

**Title: A Multicenter Double-blind, Randomized Controlled Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Psoriatic Arthritis**

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I have read the attached protocol entitled A Multicenter Double-Blind, Randomized Controlled Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Psoriatic Arthritis, dated **31 August 2016**, and agree to abide by all provisions set forth therein.

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Signature

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Name of Investigator

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Date (DD Month YYYY)

## **Protocol Synopsis**

**Title:** A Multicenter Double-Blind, Randomized Controlled Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Psoriatic Arthritis

**Study Phase:** Phase 3

**Indication:** Psoriatic Arthritis (PsA)

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**Primary Objective:** To evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy, in subjects with PsA as measured by the proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at week 24.

**Key Secondary Objective:** To evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy as measured by the proportion of subjects achieving Minimal Disease Activity (MDA) at week 24.

**Other Secondary Objectives:**

To evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy on the following:

- Other measures of arthritis activity
- Measures of non-arthritic PsA disease activity
- Key patient reported outcomes (PRO) related to physical function and quality of life

**Safety Objectives:**

- To evaluate the safety of etanercept and methotrexate

**Hypotheses:** Primary: Etanercept plus methotrexate therapy and etanercept monotherapy are more efficacious than methotrexate monotherapy as measured by the proportion of subjects with PsA achieving ACR 20 response at week 24.

Secondary: Etanercept plus methotrexate therapy and etanercept monotherapy are more efficacious than methotrexate as measured by the proportion of subjects with PsA achieving MDA response at week 24.

**Primary Endpoint:** ACR 20 response at week 24

**Key Secondary Endpoint:** MDA response at week 24

**Other Secondary Endpoints:**

- Modified Nail Psoriasis Severity Index (modified NAPS) score and change from baseline at week 24
- Leeds dactylitis score and change from baseline at week 24
- Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score and change from baseline at week 24
- ACR 20 response at all other measured timepoints
- MDA response at all other measured timepoints
- Psoriatic Arthritis Disease Activity Score (PASDAS) at all measured timepoints
- ACR 50, ACR 70, and components of ACR at all measured timepoints
- Simplified Disease Activity Index (SDAI) and change from baseline at all measured timepoints
- Clinical Disease Activity Index (CDAI) and change from baseline at all measured timepoints
- Disease activity score (28 joint) using the C-reactive protein formula (DAS28-CRP) and change from baseline at all measured timepoints

- Disability Index of the Health Assessment Questionnaire (HAQ-DI) score and change from baseline at week 24
- Medical Outcomes Short Form-36 Questionnaire (SF-36) score and change from baseline at week 24

For subjects with involved body surface area (BSA)  $\geq$  3% at baseline:

- Static Physician Global Assessment of Psoriasis (sPGA) at week 24
- BSA at week 24

**Safety Endpoints:**

- Adverse events
- Serious adverse events
- Laboratory parameters and vital signs

**Study Design:** This is a multicenter, randomized, double-blind controlled study in subjects with PsA. The study will consist of a 30-day screening period, a 48-week double-blind treatment period and a 30-day safety follow-up period. Approximately 840 subjects will be randomly assigned in a 1:1:1 ratio to one of three treatment groups (280 per group): etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 20 mg weekly, etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate, and oral methotrexate 20 mg weekly plus placebo for etanercept. Starting at week 24 visit, subjects who have an inadequate response will be provided rescue treatment of etanercept plus methotrexate for the remainder of the study. Original treatment assignments will remain blinded until all subjects reach the week 48 or early termination visit, whichever comes first.

**Sample Size:** Approximately 840 subjects will be enrolled

**Summary of Subject Eligibility Criteria:** Subjects must be adults with active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR) who are naïve to etanercept and other biologics and have no prior use of methotrexate for the treatment of PsA. Prior treatment with methotrexate is allowed if indicated for psoriasis as long as discontinuation was not due to toxicity or intolerance and treatment was discontinued  $\geq$  6 months prior to baseline. For a full list of eligibility criteria, please refer to [Section 4.1.1](#) through [Section 4.1.2](#).

**Investigational Product**

**Amgen Investigational Product Dosage and Administration:** Etanercept dosing in the planned study follows the recommended label dosing for subjects with PsA. Etanercept will be provided as a 50 mg pre-filled syringe or matching placebo for injection once weekly for 48 weeks. See [Sections 6.2.1](#).

**Non-Amgen Investigational Product Dosage and Administration:** Methotrexate dosing will begin at a dose of 10 mg on day 1 and will be titrated up to 20 mg weekly over a 4-week period. Methotrexate will be supplied as 2.5 mg capsules or as matching placebo capsules and will be taken once weekly by oral administration for 48 weeks. For those subjects receiving rescue therapy, methotrexate will be dispensed as 2.5 mg tablets. 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 week as 1 mg daily per investigator judgment OR administration according to the local standard of care. See [Section 6.3.1](#).

**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,

C-reactive protein and biomarkers, tender and swollen joint assessment and count, physician global assessment, Leeds dactylitis index, SPARCC enthesitis index, modified NAPS1, BSA, sPGA, radiographs and PROs. 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 analysis will occur after all data through week 48 is finalized. The primary analysis of the primary and key secondary endpoints will be based on the full analysis set. Treatment effect between etanercept plus methotrexate therapy and methotrexate monotherapy and between etanercept monotherapy and methotrexate monotherapy will be tested in a Bonferroni-based gatekeeping chain procedure to control the family-wise 2-sided type one error rate at 0.05. Between treatment comparisons will be made using the stratified Cochran-Mantel-Haenszel (CMH) test with baseline body mass index and prior non-biologic disease modifying antirheumatic drug (DMARD) use as the stratification factors. All other efficacy endpoints will be tested at a significance level of 0.05 without adjusting for multiplicity. Safety endpoints will be summarized descriptively based on the safety analysis set. For a full description of statistical analysis methods, please refer to [Section 10](#).

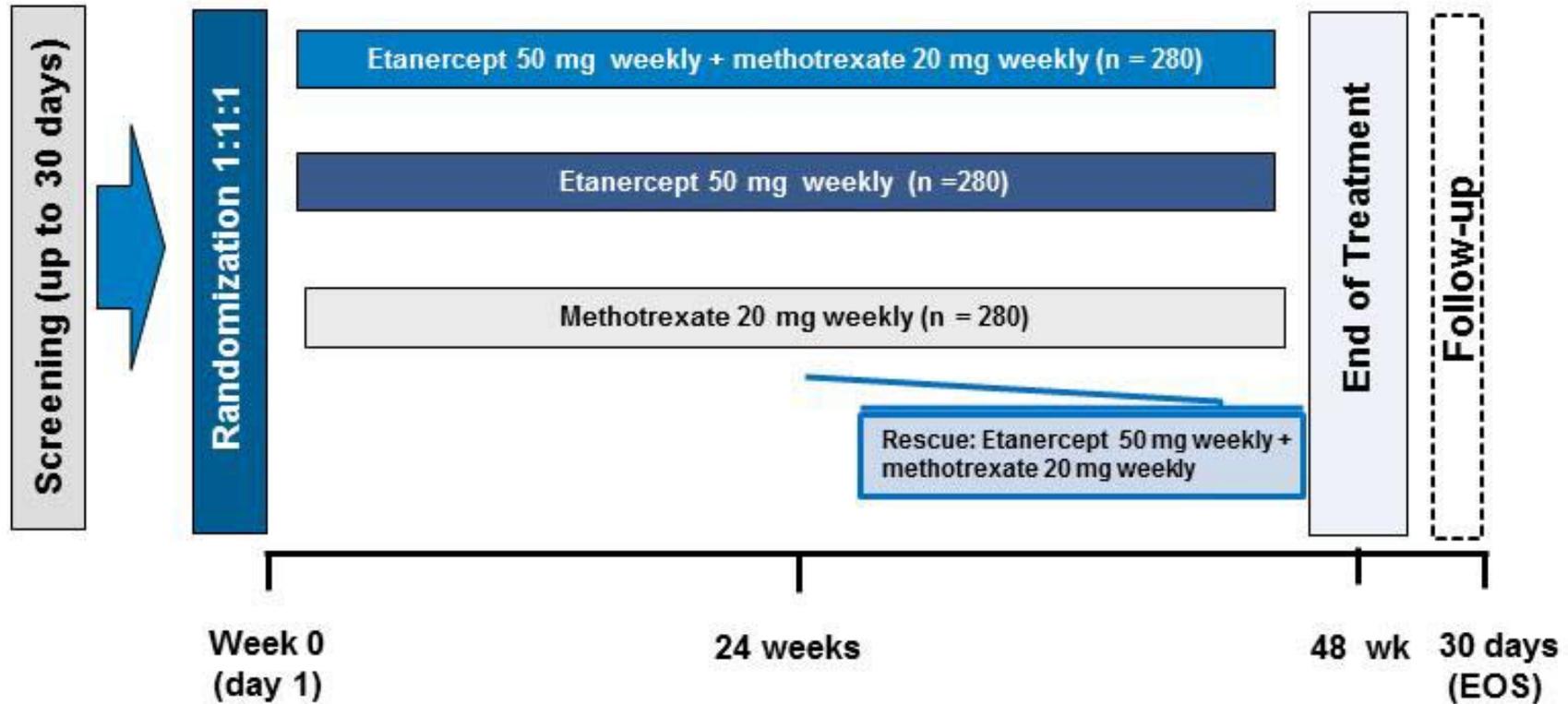
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**Sponsor:** Amgen Inc

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
ACR	American College of Rheumatology
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
CDAI	Clinical disease activity index
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic case report form
CRP	C-reactive protein
DAS28-CRP	Disease activity score (28 joint) using the C-reactive protein formula
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
EOS	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.
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
FDA	Food and Drug Administration
GCP	Good clinical practice
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Disability Index of the Health Assessment Questionnaire
<b>HBV</b>	<b>Hepatitis B virus</b>
HCP	Health care provider
ICH	International Conference on Harmonisation

Abbreviation or Term	Definition/Explanation
Interactive Voice Response System (IXRS)	Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IPIM	Investigational product instruction manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
MIPA study	Methotrexate in Psoriatic Arthritis Study
MDA	Minimal Disease Activity
Modified NAPS I	Modified Nail Psoriasis Severity Index
van der Heijde mTSS	van der Heijde Modified Total Sharp Score
NSAID	Non-steroidal anti-inflammatory drug
PASDAS	Psoriatic Arthritis Disease Activity Score
<b>PCR</b>	<b>Polymerase chain reaction</b>
PFS	Pre-filled syringe
PI	principal investigator
PPD	Purified protein derivative
PRO	Patient reported outcomes
PsA	Psoriatic arthritis
RBC	Red blood cells
SAP	statistical analysis plan
SDAI	Simplified Disease Activity Index
SF-36	Medical Outcomes Short Form-36 Questionnaire
SPARCC	Spondyloarthritis Research Consortium of Canada
sPGA	Static Physician Global Assessment of Psoriasis
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 plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy, in subjects with psoriatic arthritis (PsA) as measured by the proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at week 24.

### 1.2 Key Secondary Objective

To evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy as measured by the proportion of subjects achieving minimal disease activity (MDA) at week 24.

### 1.3 Other Secondary Objectives

To evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy on the following:

- Other measures of arthritis activity
- Measures of non-arthritic PsA disease activity
- Key patient reported outcomes (PRO) related to physical function and quality of life

### 1.4 Safety Objectives

To evaluate the safety of etanercept and methotrexate.

### 1.5 Exploratory Objectives

To evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy on the following:

- Other measures of disease activity including the skin
- Other PROs
- Inhibition of radiographic progression as measured by the van der Heijde modified Total Sharp score (mTSS) for PsA
- 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 PsA and/or subject response to etanercept.

## 2. BACKGROUND AND RATIONALE

### 2.1 Disease

PsA is a chronic inflammatory disorder of the peripheral joints and axial skeleton that occurs in 7% to 34% of patients with psoriasis ([Scarpa et al, 1984](#); [Biondi et al, 1989](#); [Espinoza et al, 1992](#); [Shbeeb et al, 2000](#)), which in turn has a prevalence of 1% to 3% in the general population ([Biondi et al, 1989](#); [Koo, 1996](#)). Articular involvement can vary

widely from an isolated monoarthritis to a very destructive diffuse arthritis mutilans. Other symptoms associated with PsA include dactylitis, enthesitis, and nail changes. Typical nail changes include pitting of the nail, onycholysis, ridges, and thickening of the nail. Although most patients have associated psoriasis, PsA can present without skin changes. Radiographic features include joint erosions, joint space loss, osteolysis that may cause penciling of the phalanx, and periostitis. PsA can lead to permanent destruction of joints and functional disabilities.

## **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 rheumatoid arthritis, PsA, 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 fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton TNF receptor linked to the Fc portion of human IgG1. Etanercept inhibits binding of TNF- $\alpha$  and TNF- $\beta$  (lymphotoxin alpha [LT- $\alpha$ ]) to cell surface TNF receptors, rendering TNF biologically inactive.

In many countries, etanercept is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with PsA.

Etanercept is also indicated for the treatment of: (1) moderately to severely active rheumatoid arthritis; (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 Investigator's Brochure or product label for additional information related to physical, chemical, and pharmaceutical properties and formulations.

## **2.3 Non-Amgen Medicinal Product Background: Methotrexate**

Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases, psoriasis, and rheumatoid arthritis. Methotrexate or its metabolites inhibit dihydrofolic acid reductase and antagonize thymidylate synthase. Methotrexate is thought to inhibit 5-aminoimidazole 4-carboxamide ribonucleotide transformylase which leads to an

increase in both intracellular and extracellular adenosine. Methotrexate is one of the most commonly used non-biologic disease modifying antirheumatic drug (DMARD) in PsA. Although the use of methotrexate is standard therapy in the medical community and it is mentioned in guidelines in the treatment of PsA, it is not an approved drug for the treatment of PsA in many countries.

Refer to the regional manufacturer package insert for additional information.

## 2.4 Rationale

Etanercept has been approved for PsA by the FDA and Health Canada and is indicated for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function. Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Methotrexate is one of the most commonly used non-biologic DMARD in PsA as monotherapy or in combination therapy with other synthetic DMARDs or with biologic DMARDs. Although methotrexate is commonly used in treating PsA, it is unclear how effective it is in PsA. The most recent randomized placebo-controlled trial of methotrexate in PsA is the Methotrexate in Psoriatic Arthritis (MIPA) study ([Kingsley et al, 2012](#)). This was a 6-month, double-blind, parallel-group study in methotrexate naïve subjects randomized to receive methotrexate (15 mg/wk; n = 109) or placebo (n = 112). In an intent-to-treat analysis, there were no statistically significant improvements in measures of disease activity across groups at 24 weeks. The odds ratios (95% CI) for Psoriatic Arthritis Response Criteria, ACR 20, and Disease activity score (28 joint) responders for the methotrexate and placebo groups were 1.77 (0.97, 3.23; p = 0.06), 2.00 (0.65, 6.22; p = 0.23), and 1.70 (0.90, 3.17; p = 0.10), respectively. In a completer analysis, percent responders for methotrexate and placebo were 34% and 21% for ACR 20 respectively for a difference of 13%. In the PsA pivotal trial, ACR 20 response at week 24 was 50% and 14% in the etanercept and placebo groups respectively for a difference of 36%. Nevertheless, comparisons with the MIPA trial need to be qualified by the fact that the subjects in the etanercept pivotal trial were not uniformly methotrexate naïve. Furthermore, in the MIPA trial the target dose of methotrexate was 15 mg QW, a less than maximal clinically used dose level.

In rheumatoid arthritis, combining TNF inhibitors such as etanercept with methotrexate leads to superior efficacy relative to each agent used alone ([Klareskog et al, 2004](#)). The role of methotrexate in combination with etanercept in PsA remains unclear. Analysis of

data from 440 PsA patients in the Norwegian DMARD longitudinal observational study showed no consistent differences in response over a 12-month period between patients who started their TNF inhibitor as monotherapy or in combination with methotrexate (Fagerli et al, 2014). Similar findings were found in a United States registry (Mease et al, 2013). No difference was found in reaching clinical disease activity index (CDAI) low disease activity or staying in low disease activity on anti-TNF monotherapy vs. combination with methotrexate in this study (Mease et al, 2013). These data suggest key differences in the response of PsA patients compared to RA patients to methotrexate and highlight the importance of characterizing the role of etanercept as a monotherapy agent in PsA.

A new disease activity state called MDA, has been developed and validated (Coates et al, 2010a and Coates et al, 2010b). MDA represents a low disease activity state and would further the 'treat-to-target' approach in PsA. The MDA criteria is specific for PsA and incorporates measures of joint and enthesal inflammation, skin disease, PROs and functional disability to assess the subject's disease activity. The results of the validation analysis support the prognostic value of the PsA MDA criteria and show that subjects achieving MDA are more likely to have a better radiologic outcome (Antoni et al, 2005a, Antoni et al, 2005b).

This study will also aim to characterize the response rates of etanercept on enthesitis, dactylitis, and psoriatic nail changes. The PRESTA trial, assessed two different regimens of etanercept (50 mg twice weekly or 50 mg once weekly) in subjects with psoriasis and PsA. Etanercept 50 mg once weekly resulted in a 70.0% and 81.3% improvement from baseline in enthesitis at week 12 and 24 respectively. Similarly, improvement in dactylitis from baseline at weeks 12 and 24 were 78.4% and 84.8%, respectively (Sterry et al, 2010). There is a paucity of data regarding the efficacy of methotrexate monotherapy on dactylitis and enthesitis in patients with PsA. A recent study looking at the effect of etanercept on the Nail Psoriasis Severity Index (NAPSI) score at week 12 and 24 improved by 50% and 72%, respectively on a weekly dose of Enbrel of 50 mgs (Ortonne et al, 2013). In another recent study comparing improvement in nail changes on methotrexate monotherapy compared to cyclosporine monotherapy, methotrexate demonstrated a 30% improvement at 12 weeks and a 54% improvement at 24 weeks in the NAPSI score (Gümüşel et al, 2011).

## 2.5 Clinical Hypotheses

Primary: Etanercept plus methotrexate therapy and etanercept monotherapy are more efficacious than methotrexate monotherapy as measured by the proportion of subjects with PsA achieving ACR 20 response at week 24.

Secondary: Etanercept plus methotrexate therapy and etanercept monotherapy are more efficacious than methotrexate as measured by the proportion of subjects PsA achieving MDA response at week 24.

## 3. EXPERIMENTAL PLAN

### 3.1 Study Design

This is a phase 3, multicenter, randomized, double-blind controlled study in subjects with active PsA naïve to biologics and with no prior use of methotrexate for the treatment of PsA. The study will consist of a 30-day screening period, a 48-week randomized double-blind treatment period, and a 30-day safety follow-up period.

Approximately 840 subjects will be randomly assigned in a 1:1:1 ratio to one of three treatment groups (280 per arm):

- Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 20 mg weekly
- Etanercept 50 mg weekly by subcutaneous injection plus oral placebo for methotrexate
- Oral methotrexate 20 mg weekly plus placebo for etanercept

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](#).

#### 3.1.1 Rescue Therapy

At or after week 24, subjects who have an inadequate response as defined in Section 3.1.2. will receive rescue therapy with etanercept plus methotrexate until the end of the treatment period. Prior to initiation of etanercept plus methotrexate rescue therapy subjects must complete the procedures outlined for the disease assessment visit as described in [Section 7.2.5](#) and [Table 1](#).

#### 3.1.2 Inadequate Response

Inadequate response is defined by having < 20% improvement in their tender and < 20% in their swollen joint counts from baseline at or after week 24. This will be calculated automatically based on the joint count. Inadequate response may be assessed at a

regularly scheduled visit or at a disease assessment visit as described in [Section 7.2.5](#). All subjects that initiate rescue treatment must complete a disease assessment follow-up visit 4 weeks later to monitor for labs (see [Section 7.2.5](#) and [Table 1](#)).

Subjects randomized to the etanercept plus methotrexate arm that have an inadequate response will continue to receive the same treatment.

### **3.2 Number of Sites**

Approximately 105 sites globally will participate in the study. Additional 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 840. There will be approximately 280 subjects per treatment arm.

Sample size considerations are provided in [Section 10.2](#).

### **3.4 Replacement of Subjects**

Subjects who are withdrawn or removed from treatment or 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 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 56 weeks including the screening and safety follow-up telephone call.

#### **3.5.2 End of Study**

End of study is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study.

## **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).

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

#### 4.1 Inclusion and Exclusion Criteria

##### 4.1.1 Inclusion Criteria

101. Subject has provided informed consent prior to initiation of any study-specific activities/procedures.
102.  $\geq 18$  years of age at screening
103. subject has had a diagnosis of PsA by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria
104. subject has  $\geq 3$  tender and  $\geq 3$  swollen joints (as part of a 68/66 joint count) at screening and at baseline
105. subject has an active psoriatic skin lesion (at least one psoriatic plaque approximately 2 cm or more in diameter)
106. subject is naïve to etanercept and any other biologic for the treatment for PsA or psoriasis
107. subject has no prior use of methotrexate for PsA. Prior treatment with methotrexate is allowed if indicated for psoriasis as long as discontinuation was not due to toxicity or intolerance and treatment discontinued  $\geq 6$  months prior to initiation of investigational product
108. for subjects receiving non-steroidal anti-inflammatory drugs (NSAIDs) (including as needed use [PRN]): the dose must be stable for  $\geq 2$  weeks prior to initiation of investigational product
109. for subjects receiving oral corticosteroids: the dose must be stable (not to exceed the equivalent of 10 mg of prednisone per day) for  $\geq 4$  weeks prior to initiation of investigational product
110. negative test for hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody
111. no known history of active tuberculosis
112. 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 Inc.
- 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
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  $\leq$  4 weeks from starting investigational product and a negative urine pregnancy test at baseline (day 1)

#### 4.1.2 Exclusion Criteria

##### *Medical Conditions*

201. subject has known history of alcoholic hepatitis, nonalcoholic steatohepatitis or immunodeficiency syndromes, including Human Immunodeficiency Virus infection.
202. subject has any active infection (including chronic or localized infections) for which anti-infectives were indicated within 4 weeks prior to the first dose of investigational product.
203. subject has a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first dose of investigational product.
204. subject had prosthetic joint infection within 5 years of screening or native joint infection within 1 year of screening.
205. subject has known alcohol addiction or dependency, uses alcohol daily, or has current substance use or abuse.
206. 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 PsA (eg, systemic lupus erythematosus with the exception of secondary Sjogren's syndrome)

##### *Excluded Medications*

207. prior or current use of cyclophosphamide, chlorambucil, nitrogen mustard, or any other alkylating agent.

208. subject has used any of the following  $\leq$  3 months prior to screening:
- abatacept
  - anakinra
  - azathioprine
  - cyclosporine
  - gold
  - mycophenolate mofetil
  - ProSORBA column
  - Systemic tacrolimus
  - Otezla (apremilast)
209. subject has used leflunomide  $\leq$  12 weeks prior to screening
210. subject has used any of the following  $\leq$  4 weeks prior to screening:
- sulfasalazine
  - intraarticular, intramuscular or intravenous corticosteroids, including adrenocorticotrophic hormone
  - intraarticular hyaluronic acid injections
  - live vaccines
211. for subjects not on continuous analgesics, subject has taken the following within 12 hours prior to screening: acetaminophen, NSAID, 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*

212. Subject has laboratory abnormalities during screening, including the following:
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)  $>$  1.5 x the upper limit of normal (ULN)
  - Platelet count  $<$  125,000/mm<sup>3</sup>
  - White blood cell count  $<$  3,000 cells/mm<sup>3</sup>
  - Absolute neutrophil count  $<$  1500/mm<sup>3</sup>
  - Estimated creatinine clearance  $<$  50 mL/min (Cockcroft-Gault formula, calculated value to be provided to sites)
213. 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.

*Other*

214. 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).
215. 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).
216. 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.
217. 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.
218. 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.
219. Subject has known sensitivity to any of the products or components to be administered during dosing.
220. 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, PROs) to the best of the subject and investigator's knowledge.
221. 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.
222. Currently receiving treatment in another investigational device or drug study, or participated in any study involving administration of an investigational drug or device within 30 days or 5 terminal elimination half-lives, whichever is longer, before enrollment.
223. Other investigational procedures while participating in this study are excluded.

## **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 eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in the enrollment CRF.

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 the Interactive Voice Response System (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 re-screened. This number will not necessarily be the same as the randomization number assigned for the study.

Subjects not meeting eligibility criteria are permitted to re-screen twice (see [Section 7.2.1](#) and [7.2.2](#)).

### **5.1 Randomization/Treatment Assignment**

Subjects that meet all eligibility criteria will be randomized at baseline to receive etanercept plus methotrexate, etanercept plus placebo for methotrexate or methotrexate plus placebo for etanercept in a 1:1:1 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 at randomization. The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

### **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.

Other than rescue therapy situations, in the event of inadvertent unblinding (ie, the blind was not intended to be broken as described above), the investigator should immediately notify Amgen. Each scenario will be reviewed individually to determine if the impacted subject(s) are able to continue receiving investigational product.

Unblinding at the study site for any other reason, including the scenarios described above, 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 Amgen within 1 working day after the event.

## **6. TREATMENT PROCEDURES**

### **6.1 Classification of Products and/or Medical Device(s)**

The Amgen Investigational Product used in this study includes: etanercept or placebo for etanercept.

The non-Amgen Investigational product used in this study includes: 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 [CCI]. Each single-use pre-filled syringe (PFS) contains 0.98 mL of 50 mg/ml etanercept in a formulation consisting of [CCI]mM sodium chloride, [CC]mM sodium phosphate, [CC]mM L-arginine-HCL, and [CC] 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 PsA (subcutaneous injection, 50 mg once weekly). The treatment period of this study is 48 weeks. 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. Subjects will receive 1 dose of etanercept 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 electronic case report form (eCRF). Subsequent doses of investigational product should resume on the original schedule. 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 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 start date, quantity administered and box number of investigational product are to be recorded in each subject's 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 capsules or as matching placebo capsules. For those subjects receiving rescue therapy, methotrexate will be dispensed as 2.5 mg tablets.

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

#### **6.2.2.1 Dosage, Administration, and Schedule**

Methotrexate dosing will be initiated at 10 mg weekly and will be titrated up to a final dose of 20 mg weekly over a 4-week period. The treatment period for this study is 48 weeks. Methotrexate will be provided as 2.5 mg capsules, or as placebo capsules, and will be taken once weekly by oral administration. Capsules should be swallowed whole. Subjects will receive 1 dose of methotrexate or placebo per week (scheduled approximately 7 days apart) for 48 weeks. 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 eCRF. Double or extra doses should not be taken. The start date, quantity administered, and bottle/package number of methotrexate is to be recorded on the subject's diary and entered into the eCRF.

#### **6.2.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation**

Methotrexate (or placebo for methotrexate) will be initiated at a dosage of 10 mg weekly at week 0 (day 1). The dose will be increased by 2.5 mg weekly up to 20 mg over a 4 week period. In cases of typical methotrexate toxicities (eg, increased aspartate transaminase or alanine transaminase, or gastrointestinal adverse effects, severe stomatitis), the methotrexate dose may be reduced up to 10 mg weekly. The reason for dose change of methotrexate is to be recorded on each subject's 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.

#### **6.3.2 Dosage, Administration, and Schedule**

The dose of folic acid will be 5 to 7 mg per week as 1 mg daily per investigator judgment OR administration according to the local standard of care. The dose of folic acid may be adjusted OR folinic acid (leucovorin) can be added not to exceed 5 mg per week 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 (DILI) ([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 Observation 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 must remain stable up to week 24. After week 24 the dose can be reduced or discontinued during the study if necessary for safety reasons or standard of care.

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 must not be used within 24 hours of a scheduled study visit.

### **6.5.2 Corticosteroids**

Subjects entering the study while taking oral corticosteroids must remain on a stable dose until week 24.

Corticosteroids may be used by any subject who meets the criteria for inadequate response and begins rescue treatment as described in [Section 3.1.2](#).

### **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:

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

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## 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 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, and the radiographic assessments, all study procedures for a visit should be completed on the same day. Radiographs may be done within  $\pm 1$  week of the visit date. 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.

Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

### **7.1 Schedule of Assessments**

**Table 1. Schedule of Assessments**

Weeks	30-day Screening	Treatment Period								Disease Assessment (DA)		30-day Follow-Up Safety (EOS) <sup>9</sup>
		0 (day 1)	4	8	12	16	24	36	48/ET	DA Visit <sup>e</sup>	DA Follow-up <sup>e</sup>	
<b>GENERAL &amp; SAFETY ASSESSMENTS</b>												
Informed consent	X											
Randomization via IXRS		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 <sup>a</sup>	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	X	X	
Height	X											
<b>LABORATORY ASSESSMENTS</b>												
Pregnancy test (serum) <sup>b</sup>	X											
Pregnancy test (urine) <sup>b,c</sup>		X			X		X	X	X			
Tuberculosis testing <sup>d</sup>	X											
Hematology and chemistry profile	X		X	X	X		X	X	X	X	X	
Hepatitis B surface antigen & core antibody; Hepatitis C virus antibody <sup>f</sup>	X											
High Sensitivity C-reactive Protein		X	X	X	X	X	X	X	X	X	X	
Urinalysis	X								X			
Biomarker blood sample		X		X			X		X			
<b>INVESTIGATIONAL PRODUCT DISPENSING</b>												
Etanercept/placebo for etanercept dispensation		X	X	X	X		X	X		X <sup>g</sup>	X	
Methotrexate/placebo for methotrexate dispensation		X	X	X	X		X	X		X <sup>g</sup>	X	
Folic Acid <sup>h</sup>		X			X		X	X				
<b>SUBJECT DIARY DISPENSING</b>												
Dispense subject diary		X	X	X	X	X	X	X				
Review subject diary			X	X	X	X	X	X	X	X	X	
<b>DISEASE ASSESSMENTS</b>												
Swollen and Tender joint count	X	X	X	X	X	X	X	X	X	X	X	
Physician Global Assessment of Disease Activity (VAS 0 to 100)		X	X	X	X	X	X	X	X	X	X	
Leeds Dactylitis Index		X	X		X		X	X	X	X	X	
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index		X	X		X		X	X	X	X	X	
Modified Nail Psoriasis Severity Index (NAPSI)		X	X		X		X	X	X			
Static Physician Global Assessment of Psoriasis		X	X		X		X	X	X	X	X	
Body Surface Area		X	X		X		X	X	X	X	X	
Radiographs (hands, feet)		X					X		X			

Footnotes defined on next page

**Table 1. Schedule of Assessments**

Weeks	30-day Screening	Treatment Period								Disease Assessment (DA)		30-day Follow-Up Safety (EOS) <sup>g</sup>
		0 (day 1)	4	8	12	16	24	36	48/ET	DA Visit <sup>e</sup>	DA Follow-up <sup>e</sup>	
<b>PATIENT REPORTED OUTCOMES</b>												
Patient global assessment of pain (VAS 0 to 100)		X	X	X	X	X	X	X	X	X	X	X
Patient global assessment of disease activity (VAS 0 to 100)		X	X	X	X	X	X	X	X	X	X	X
Disability Index of the Health Assessment Questionnaire (HAQ-DI)		X	X	X	X	X	X	X	X	X	X	X
Medical Outcomes Short Form-36 Questionnaire (SF-36)		X			X		X	X	X			

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ET: early termination; DA: Disease Assessment; EOS: end of study; **HBV: hepatitis B virus**; IXRS: Interactive voice response system; **PCR: polymerase chain reaction**; VAS: visual analog scale

<sup>a</sup>Screening physical exam will be a full exam; subsequent exams per standard of care to monitor for any changes

<sup>b</sup>For all women, unless at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

<sup>c</sup>Additional pregnancy testing may be completed at the discretion of the investigator

<sup>d</sup>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.

<sup>e</sup>Disease Assessment Visit - disease activity may be assessed at a regularly scheduled visit or at a Disease Assessment visit as described in [Section 7.2.5](#). If subject initiates rescue treatment then they must return for a Disease Assessment Follow-up visit 4 to 5 weeks later.

<sup>f</sup>If subjects meet the criteria for inadequate response as described in [Section 3.1.2](#) they will be allowed to receive rescue treatment with etanercept plus methotrexate

<sup>g</sup>Subjects will be contacted by phone by the site staff to collect any serious adverse events

<sup>h</sup>Frequency of dispensation will vary with quantity dispensed and individual subject dose

<sup>i</sup> **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 above 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 eligibility criteria at the end of the 30-day window, the subject will be registered as a screen fail. Abnormal laboratory assessments used to determine subject eligibility may be repeated once during the primary screening period before the subject is considered a screen failure. **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 re-screen two additional times per Section 7.2.2.

### 7.2.2 Re-screening

Subjects who are unable to complete or meet all 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. 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. Subjects who screen fail for not meeting inclusion criterion 106 or 111 are not permitted to re-screen.

### 7.2.3 Baseline Visit (Day 1)

Subjects meeting all 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 self-administration per [Table 1](#).

#### **7.2.4 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  $\pm 7$  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.

#### **7.2.5 Disease Assessment Visit and Disease Assessment Follow-up Visit**

Subjects can be seen at any time at or after week 24 to assess disease activity to evaluate if a subject can receive rescue treatment due to inadequate response to treatment. If a subject meets the criteria for inadequate response as defined in [Section 3.1.2](#), he/she will initiate rescue treatment with etanercept (50 mg QW) plus methotrexate (titrated up to 20 mg QW). Sites will register the requirement for rescue in the IXRS for assignment of rescue therapy. Refer to the IPIM for additional details. Subjects will continue to receive etanercept plus methotrexate for the remaining study visits per [Table 1](#). The procedures completed during the Disease Assessment visit are listed in the Schedule of Assessments ([Table 1](#)). Subjects who initiate rescue treatment must complete a Disease Assessment Follow-up visit 4 to 5 weeks later to complete all the procedures listed in the Schedule of Assessments ([Table 1](#)).

#### **7.2.6 Subject End of Treatment/Early Termination**

Subjects will complete an end of treatment visit at week 48 within a window of  $\pm 7$  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.

#### **7.2.7 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 full PsA history and other significant medical history should be recorded starting at the time of the original diagnosis. Other relevant medical and surgical history that started within 5 years and information on the subject's concurrent medical conditions will be recorded. Record all findings on the medical history eCRF.

### **7.3.4 Medication History**

The subject's full history of psoriasis and PsA medications starting at the time of diagnosis and up to screening will be recorded on the eCRF. This information will include the subject's non-biologic DMARDs, NSAIDs, corticosteroids, biologics, and investigational medication history. For PsA 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 PsA Disease Assessments**

All joint assessments will be performed by an experienced assessor who has been certified and trained by Amgen. Each subject should have their assessments done by the same assessor throughout the study, if possible. If necessary, study visits may be rescheduled within the allowed window period per visit in order to accommodate when the same assessor will be available.

#### **7.3.8.1 Swollen/Tender Joint Counts**

All joint assessments will be performed by an experienced assessor who has been trained by viewing Amgen's Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) training module and must be identified on the delegation of authority for this responsibility. The user ID of the joint assessor will be recorded at each assessment. The score for each joint will be recorded directly into the electronic PRO tablet which will serve as the source documentation and will not be transposed to the eCRF. Joints that have been replaced are considered inevaluable.

*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 Leeds Dactylitis Index**

Assessment will be performed by the same assessor as the joint counts. The assessor will be trained by viewing the GRAPPA training module to perform the Leeds Dactylitis measurement.

The assessor will assess all fingers and toes for tenderness in the area between the joints and will score each on a scale of 0 to 3 where 0 = not tender; 1 = tender; 2 = tender and wince; 3 = tender and withdraw. Using a Leeds dactylometer, the circumference of only the tender digits and their contralateral counterpart will be measured and reported on the eCRF.

#### **7.3.8.3 Spondyloarthritis Research Consortium of Canada Enthesitis Index**

Assessment will be performed by the same assessor as the joint counts. The assessor will be trained by viewing the GRAPPA training module to perform the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis assessment. The SPARCC enthesitis index assesses enthesitis at 18 sites with a resultant score of 0 to 16.

Tenderness at each site is assessed as 0 = non-tender or 1 = tender. Enteses assessed are left and right medial and lateral epicondyles, supraspinatus insertion into greater tuberosity of humerus, greater trochanter, quadriceps insertion into superior border of patella, patellar ligament insertion into inferior pole of patella, tibial tubercle, Achilles tendon insertion into calcaneum and bilateral plantar fascia insertion into the calcaneum. Higher count represents greater enthesitis burden. Tenderness at the inferior pole of patella and/or tibial tubercle will be scored as a maximum score of 1.

#### **7.3.8.4 Radiographs**

Radiographs of bilateral hands and feet will be taken in the required views: posterior/anterior for the hands and anterior/posterior for the feet. Radiographs will be done locally and read centrally.

The central imaging vendor will measure using the van der Heijde mTSS method for PsA. This method is based on the Sharp-van der Heijde method for assessing erosions and joint space narrowing of the hands and feet in RA and is adapted for evaluation of PsA by including the distal interphalangeal joints of the hand and scoring not only for erosions and joint space narrowing but also for subluxation, ankylosis, gross osteolysis, and pencil in cup phenomena. Erosions are scored from 0 to 3 in each joint and joint space narrowing is scored from 0 to 4 at each joint and includes assessment for ankylosis. Gross osteolysis and pencil in cup are scored separately. The maximum possible total score is 528. The radiographs will be read at a central location by two independent readers.

### **7.3.9 Psoriasis Disease Assessments**

#### **7.3.9.1 Static Physician Global Assessment of Psoriasis**

The assessor who conducts the tender and swollen joint counts will be trained and certified by GRAPPA training module to perform the Static Physician Global Assessment of Psoriasis (sPGA). The sPGA is designed to evaluate the physician's global assessment of the subject's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale of 0 (clear) to 5 (severe).

#### **7.3.9.2 Body Surface Area Involvement**

The assessor who conducts the tender and swollen joint counts will be trained and certified by GRAPPA training module to perform the assessment for involved body surface area (BSA). BSA is a numerical score (0 to 100) used to measure the proportion of the subject's total BSA involvement with psoriasis.

#### **7.3.9.3 Modified Nail Psoriasis Severity Index**

The assessor who conducts the tender and swollen joint counts will be trained and certified by GRAPPA to perform the modified NAPSI assessment. The modified NAPSI scale is an objective, numeric, and reproducible grading system for nail psoriasis that incorporates the many different features of nail psoriasis. For assessments in this study (including selection of the target nail), a nail is graded on the following 8 clinical features and the modified NAPSI score results.

- pitting (scores 0-3, depending on the number of pits)
- nail plate crumbling (scores 0-3, depending on % of nail involvement)
- onycholysis and oil drop discoloration considered together (scores 0-3, depending on % of nail involvement)
- leukonychia (0 or 1 – absent or present)
- red spots in lunula (0 or 1 – absent or present)
- nail bed hyperkeratosis (0 or 1 – absent or present)
- splinter hemorrhages (0 or 1 – absent or present)

In randomized subjects with nails involved with psoriasis, each finger nail will be scored at baseline to determine the worst nail (ie, the nail with the highest modified NAPSI score); this nail will be followed for the remainder of the study. If multiple nails have the same worst score, only 1 target nail will be followed. Identify the selected nail in the source document and eCRF, if applicable.

#### **7.3.9.4 Physician Global Assessment of Disease Activity**

This assessment will be completed 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 PI for the study must complete the global assessments independently from each other.

#### **7.3.10 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.

##### **7.3.10.1 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.

##### **7.3.10.2 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 arthritis activity at all” on the left end of the line and “100” and “Worst arthritis activity imaginable” on the right end of the line. The subject and physician must complete the global assessments independently from each other. This questionnaire should take approximately 1 minute to complete.

##### **7.3.10.3 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.

##### **7.3.10.4 Medical Outcomes Short Form-36 Questionnaire**

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) limitations 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 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 C-reactive protein, and any other laboratory tests required. 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, C-reactive protein, urinalysis, and other testing to be conducted on blood and urine samples are listed below ([Table 2](#)).

**Table 2. Analyte Listing**

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

<sup>a</sup> For all women, unless at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

<sup>b</sup> 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.

<sup>c</sup> **At screening if the subject is positive for hepatitis B core antibody, the confirmatory reflex testing will be performed using HBV DNA PCR.**

#### 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](#).

##### 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.

##### 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 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. Biomarker development may be pursued by use of advanced biochemical analyses, such as proteomic methods or ribonucleic acid transcript profiling. A cell pellet from the blood plasma tube may be utilized to assess the impact of etanercept and/or methotrexate on circulating immune cells via deoxyribonucleic acid (DNA) methylation analysis, a pharmacodynamic assessment of methylation patterns of relevant genes. The DNA extracted will not be used for optional pharmacogenetic analyses unless the subject signs the additional consent.

#### **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 PsA 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](#).

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### **8.3 Reasons for Removal From Treatment or Study**

#### **8.3.1 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, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, death or lost to follow-up)
- disease flare requiring treatment not allowed in the protocol (eg, colitis, asthma)

#### **8.3.2 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

## **9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING**

### **9.1 Adverse Events**

#### **9.1.1 Definition of 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 (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened 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.

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 Definition of 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, DILI (see [Appendix A](#) for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

## **9.2 Reporting of Adverse Events**

### **9.2.1 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 first dose of investigational product(s) through the end of treatment period are reported using the applicable CRF (eg, Adverse Event Summary).

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. 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 applicable eCRF.

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 eSAE 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. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary 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 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 procedures and statutes.

### 9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

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

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet ([Appendix C](#)). The Pregnancy Surveillance Program will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur through 4 weeks after the last dose of etanercept.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet ([Appendix C](#)).

## 10. STATISTICAL CONSIDERATIONS

### 10.1 Study Endpoints, Analysis Sets, and Covariates

#### 10.1.1 Study Endpoints

##### 10.1.1.1 Primary Endpoint

- ACR 20 response at week 24

##### 10.1.1.2 Key Secondary Endpoint

- MDA response at week 24

##### 10.1.1.3 Other Secondary Endpoints

- Modified NAPSI score and change from baseline at week 24
- Leeds dactylitis score and change from baseline at week 24
- SPARCC enthesitis score and change from baseline at week 24
- ACR 20 response at all other measured timepoints
- MDA response at all other measured timepoints
- Psoriatic Arthritis Disease Activity Score (PASDAS) at all measured timepoints
- ACR 50, ACR 70, and components of ACR at all measured timepoints

- Simplified Disease Activity Index (SDAI) and change from baseline at all measured timepoints
- Clinical Disease Activity Index (CDAI) and change from baseline at all measured timepoints
- Disease activity score (28 joint) using the C-reactive protein formula (DAS28-CRP) and change from baseline at all measured timepoints
- HAQ-DI score and change from baseline at week 24
- SF-36 score and change from baseline at week 24

For subjects with involved BSA  $\geq 3\%$  at baseline:

- sPGA at week 24
- BSA at week 24

#### **10.1.1.4 Safety Endpoints**

- Adverse events
- Serious adverse events
- Laboratory parameters and vital signs

#### **10.1.1.5 Exploratory Endpoints**

- Change from baseline in van der Heijde mTSS at week 24 and week 48
- Non-progression in van der Heijde mTSS defined as change  $\leq 0$  from baseline at week 24 and week 48
- Modified NAPSI score and change from baseline at all other measured timepoints
- Leeds dactylitis score and change from baseline at all other measured timepoints
- SPARCC enthesitis score and change from baseline at all other measured timepoints
- HAQ-DI and change from baseline at all other measured timepoints
- SF-36v2 and change from baseline at all other measured timepoints

For subjects with involved body surface area  $\geq 3\%$  at baseline:

- sPGA at all other measured timepoints
- BSA at all other measured timepoints

### **10.1.2 Analysis Sets**

#### **10.1.2.1 Full Analysis Set**

The full analysis set will include all randomized subjects. Subjects will be analyzed according to their randomized treatment group. Demographics, baseline disease characteristics, and non-psoriasis efficacy analyses will be based on the full analysis set.

#### **10.1.2.2 Psoriasis Efficacy Analysis Set**

The psoriasis efficacy analysis set will consist of all randomized subjects with baseline BSA  $\geq 3\%$ . Analyses of psoriasis efficacy endpoints (eg, sPGA, BSA) will be based on the psoriasis efficacy analysis set.

#### **10.1.2.3 Safety Analysis Set**

The safety analysis set will consist of all randomized subjects who receive at least one dose of investigational product. Subjects will be analyzed according to the actual treatment received. Analyses of safety endpoints will be based on the safety analysis set.

#### **10.1.3 Covariates and Subgroups**

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

- Age ( $\leq 65$ ,  $> 65$ )
- Sex (male, female)
- Race (Caucasian, Non-Caucasian)
- Ethnicity (Hispanic or Latino vs Non-Hispanic or Latino)
- Baseline body mass index (BMI) ( $\leq 30$ ,  $> 30$ )
- Baseline weight ( $\leq 100$  kg,  $> 100$  kg)
- Baseline BSA ( $\leq 3\%$ ,  $> 3\%$ )
- Prior use of non-biologic DMARD (yes, no)
- Disease duration ( $\leq$  median,  $>$  median)

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**

A total of 840 subjects will be enrolled in the study and randomized in a 1:1:1 ratio to etanercept plus methotrexate therapy, etanercept monotherapy and methotrexate monotherapy.

To preserve the family-wise 2-sided type one error rate at 0.05 for the multiple comparisons of the etanercept plus methotrexate therapy and etanercept monotherapy groups with methotrexate monotherapy, a Bonferroni-based gatekeeping chain procedure ([Burman et al, 2009](#) and [Millen et al, 2011](#)) will be used to determine statistical significance for the primary and key secondary endpoints as described in

[Section 10.5.2](#). This procedure will split alpha of 0.05 equally to test in parallel the primary and key secondary endpoints (ACR 20, MDA) for etanercept plus methotrexate therapy vs. methotrexate monotherapy and etanercept monotherapy vs. methotrexate monotherapy sequentially within each parallel path. If one of the parallel paths rejects both hypotheses sequentially, and the other parallel path has at least one hypothesis not rejected, then unspent alpha of 0.025 from the successful path will be propagated to the hypotheses in the other path to re-test them sequentially at a level of 0.05.

The sample size is based on the adequacy to evaluate the efficacy of etanercept monotherapy compared with methotrexate monotherapy as measured by the primary endpoint of ACR 20 response at week 24 at a significance level of 0.025 based on the Bonferroni-based gatekeeping chain procedure.

There are no published studies of etanercept monotherapy versus methotrexate monotherapy for the treatment of PsA. Therefore for the purpose of this study the assumed response rates for ACR 20 for the etanercept monotherapy and methotrexate monotherapy arms are derived from separate studies. In the etanercept PsA pivotal phase 3 study (20021630 Study) the ACR 20 response rate at week 24 was 50% for the etanercept arm. However, subjects were allowed to be on a stable dose of methotrexate at study entry. Assuming a methotrexate naïve population would respond better, the response rate for the etanercept monotherapy arm in this planned phase 3 study is assumed to be 60%.

In a recent randomized placebo-controlled trial of methotrexate monotherapy in PsA ([Kingsley et al, 2012](#)) the ACR 20 response rate for the methotrexate monotherapy arm was 34%. However, the dose of methotrexate was 15 mg QW. Assuming a higher dose of methotrexate (ie, 20 mg QW) would yield better responses, the response rate for the methotrexate monotherapy arm in this planned phase 3 study is assumed to be 44%.

Therefore, in order to detect a difference of 16% between the etanercept monotherapy and methotrexate monotherapy arms, using a two-sided Chi-square test at a significance level of 0.025 and 90% marginal power, each treatment arm will have approximately 280 subjects adjusting for an anticipated 10% dropout.

This sample size will provide marginal power > 90% to detect a treatment difference in ACR 20 response at week 24 between the etanercept plus methotrexate therapy arm and the methotrexate monotherapy arm at a two-sided 0.025 significance level. As previously mentioned, the ACR response rate at week 24 is assumed to be 44% for the

methotrexate monotherapy arm. The ACR response rate at week 24 for the etanercept plus methotrexate therapy arm is assumed to be 5% higher than the etanercept monotherapy arm (ie, 65%). This is based on a longitudinal observational study assessing the role of TNF-inhibitor plus methotrexate combination therapy versus TNF-inhibitor monotherapy ([Fagerli et al, 2014](#)).

In addition, this sample size will provide marginal power > 90% to detect treatment differences in MDA response at week 24 between both etanercept arms and the methotrexate arm at a two-sided 0.025 significance level, assuming response rates of 15%, 30%, and 35% for the methotrexate monotherapy, etanercept monotherapy, and etanercept plus methotrexate therapy arms, respectively. In recent PsA trials, the MDA 24-week response rates for the placebo arm range from 3 to 7% ([Coates et al, 2010a](#); [Kavanaugh et al, 2013](#)). Therefore, for the methotrexate monotherapy arm, the response rate is assumed to be higher at 15%. In the pivotal phase 3 randomized placebo-controlled trial of etanercept in PsA, the MDA response rate for the etanercept monotherapy arm is estimated to be approximately 20% at week 24 (data on file). For a methotrexate naïve population, the response rate is assumed to be higher at 30%. In addition, the etanercept plus methotrexate therapy arm is assumed to have a 5% improvement over the etanercept monotherapy arm.

### **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](#), [Section 9.2.2](#) and Statistical Analysis Plan [SAP]).

### **10.4 Planned Analyses**

#### **10.4.1 Primary Analysis**

The objective for the primary analysis is to evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy in subjects with PsA at week 24 as measured by the proportion of subjects achieving an ACR 20 response. The primary analysis will be performed when the last subject completes the week 48 visit or terminates early from the study, at which time the study will be unblinded.

For the primary and key secondary efficacy endpoints, treatment effect will be tested using a Bonferroni-based gatekeeping chain procedure ([Burman et al, 2009](#) and [Millen et al, 2011](#)) as described in Section 10.5.2 to control the family-wise 2-sided type one error rate at 0.05. Between-treatment comparisons will be made using the stratified Cochran-Mantel-Haenszel (CMH) test with baseline BMI and prior non-biologic DMARD use as the stratification factors. Missing data will be imputed using non-responder imputation for the primary analysis.

For other efficacy endpoints, the significance level will be 0.05 without adjusting for multiplicity and data will be analyzed as observed.

## **10.5 Planned Methods of Analysis**

### **10.5.1 General Considerations**

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively by randomized treatment group.

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 error, standard deviation, median, minimum, and maximum.

Treatment effect will be tested for the primary and key secondary endpoints using a Bonferroni-based gatekeeping chain procedure to control the family-wise 2-sided type one error rate at 0.05. The significance level for the analyses of other secondary endpoints and exploratory endpoints will be 0.05 without adjusting for multiplicity and the p-values for these endpoints will therefore be treated as a descriptive statistic only.

Safety endpoints will be tabulated by actual treatment received during the study. No formal statistical testing will be performed for safety analyses.

Details of all statistical methods will be provided in the SAP.

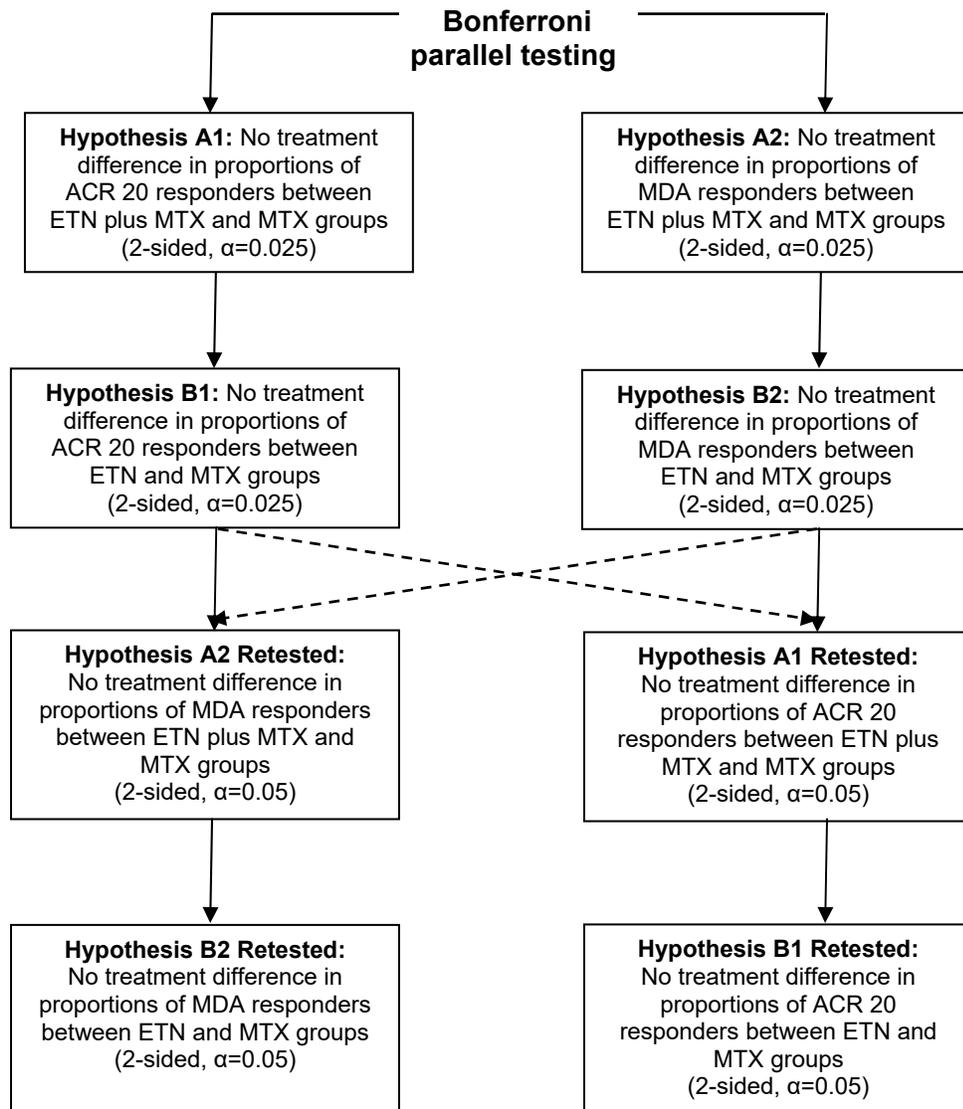
### **10.5.2 Primary and Key Secondary Efficacy Endpoints**

The primary analysis for the primary endpoint and key secondary endpoints, ACR 20 response and MDA response at week 24, will be performed using the full analysis set. Treatment effect will be tested using the stratified CMH test with baseline BMI and prior non-biologic DMARD use as the stratification factors.

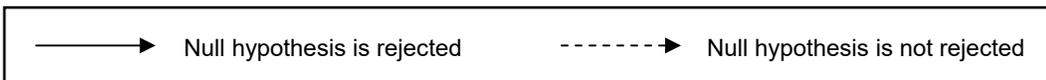
To control the family-wise 2-sided type one error rate at 0.05 for the multiple comparisons of the etanercept plus methotrexate therapy and etanercept monotherapy

groups with methotrexate monotherapy across the primary and key secondary endpoints, the hypotheses will be tested using a Bonferroni-based gatekeeping chain procedure (Burman et al, 2009 and Millen et al, 2011) as shown in Figure 1. This procedure will split alpha of 0.05 equally to test in parallel the primary and key secondary endpoints (ACR 20, MDA) for etanercept plus methotrexate therapy vs. methotrexate monotherapy and etanercept monotherapy vs. methotrexate monotherapy sequentially within each parallel path. If one of the parallel paths rejects both hypotheses sequentially, and the other parallel path has at least one hypothesis not rejected, then unspent alpha of 0.025 from the successful path will be propagated to the hypotheses in the other path to re-test them sequentially at a level of 0.05. For example, suppose the nominal p-values for hypotheses A1, B1, A2, and B2 (Figure 1) are 0.01, 0.02, 0.03, and 0.055, respectively. In the first round of testing, hypotheses A1 and B1 are rejected, whereas hypotheses A2 and B2 are not rejected. However, since both hypotheses A1 and B1 are rejected, the procedure gives a second chance to re-test hypotheses A2 and B2 (according to the left arm of the figure) at a lower threshold of 0.05 rather than the original threshold of 0.025. Note that in this example A2 is rejected and hypothesis B2 is not rejected.

Figure 1. Bonferroni-based Gatekeeping Chain Procedure



ETN: Etanercept; MTX: Methotrexate



For the primary analysis of the primary and key secondary endpoints, missing data will be imputed as nonresponder. Sensitivity analyses using observed data and using last observation carried forward imputation will also be performed.

### **10.5.3 Other Secondary Efficacy Endpoints**

The primary analysis of other secondary endpoints will be performed using the full analysis set for non-psoriasis endpoints or the psoriasis efficacy analysis set for psoriasis endpoints. For binary endpoints, treatment effect will be tested using the stratified CMH test with BMI and prior non-biologic DMARD use as the stratification factors. For continuous endpoints that exhibit normal distribution, ANCOVA model will be used. The model will include treatment groups and baseline BMI and prior non-biologic DMARD as covariates. For continuous endpoints that are not normally distributed, endpoint data will be first transformed to their joint ranks and then further transformed by the Van der Waerden transformation to normalize them before applying ANCOVA model. The significance level for other secondary endpoints will be 0.05 without adjusting for multiplicity and p-values will therefore be treated as a descriptive statistic only.

Data will be analyzed as observed with no imputation for missing data.

### **10.5.4 Safety Endpoints**

Safety endpoints will be summarized descriptively for all subjects by treatment group 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, radiographs, and correspondence.

In this study, the IXRS system captures the following data points and these are considered source data: subject identification number and 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, electronic PROs may be considered 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 the 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<sup>®</sup> (if used) for concomitant medications may be entered in the local language.

#### **12.6 Publication Policy**

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), 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.

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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](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 synopsised 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 TBL 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 $\geq 2$ 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: TBL > 3 x ULN at any time
- OR: ALP > 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 and bilirubin (total and direct) within 24 hours
- In cases of TBL > 2x ULN retesting of liver tests, bilirubin (total and direct) 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 with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 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) 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.



 Study # 20130207 etanercept	<b>Electronic Adverse Event Contingency Report Form</b> For Restricted Use
---	---

	Site Number	Subject ID Number													
5. Was IPDrug under study administered/taken prior to this event? <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete all of Section 5															
IPDrug/Amgen Device:	Date of Initial Dose		Date of Dose		Prior to, or at time of Event		Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #							
	Day	Month	Year	Day	Month	Year			Dose	Route	Frequency				
etanercept	<input type="checkbox"/> blinded <input type="checkbox"/> open label								Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown						
PP8	<input type="checkbox"/> blinded <input type="checkbox"/> open label								Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown						
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete:															
Medication Name(s)	Start Date			Stop Date			Co-supppt		Continuing		Dose	Route	Freq.	Treatment Med	
	Day	Month	Year	Day	Month	Year	No	Yes	No	Yes				No	Yes
7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)															
8. RELEVANT LABORATORY VALUES (include baseline values) Any Relevant Laboratory values? <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete:															
Date	Test														
	Unit														
Day	Month	Year													
9. OTHER RELEVANT TESTS (diagnostics and procedures) Any Other Relevant tests? <input type="checkbox"/> No <input type="checkbox"/> Yes if yes, please complete:															
Date		Additional Tests				Results				Units					
Day	Month	Year													



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#

<b>1. Case Administrative Information</b>				
Protocol/Study Number: <u>20130207</u>				
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
<b>2. Contact Information</b>				
Investigator Name _____			Site # _____	
Phone (____) _____		Fax (____) _____		Email _____
Institution _____				
Address _____				
<b>3. Subject Information</b>				
Subject ID # _____		Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male		Subject DOB: mm ____ / dd ____ / yyyy ____
<b>4. Amgen Product Exposure</b>				
Amgen Product	Dose at time of conception	Frequency	Route	Start Date mm ____ / dd ____ / yyyy ____
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
<b>5. Pregnancy Information</b>				
Pregnant female's LMP mm ____ / dd ____ / yyyy ____		<input type="checkbox"/> Unknown		
Estimated date of delivery mm ____ / dd ____ / yyyy ____		<input type="checkbox"/> Unknown <input type="checkbox"/> N/A		
If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____				
Has the pregnant female already delivered? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____				
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If any Adverse Event was experienced by the infant, provide brief details: _____				
_____				
_____				
<b>Form Completed by:</b>				
Print Name: _____			Title: _____	
Signature:  _____			Date: _____	

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

**AMGEN** Lactation 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: 20130207

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: \_\_\_\_\_

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2.

Page 1 of 1

### Amendment 3

**Protocol Title: A Multicenter Double-blind, Randomized Controlled Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Psoriatic Arthritis**

Amgen Protocol Number (Etanercept) 20130207

Amendment 1:	20 May 2015
Superseding Amendment 1:	09 July 2015
Amendment 2:	30 October 2015
<b>Amendment 3:</b>	<b>31 August 2016</b>

#### **Rationale:**

Updated CTCAE grading version to 4.0 to reflect most recent version and added “confirmatory reflex testing by HBV DNA PCR for subjects with Hepatitis-B positive core antibody.” and removed the “in order to confirm viral load is not detected” language.



**Section: 5.2 Site Personnel Access to Individual Treatment Assignments**

**Paragraph 3, sentence 2**

**Replace:**

The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment.

**With:**

The investigator is strongly encouraged to contact the Amgen **Global Clinical Trial** Manager before unblinding any subject's treatment assignment.

**Section: 7.1 Schedule of Assessments**

**Table 1**

**Replace:**

	30-day Screening	Treatment Period								Disease Assessment (DA)		30-day Follow-Up
Weeks		0 (day 1)	4	8	12	16	24	36	48/ET	DA Visit <sup>e</sup>	DA Follow-up <sup>e</sup>	Safety (EOS) <sup>g</sup>
GENERAL & SAFETY ASSESSMENTS												

Hepatitis B surface antigen & core antibody; Hepatitis C virus antibody	X											
---	---	--	--	--	--	--	--	--	--	--	--	--

**With:**

	30-day Screening	Treatment Period								Disease Assessment (DA)		30-day Follow-Up
Weeks		0 (day 1)	4	8	12	16	24	36	48/ET	DA Visit <sup>e</sup>	DA Follow-up <sup>e</sup>	Safety (EOS) <sup>g</sup>
GENERAL & SAFETY ASSESSMENTS												

Hepatitis B surface antigen & core antibody; Hepatitis C virus antibody <sup>j</sup>	X											
--	---	--	--	--	--	--	--	--	--	--	--	--

**Section: 7.1 Schedule of Assessments**

**Table Abbreviations**

**Added:**

**HBV: hepatitis B virus; PCR: polymerase chain reaction;**

**Section: 7.1 Schedule of Assessments**

**Footnote i**

**Added:**

**<sup>i</sup> At screening if the subject is positive for hepatitis B core antibody, the confirmatory reflex testing will be performed using HBV DNA PCR.**

**Section: 7.2.1 Screening**

**Sentence 6**

**Added:**

**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).**

**Section: 7.4 Laboratory Assessments**

**Table 2**

**Replace:**

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

**With:**

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

## Section: 7.4 Laboratory Assessments

### Table 2, footnote C

**Add:**

<sup>c</sup> At screening if the subject is positive for hepatitis B core antibody, the confirmatory reflex testing will be performed using HBV DNA PCR.

## Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

### Paragraph 3, sentence 1

**Replace:**

The adverse event grading scale used will be the Common Toxicity Criteria Version 2.

**With:**

The adverse event grading scale used will be the Common Toxicity Criteria Version 4.

## Section: 11.1 Informed Consent

### Paragraph 1, sentence 2

**Replace:**

Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator.

**With:**

Updates to the template are to be communicated formally in writing from the Amgen **Global Clinical Trial** Manager to the investigator.

## Section: Appendix A

### Adverse Event Grading Scale

**Replace:**

The Common Toxicity Criteria Version 2.0 is available at the following link:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcv20\\_4-30-992.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf)

**With:**

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

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

## Amendment 2

**Protocol Title: A Multicenter Double-Blind, Randomized Controlled Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Psoriatic Arthritis**

Amgen Protocol Number (Etanercept) 20130207

EudraCT Number 2014-004869-24

Original Protocol:	29 July 2014
Amendment 1 Date:	20 May 2015
Superseding Amendment 1 Date:	09 July 2015
Amendment 2 Date:	30 October 2015

### **Rationale:**

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

## Superseding Amendment 1

### Protocol Title: A Multicenter Double-Blind, Randomized Controlled Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Psoriatic Arthritis

Amgen Protocol Number (Etanercept) 20130207

Original Protocol: 29 July 2014

Amendment 1 Date: 20 May 2015

Superseding Amendment 1 Date: 09 July 2015

#### Rationale:

The protocol is being amended to:

- Provide updated pregnancy and contraception language. Updated language for pregnancy and contraception became available immediately following approval of Amendment 1, thus, a superseding amendment to Amendment 1 was created to include the updated language. Changes related to both Amendment 1 and Superseding Amendment 1 are detailed below. Likewise, changes in bold include all changes from Amendment 1 and Superseding Amendment 1.
- 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
- Update and clarify inclusion/exclusion criteria regarding tender and swollen joint counts, minimum number of weeks required for stable dosing of NSAIDs, excluded medications, and minimum number of months since use of excluded medications.
- Provide clarification regarding exclusion criteria to expand wording related to substances of abuse
- Provide clarifications regarding joint assessments, to strengthen wording related to continuity of assessors in the study, and allowing for assessments by principal investigators
- Add folic acid and folinic acid dosing information
- Add additional information regarding laboratory assessments used to determine subject eligibility
- Clarify process for when inadvertent unblinding occurs
- Provide updates throughout to reflect the number of global participating sites
- Clarify formulation of methotrexate used for rescue therapy
- Add the EudraCT number
- Update the Key Sponsor Contact
- Provide an updated eSAE example form, pregnancy worksheet, and lactation worksheet
- Make minor corrections and clarifications throughout