The subject's complete history of RA medications will be recorded on the eCRF. This information will include the subject's DMARDs, NSAIDS, corticosteroid, biologics, and investigational medication history. All other medications taken within 6 months prior to screening will be recorded on the eCRF. For RA medications, the following information will be recorded in the eCRF: medication name, indication, dose, unit, route, frequency, and start and stop dates. For all other medications, only the medication name, indication, and start and stop dates will be recorded in the eCRF.

7.3.5 Physical Examination

The screening physical examination is per standard of care. Physical examination findings at screening should be recorded on the appropriate eCRF (eg, medical history). The physical examination at subsequent study visits will consist of an interim examination to monitor for any changes from the screening physical examination. Any clinically significant changes in physical examination per the Principal Investigator's opinion should be recorded on the adverse events eCRF.

7.3.6 Physical Measurement

Height in inches/centimeters and weight in pounds/kilograms should be measured without shoes.

7.3.7 Vital Signs

The following measurements must be performed: systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. The body region used to assess temperature for a subject should remain consistent throughout the study and documented on the vital signs eCRF. If abnormalities are found and they are considered an adverse event, record on the adverse event summary page.

7.3.8 Rheumatoid Arthritis Disease Assessments

7.3.8.1 Swollen/Tender Joint Counts

All joint assessments will be performed by an experienced trained joint assessor who has been certified as trained by Amgen and must be identified on the delegation of authority for this responsibility. Each subject should have their joint assessments done

by the same assessor throughout the study when possible and the user identification of the joint assessor is captured in the electronic PRO (ePRO) tablet. If necessary, study visits may be rescheduled within the specified window of ± 7 days to accommodate when the specific assessor will be available. The score for each joint will be recorded directly into the ePRO tablet which will serve as the source documentation and will not be transposed to the eCRF.

Joints that have been replaced are considered inevaluable. For the screening and baseline joint assessments, distal interphalangeal joints should be evaluated, but should not be included in the total count to determine eligibility.

Swollen Joint Count Assessments – A total of 66 joints will be scored for presence or absence of swelling.

Tender Joint Count Assessments – A total of 68 joints will be scored for presence or absence of tenderness.

7.3.8.2 Physician Global Assessment of Disease Activity

The global assessment of the subject's arthritis will be assessed by either the joint assessor or the principal investigator (PI) for the study by completion of a visual analog scale (VAS). The VAS is 100 mm in length with "0" and "No Activity at All" on the left end of the line and "100" and "Worst Activity Imaginable" at the right end of the line. The subject and joint assessor or the PI for the study must complete the global assessments independently from each other.

7.3.8.3 Simplified Disease Activity Index (SDAI)

The SDAI is the numerical sum of five outcome parameters: tender joint count and swollen joint count based on a 28-joint assessment, patient global assessment of disease activity, physician global assessment of disease activity and C-reactive protein (CRP in mg/dL). SDAI is calculated by the sponsor.

7.3.9 Patient Reported Outcomes

PRO assessments should be completed first (before other study procedures and administration of study medication) at each visit where they are required.

7.3.9.1 Patient Global Assessment of Joint Pain

The severity of the subject's joint pain will be assessed by completion of a VAS. The horizontal line is 100 mm in length with "0" and "no pain at all" on the left end of the line and "100" and "worst pain imaginable" on the right end of the line. This questionnaire should take approximately 1 minute to complete.

7.3.9.2 Patient Global Assessment of Disease Activity

The subject's global assessment of their arthritis disease activity will be assessed by completion of a VAS. The horizontal line is 100 mm in length with "0" and "No RA Activity At All" on the left end of the line and "100" and "Worst RA Activity Imaginable" on the right end of the line. The subject and health care provider must complete the global assessments independently from each other. This questionnaire should take approximately 1 minute to complete.

7.3.9.3 Disability Index of the Health Assessment Questionnaire

The Disability Index of the Health Assessment Questionnaire (HAQ-DI) will be utilized to assess the subject's physical function or disability according to the subject. The HAQ-DI asks about the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores). Responses in each functional area are scored from 0 indicating no difficulty to 3 indicating inability to perform a task in that area. The study staff should not clarify any of the questions for the subject. This questionnaire should take approximately 5 minutes to complete.

7.3.9.4 Medical Outcomes Short Form-36 Questionnaire (SF-36)

The Medical Outcomes Short Form-36 Questionnaire (SF-36) is a 36-item instrument that measures general health status. It includes 8 multi-item scales, each of which assess 1 of the following 8 health concepts: 1) **l**imitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The SF-36 assesses the subject's perception of health status over the previous month and takes about 15 minutes to complete.

7.4 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory with the exception of erythrocyte sedimentation rate (ESR), urine pregnancy, PPD, and Quantiferon (may be done by central or local laboratory). The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, serum pregnancy, urinalysis, high sensitivity CRP, and any other laboratory tests required. ESR, urine pregnancy and PPD testing, if applicable, will be performed

locally with kits provided by the central laboratory (except PPD). The results of this testing will be maintained in the source documents at the site. Amgen or designee will be responsible for biomarker development and pharmacogenetic assessments, and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay (depending on the assessment). The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples. All blood samples will be obtained by venipuncture before investigational product administration. The date and time of sample collection will be recorded in the source documents at the site. Specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples are listed below (Table 2).

Table 2. Analyte Listing

Chemistry	Urinalysis	Hematology	Other Labs
Sodium	Specific gravity	RBC	Serum beta hCG[a]
Potassium	pH	WBC	Hepatitis B surface antigen and Hepatitis B core antibody[b]
Chloride	Blood	Absolute neutrophil count	Hepatitis C virus antibody
Bicarbonate	Protein	Hemoglobin	High sensitivity C-reactive protein
Total protein	Glucose	Hematocrit	Tuberculosis Testing[c]
Albumin	Bilirubin	MCV	Rheumatoid Factor
Calcium	Microscopic (Reflex testing if abnormal)	MCH	Anti-CCP
Adjusted calcium		MCHC	
Magnesium		RDW	
Phosphorus		Platelets	
Glucose		WBC Differential • Bands/stabs • Eosinophils • Basophils • Lymphocytes • Neutrophils • Monocytes	
BUN or Urea			
Creatinine			
Uric acid			
Total bilirubin			
Direct bilirubin			
Alkaline phosphatase			
LDH			
AST (SGOT)			
ALT (SGPT)			

[a] For all women, unless at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
[b] At screening, if the subject is positive for hepatitis B core antibody, the confirmatory reflex testing will be performed using HBV DNA PCR.
[c] Subjects must receive either a PPD test or Quantiferon test at screening. National guidelines should be followed for appropriate tuberculosis screening in the setting of anti-TNF therapy.

7.4.1 Tuberculosis Testing

National guidelines should be followed for appropriate tuberculosis screening in the setting of anti-TNF therapy.

All subjects must receive either a PPD or Quantiferon test at screening per Section 4.1.1. PPD testing should be performed unless contraindicated.

7.4.1.1 PPD

The PPD test must be read by a trained healthcare professional 48 to 72 hours after the test is placed. PPD reader must be identified on the delegation of authority for this responsibility.

7.4.1.2 Quantiferon

If a subject does not receive a PPD test, then a Quantiferon test must be performed per Section 4.1.1. Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of samples (if applicable).

7.4.2 Erythrocyte Sedimentation Rate

ESR will be performed locally at each site and the ESR data will be submitted to the central laboratory per the instructions in the study manual provided by the central laboratory. The central laboratory will provide all supplies. The screening and baseline ESR may be performed by any trained staff at the site. Once the subject has been randomized, the ESR may only be performed by a trained individual at the site who does not perform any study assessments with subjects on the study. Staff performing the ESR must be identified on the delegation of authority for this responsibility. The results of the ESR performed after the subject has been randomized must be maintained in a blinded fashion so that it may not be viewed by staff who perform any study assessments with the subjects.

7.4.3 Urine Pregnancy Test

Urine pregnancy tests will be performed locally at each site. The central laboratory will provide the urine pregnancy tests on visits where required. Urine pregnancy tests must be given prior to dispensing investigational product. If a urine pregnancy test is positive, investigational product must be held; if pregnancy is confirmed, then investigational product must be discontinued.

7.5 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic

intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to etanercept and/or methotrexate.

7.6 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of RA and/or to identify subjects who may have positive or negative response to Amgen and non-Amgen investigational product. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

7.7 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand inflammatory conditions, the dose response and/or prediction of response to etanercept or methotrexate, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other

exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study. The data generated may potentially not be included in the subject's study data, except in the case of a possibly related serious adverse event, where data will be collected.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Run-in, Treatment, or Study

8.3.1 Reasons for Removal From Run-in

Reasons for removal from the run-in include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria, pregnancy)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up
- other protocol-specified criteria
  - as per Section 4.2.1 and Section 4.2.2

8.3.2 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- disease flare requiring treatment not allowed in the protocol (eg, colitis, asthma)

8.3.3 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up
- other protocol-specified criteria

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on-study, is not considered an adverse event.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury (DILI) (see Appendix A for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the end of treatment period are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to investigational product(s), and
- Action taken.

The adverse event grading scale used will be the Common Toxicity Criteria Version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product(s). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s)?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The Investigator is expected to follow reported adverse events until stabilization or reversibility.

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Adverse Event Summary CRF.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product(s) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an eSAE Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/eSAE Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may be asked to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators

will receive notification of related serious adverse event reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice (GCP).

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local regulatory requirements and procedures.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking etanercept, report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 4 weeks after the last dose of etanercept.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female subject breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- SDAI remission (≤ 3.3) at week 48

10.1.1.2 Secondary Endpoints

- SDAI score and change from baseline at all measured timepoints
- DAS-28-ESR and change from baseline at all measured timepoints
- DAS-28-CRP and change from baseline at all measured timepoints
- CDAI and change from baseline at all measured timepoints
- SDAI remission (≤ 3.3) at all measured timepoints
- Boolean remission at all measured timepoints
- Disease worsening defined as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization
- Time to disease worsening defined as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2 weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization

In subjects that receive rescue treatment during the double-blind treatment period

- Time to recapture SDAI remission after starting rescue treatment
- SDAI remission at week 48

10.1.1.3 Safety Endpoints

- Adverse events
- Serious adverse events
- Laboratory parameters

10.1.1.4 Exploratory Endpoints

- Components of SDAI at all measured timepoints
- HAQ-DI at all measured timepoints
- SF-36 domains, physical component summary, and mental component summary at all measured timepoints
- Biomarkers
- Pharmacogenetic parameters

10.1.2 Analysis Sets

10.1.2.1 Primary Analysis Set

The primary analysis set will include all randomized subjects. The analysis will be conducted according to the original randomization regardless of the actual treatment received during the study (as per intent-to-treat principle). All the primary, secondary, and exploratory efficacy endpoints will be evaluated on the primary analysis set.

10.1.2.2 Safety Analysis Set

This subset will include all randomized subjects who received at least one dose of any investigational product during the study. For all safety endpoints, subjects will be analyzed based on the actual treatment received.

10.1.3 Covariates and Subgroups

The following baseline covariates will be considered to assess their influence on the primary and secondary endpoints:

- age (years) (continuous)
- sex (male/female)
- race
- ethnicity (Hispanic or Latino vs Non-Hispanic or Latino)
- disease duration (years)
- baseline methotrexate dose
- other covariates may be evaluated as necessary

Subgroup analyses, which would be considered exploratory, may be performed if an examination of the above covariates suggests that any treatment difference for the primary and secondary endpoints depends on any baseline covariates.

10.2 Sample Size Considerations

The sample size was determined from a hypothesis of superiority of etanercept monotherapy over methotrexate monotherapy. The proportion of subjects achieving SDAI remission after 52 weeks of double-blind treatment in the PRESERVE and COMET studies was used to estimate the treatment effects. PRESERVE was a two-period study conducted in subjects with RA who had moderate disease activity despite a stable dose of oral methotrexate for a minimum of 8 weeks at the time of screening. Among all subjects who were in SDAI remission at both week 28 and week 36 (the last two visits of the open-label run-in period), the proportion of subjects who were still in remission after the 52-week double-blind period was 86.1% and 38.1%

for the etanercept plus methotrexate therapy and methotrexate monotherapy treatment groups, respectively. COMET was a two-period study conducted in subjects with active early RA. Among all subjects who received etanercept plus methotrexate therapy in Period 1 and were in SDAI remission at week 52, the last visit of Period 1, the proportion of subjects who were in still in remission after the 52-week double-blind Period 2 was 78.3% and 72.4%, respectively, for the etanercept plus methotrexate therapy and etanercept monotherapy treatment groups. Given key differences noted in this study, including the sustained period of remission prior to withdrawal, the response rate in the methotrexate monotherapy arm is approximated to be higher at 50%, **with** the response rate in the etanercept monotherapy arm **at approximately** 7**2**%. It is expected that compared to PRESERVE, subjects in the current study will have more stable disease at the time of randomization. Namely, subjects must be in very good disease control for 6 months prior to study entry and must be in SDAI remission at the end of a 24-week open-label run-in period.

The sample size is based on the adequacy to evaluate the efficacy of etanercept monotherapy compared to methotrexate monotherapy as measured by the primary endpoint of SDAI remission at week 48 at a significance level of 0.05. Based on a two-sided chi-square test with 90% power, 1**0**0 subjects per arm are required at randomization.

Using an assumed attrition rate of 30% in the open-label run-in period, due to exclusion of subjects with disease worsening during the run-in period, or other reasons, approximately **358** subjects will be enrolled in order to have approximately **250** subjects randomized in a 2:2:1 ratio to one of three treatment groups: etanercept monotherapy (n = 1**0**0), methotrexate monotherapy (n = 1**0**0)**,** and etanercept plus methotrexate combination therapy (n = **50**). Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately **250** subjects are randomized to treatment.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators, or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2, and Statistical Analysis Plan [SAP]).

10.4 Planned Analyses

10.4.1 Primary analysis

Primary analysis activities are commenced based on achieving the End of Study milestone described in Section 3.5.2.

10.4.2 Interim Analyses

No interim analysis is planned for this study.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Baseline demographics and disease characteristics will be summarized descriptively.

Summary descriptive statistics by each treatment group will be provided. For categorical endpoints, the descriptive statistics will contain the frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, minimum, maximum and 95% confidence interval.

Non-responder imputation will be employed for the missing values of the primary endpoint. Secondary efficacy endpoints will be summarized using observed cases only. As supportive analysis, the primary endpoint will also be summarized using observed cases.

The statistical test for the primary efficacy endpoint will be two-sided with a significance level of 0.05.

10.5.2 Primary Efficacy Endpoint

The primary analysis for the primary endpoint for this study**,** SDAI remission at week 48, will be performed using the primary analysis set. The primary endpoint will be measured by the proportion of subjects who maintain SDAI remission (SDAI ≤ 3.3) at week 48.

SDAI remission at week 48 for the etanercept monotherapy treatment arm will be compared to the methotrexate monotherapy arm using the chi-square test.

Both subjects who drop out and subjects receiving rescue therapy due to disease worsening during the double-blind period will be considered non-responders. Furthermore, the randomized subjects who did not receive any dose of any of the investigational products will be considered non-responders in the primary analysis.

As a sensitivity analysis, subjects who receive rescue therapy or that drop out will have their post-rescue SDAI responses set to missing and a multiple imputation technique to impute these values will be employed. The multiple imputation method is less

conservative than the non-responder imputation method and will be prospectively described in more detail in the SAP.

A subject's SDAI score is calculated as follows:

SDAI = 28-joint tender joint count + 28-joint swollen joint count + Patient Global Assessment of Disease Activity + Physician Global Assessment of Disease Activity + C-reactive protein (mg/dL).

10.5.3 Secondary Efficacy Endpoints

- Simplified Disease Activity Index remission (≤ 3.3) at week 48 for the etanercept plus methotrexate treatment arm will be compared to the methotrexate monotherapy arm using the chi-square test and will be presented with nominal p-values only (eg, no adjustment for multiplicity will be done).
- The proportion of subjects achieving SDAI remission, SDAI continuous score and SDAI change from baseline at all study timepoints will be summarized by treatment group. DAS28-ESR, DAS28-CRP and CDAI and their changes from baseline will be also summarized at all study timepoints by treatment group. Proportion of subjects achieving Boolean remission will be tabulated at all study timepoints by treatment group. Proportion of subjects with disease worsening (defined as an SDAI > 3.3 and ≤ 11 during two consecutive visits at least 2-weeks apart or SDAI > 3.3 and ≤ 11 on three or more separate visits or SDAI > 11 after randomization) as well as time to disease worsening will be evaluated.
- In subjects that receive rescue treatment during the double-blind treatment period time to recapture of SDAI remission after starting rescue treatment will be analyzed. Additionally, the proportion of subjects who recapture SDAI remission at week 48 will be summarized.

10.5.4 Exploratory Endpoints

Exploratory endpoints will also be summarized by treatment group at all timepoints. Exploratory endpoints include 28-swollen joint count, 28-tender joint count, Physician Global Assessment of Disease Activity (0-10 VAS), Patient Global Assessment of Disease Activity (0-10 VAS), HAQ-DI and SF-36.

10.5.5 Safety Endpoints

Safety analyses will be based on the safety analysis set. Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

Laboratory parameters with grade 3 or above will be summarized by study visit and treatment group. Vital signs will be reported in baseline summaries. Shift tables of the

worst on-study laboratory toxicity for analytes of interest based on Common Toxicity Criteria relative to baseline will be tabulated by treatment group (as described in the SAP).

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Global Clinical Trial Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent

form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an Investigator who provided significant contributions to either the design or interpretation of the study
- an Investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, and correspondence.

In this study, the IXRS system captures the following data points and these are considered source data: subject identification number, randomization number among others.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, ePROs may be considered as source documents.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The clinical monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The clinical monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global R&D Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate

the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self-Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. CRFs must be

completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

13. REFERENCES

Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum*. 2006;36:182-188.

Emery P, Breedveld F, van der Heijde D, et al. Two-Year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis. A two-year, double blind, randomized study. *Arthritis Rheum*. 2010;62:674-682.

Emery P, Hamoudeh M, FitzGerald OM, Combe B, Gaylord S, et al. Induction of remission in patients with up to 12 months of moderate-to-severe rheumatoid arthritis symptoms treated with etanercept plus methotrexate for 52 weeks. *Arthritis Rheum* 2012;64(Supp 10) S1077.

Klareskog L, van der Heijde D, Jager JP, Gough A, Kalden J et al. Therapeutic effect of combination of etanercept and methotrexate compared to each treatment alone in patients with rheumatoid arthritis: double-blind randomized controlled trial. *Lancet*. 2004; 363(9410):675-681

Pope J, Haraoui B, Thorne JC et al. The Canadian Methotrexate and Etanercept Outcome Study: a randomized trial of discontinuing versus continuing methotrexate after 6 months of etanercept and methotrexate therapy in rheumatoid arthritis. *Ann Rheum Dis*. 2013;0:1-8

Smolen JS, Nash P, Durez, P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomized controlled trial. *Lancet.* 2013;381:918-929 .

Van Vollenhoven R, Franck-Larsson M, Leirisalo-Repo M, et al. In rheumatoid arthritis patients with stable low disease activity on methotrexate plus etanercept, continuation of etanercept 50 mg or 25 mg weekly are both clinically superior to discontinuation: results from a randomized, 3-arm, double–blind study. *Ann Rheum Dis*. 2013a;72:A434-A435.

Van Vollenhoven R, Franck-Larsson M, Leirisalo-Repo M, et al. In rheumatoid arthritis patients with stable low disease activity on methotrexate plus etanercept, continuation of etanercept 50 mg or 25 mg weekly are both clinically superior to discontinuation: results from a randomized, 3-arm, double–blind study. Poster presented at: EULAR; June 12-15, 2013b; Madrid, Spain. Poster FRI0185.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Toxicity Criteria Version 4.0 is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications\ctc.htm

General United States Food and Drug Administration Guidance on Hepatotoxicity Stopping and Rechallenge Rules

As noted in Section 6.4, a Food and Drug Administration Guidance exists for drug-induced liver injury (DILI). This guidance is general for all investigational and marketed products, and is synopsized here as a reference. It provides criteria for reporting, monitoring, and withholding investigational product in the event that a subject develops signs or symptoms of hepatotoxicity during a clinical trial.

Criteria for Permanent Withholding of Investigational Product due to Potential Hepatotoxicity

Investigational product should be discontinued permanently and the subject should be followed for possible drug-induced liver injury, if ALL of the criteria below are met:

- TBL > 2 x ULN or international normalized ratio > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
≤ 1.5 ULN	> 3 x ULN

- AND no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or total bilirubin values include, but are not limited to the following:
- obstructive gall bladder or bile duct disease
- viral or alcoholic hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella)
- progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)
- hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right-sided heart failure
- concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome); alpha-one antitrypsin deficiency
- autoimmune hepatitis
- nonalcoholic steatohepatitis or other "fatty liver disease"

It should be noted that some of the circumstances above may nevertheless warrant discontinuation of investigational product without requiring assessment for drug-induced liver injury.

Criteria for Conditional Withholding of Investigational Product due to Potential Hepatotoxicity

For subjects that do not meet the criteria for permanent withholding of investigational product outlined above, investigational product should be withheld if ANY of the following criteria are met, and the subject should be evaluated for drug-induced liver injury:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8 x ULN at any time
Any	> 5 x ULN but < 8 x ULN for ≥ 2 weeks
Any	> 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule

- OR: clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3 x ULN, investigational product should be withheld.
- OR: total bilirubin > 3 x ULN at any time
- OR: alkaline phosphatase > 8 x ULN at any time

Investigational product should be withheld pending investigation into alternative causes of drug-induced liver injury. If investigational product is withheld, the subject should be followed according to recommendations above for possible drug-induced liver injury. Rechallenge may be considered if an alternative cause is discovered and the laboratory abnormalities resolve to normal or baseline.

Criteria for Rechallenge of investigational product after Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, principal investigator, and Amgen.

If signs or symptoms recur with rechallenge, then investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation should never be rechallenged.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL according to the criteria specified in Section 6.4 (3 x ULN for AST/ALT and 2 x ULN for TBL) require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified above or who experience AST or ALT elevations >3 x ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents

  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix B. eSerious Adverse Event Contingency Form

AMGEN Study # 20110186 Etanercept	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the **EDC system (eg, Rave)**, provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Etanercept No✓ Yes✓ / Methotrexate No✓ Yes✓ / PFS No✓ Yes✓ / <Pldevice> No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Etanercept/Prefilled Syringe (PFS)	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Methotrexate	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN Study # 20110186 Etanercept	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20110186 Etanercept	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20110186

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm____ / dd____ / yyyy____ ☐ Unknown

Estimated date of delivery mm____ / dd____ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____ / dd____ / yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm____ / dd____ / yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011

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AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20110186

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Amendment 5

Protocol Title: A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

Amgen Protocol Number (Etanercept) 20110186

EudraCT Number: 2014-004868-38

NCT Number: 02373813

Amendment Date: 17 October 2017

Rationale:

This protocol is being amended to:

- Reduce study sample size due to adjustments in estimated effect sizes for treatment groups.

Description of Changes

Section: Global

Change: Version date updated throughout document from 20 December 2016 to **17 October** 20**17**.

Section: Global

Replace:

International Conference on Harmonisation

With:

International **Council for** Harmonisation

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title Page

Add:

NCT Number: 02373813

Section: Title Page

Add:

Date:	29 July 2014
Amendment 1	18 May 2015
Superseding Amendment 1:	08 July 2015
Amendment 2	30 October 2015
Amendment 3	03 November 2016
Amendment 4	20 December 2016
Amendment 5	**17 October 2017**

Section: Protocol Synopsis, Study Design, Paragraph 2

Replace:

Approximately 465 subjects will be enrolled and approximately 325 subjects will be randomly assigned in a 2:2:1 ratio to one of three treatment groups: etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate (n = 130),

oral methotrexate 10 to 25 mg weekly plus placebo for etanercept (n = 130) and etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly (n = 65).

With:

Approximately **358** subjects will be enrolled and approximately **250** subjects will be randomly assigned in a 2:2:1 ratio to one of three treatment groups: etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate (n = 1**0**0), oral methotrexate 10 to 25 mg weekly plus placebo for etanercept (n = 1**0**0) and etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly (n = **50**).

Section: Protocol Synopsis, Sample Size

Replace:

Approximately 465 subjects enrolled and approximately 325 subjects randomized.

With:

Approximately **358** subjects enrolled and approximately **250** subjects randomized.

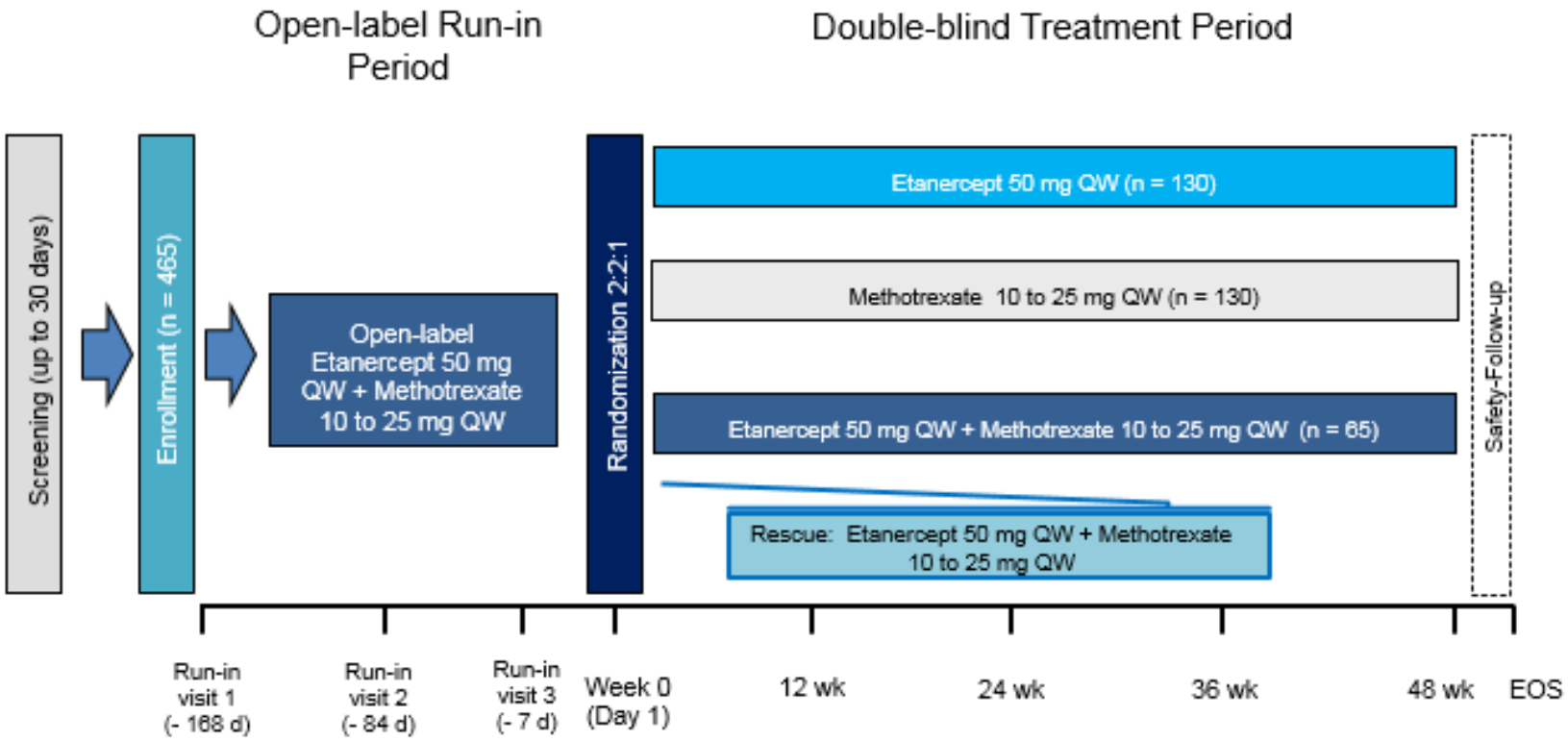
Section: Protocol Synopsis, Non-Amgen Investigational Product Dosage and Administration

Delete:

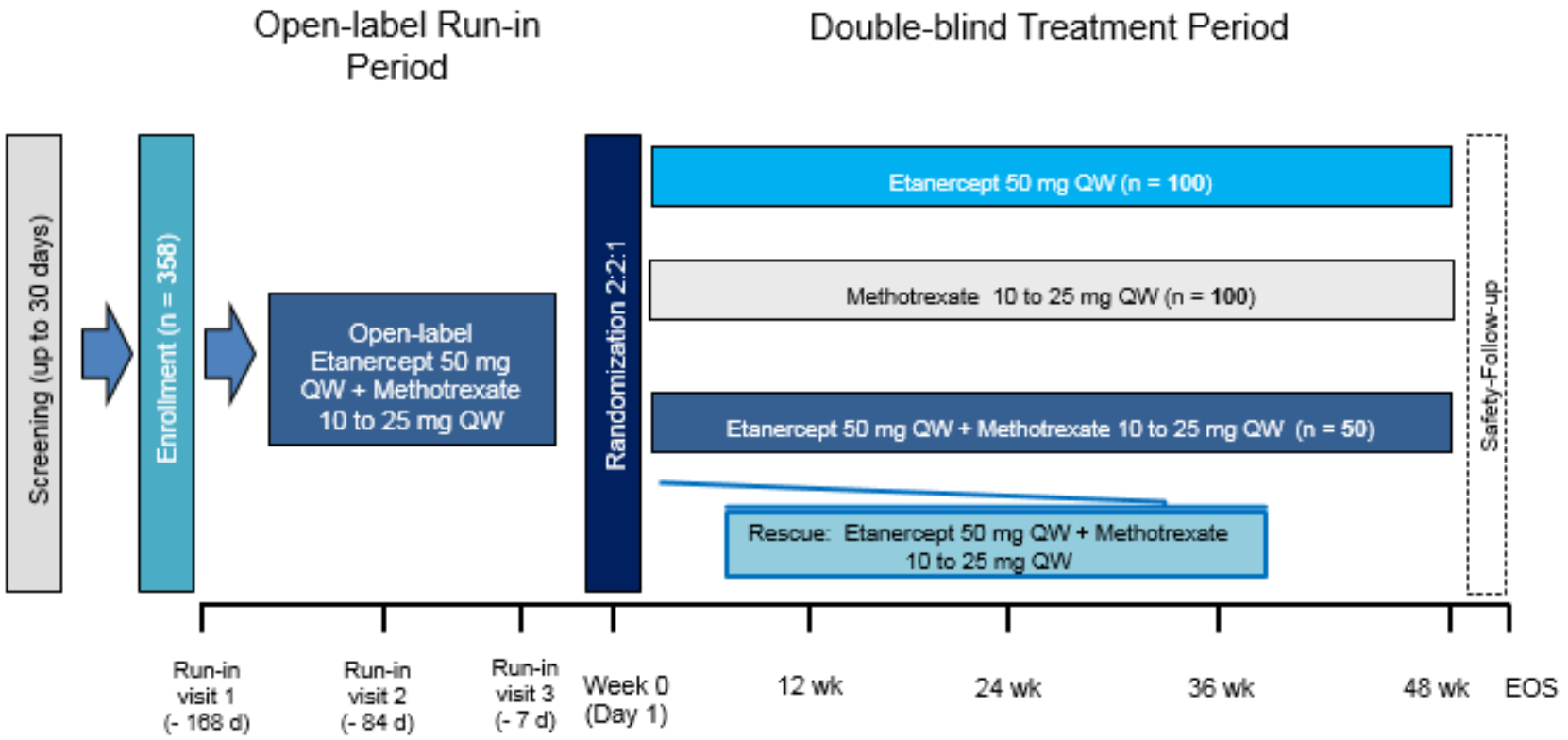
During the double-blind treatment period, methotrexate will be supplied as 2.5 mg methotrexate ~~tablets,~~ capsules, or as matching placebo capsules and will be taken once weekly by oral administration for 48 weeks.

Section: Study Design and Treatment Schema

Replace:



With:


Open-label Run-in Period
Double-blind Treatment Period
Screening (up to 30 days)
Enrollment (n = 358)
Open-label Etanercept 50 mg QW + Methotrexate 10 to 25 mg QW
Randomization 2:2:1
Etanercept 50 mg QW (n = 100)
Methotrexate 10 to 25 mg QW (n = 100)
Etanercept 50 mg QW + Methotrexate 10 to 25 mg QW (n = 50)
Rescue: Etanercept 50 mg QW + Methotrexate 10 to 25 mg QW
Safety-Follow-up
Run-in visit 1 (- 168 d)
Run-in visit 2 (- 84 d)
Run-in visit 3 (- 7 d)
Week 0 (Day 1)
12 wk
24 wk
36 wk
48 wk
EOS

Section: 3.1 Study Design, Paragraph 2-3 and Bullet 1-3

Replace:

The study will enroll approximately 465 subjects. During the run-in period subjects will receive open-label etanercept and methotrexate at the same dose they were receiving during screening. It is expected that approximately 30% of subjects will early terminate the run-in period. Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately 325 subjects are randomized to treatment.

Approximately 325 subjects will be randomly assigned in a 2:2:1 ratio to one of three treatment groups:

- Etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate (n = 130)
- Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept (n = 130)
- Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly (n = 65)

With:

The study will enroll approximately **358** subjects. During the run-in period subjects will receive open-label etanercept and methotrexate at the same dose they were receiving during screening. It is expected that approximately 30% of subjects will early terminate the run-in period. Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately **250** subjects are randomized to treatment.

Approximately **250** subjects will be randomly assigned in a 2:2:1 ratio to one of three treatment groups:

- Etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate (n = 1**0**0)
- Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept (n = 1**0**0)
- Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly (n = **50**)

Section: 3.3 Number of Subjects, Paragraph 2-3

Replace:

The number of subjects expected to be enrolled in the study is approximately 465 of which approximately 325 will be randomized to the double-blind treatment period.

Amgen may choose to alter the sample size of enrolled subjects to ensure that approximately 325 subjects are randomized to the double-blind treatment period.

With:

The number of subjects expected to be enrolled in the study is approximately **358** of which approximately **250** will be randomized to the double-blind treatment period.

Amgen may choose to alter the sample size of enrolled subjects to ensure that approximately **250** subjects are randomized to the double-blind treatment period.

Section: 3.5.2 End of Study

Replace:

End of Study will be the time when the last subject is assessed or receives an intervention for evaluation in the study.

With:

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study**: The end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study **(ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.**

Section: 10.2 Sample Size Considerations, Paragraph 1

Delete:

The sample size was determined from a hypothesis of superiority of ~~both etanercept plus methotrexate therapy and~~ etanercept monotherapy over methotrexate monotherapy.

Section: 10.2 Sample Size Considerations, Paragraph 1

Replace:

Given key differences noted in this study, including the sustained period of remission prior to withdrawal, the response rate in the methotrexate monotherapy arm is

approximated to be higher at 50%, while the response rate in the etanercept monotherapy arm is a more conservative 70%.

With:

Given key differences noted in this study, including the sustained period of remission prior to withdrawal, the response rate in the methotrexate monotherapy arm is approximated to be higher at 50%, **with** the response rate in the etanercept monotherapy arm **at approximately** 7**2**%.

Section: 10.2 Sample Size Considerations, Paragraph 2

Replace:

Based on a two-sided chi-square test with 90% power, 130 subjects per arm are required at randomization.

With:

Based on a two-sided chi-square test with 90% power, 1**0**0 subjects per arm are required at randomization.

Section: 10.2 Sample Size Considerations, Paragraph 3

Replace:

Using an assumed attrition rate of 30% in the open-label run-in period, due to exclusion of subjects with disease worsening during the run-in period, or other reasons, approximately 465 subjects will be enrolled in order to have approximately 325 subjects randomized in a 2:2:1 ratio to one of three treatment groups: etanercept monotherapy (n = 130), methotrexate monotherapy (n = 130) and etanercept plus methotrexate combination therapy (n = 65). Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately 325 subjects are randomized to treatment.

With:

Using an assumed attrition rate of 30% in the open-label run-in period, due to exclusion of subjects with disease worsening during the run-in period, or other reasons, approximately **358** subjects will be enrolled in order to have approximately **250** subjects randomized in a 2:2:1 ratio to one of three treatment groups: etanercept monotherapy (n = 1**0**0), methotrexate monotherapy (n = 1**0**0)**,** and etanercept plus methotrexate combination therapy (n = **50**). Amgen may choose to alter the sample size of subjects enrolled in order to ensure that approximately **250** subjects are randomized to treatment.

Amendment 4

Protocol Title: A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

Amgen Protocol Number (Etanercept) 20110186

EudraCT Number: 2014-004868-38

Amendment Date: 20 December 2016

Rationale:

This protocol amendment change document captures changes made from Version 2 to Version 3, as well as changes made from Version 3 to Version 4. Version 3 was approved 03 November 2016; however, submission of the protocol to sites was halted once it was learned there would be updates specific to VHP countries in Europe.

This protocol is being amended to:

- Update clinical hypothesis to align with the primary objective of the study.
- Update CTCAE grading version to 4.0 to reflect the most recent version.
- Update inclusion and exclusion criteria in order to decrease the stringency of subject eligibility.
- Reduce strictness of subject re-screening criteria.
- Reduce study sample size due to adjustments in estimated effect sizes for treatment groups.
- Remove prior use of a biologic agent as a covariate influencing primary and secondary endpoints.
- Remove sequential testing in order to align with the updated clinical hypothesis.

Amendment 3

Protocol Title: A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

Amgen Protocol Number (Etanercept) 20110186

EudraCT Number: 2014-004868-38

Amendment Date: 03 November 2016

Rationale:

This protocol is being amended to:

- Update clinical hypothesis to align with the primary objective of the study.
- Update CTCAE grading version to 4.0 to reflect the most recent version.
- Update inclusion and exclusion criteria in order to decrease the stringency of subject eligibility.
- Reduce study sample size due to adjustments in estimated effect sizes for treatment groups.
- Remove prior use of a biologic agent as a covariate influencing primary and secondary endpoints.
- Remove sequential testing in order to align with the updated clinical hypothesis.

Amendment 2

Protocol Title: A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

Amgen Protocol Number (Etanercept) 20110186

EudraCT Number: 2014-004868-38

Original Protocol:	29 July 2014
Amendment 1 Date:	18 May 2015
Superseding Amendment 1 Date:	08 July 2015
Amendment 2 Date:	30 October 2015

Rationale:

The protocol is being amended to be consistent with international regulations and requirements.

Amendment 1

Protocol Title: A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

Amgen Protocol Number (Etanercept) 20110186

Original Protocol:	29 July 2014
Amendment Date:	18 May 2015

Rationale:

The protocol is being amended to:

- Provide clarification for reporting hepatotoxicity as a serious adverse event
- Clarify indications regarding use of etanercept in the US and Canada, and add medical information phone number as a reference for countries other than US and Canada
- Provide clarification for inclusion criteria for etanercept use, specifying the dose
- Provide clarification for inclusion criteria for methotrexate use, accommodating conversion from subcutaneous to oral route
- Provide clarification regarding formulation of methotrexate, as it is available in tablets, but will be encapsulated when given as placebo
- Provide clarifications regarding joint assessments, to strengthen wording related to continuity of assessors in the study, and allowing for assessments by principal investigators
- Provide updates throughout to reflect the number of global participating sites
- Add the EudraCT number
- Add medical information phone number as a reference for countries other than US and Canada
- Make minor corrections and clarifications throughout