Title: Open Label Study to Evaluate the Efficacy of Etanercept Treatment in Subjects With Moderate to Severe Plaque Psoriasis Who Have Failed Therapy With Apremilast

Amgen Protocol Number (Etanercept) 20150252

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Date: 5 February 2016

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Investigator's Agreement

I have read the attached protocol entitled, Open Label Study to Evaluate the Efficacy of Etanercept Treatment in Subjects With Moderate to Severe Plaque Psoriasis Who Have Failed Therapy With Apremilast, dated 5 February 2016, and agree to abide by all provisions set forth therein.

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

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

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

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

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: Open Label Study to Evaluate the Efficacy of Etanercept Treatment in Subjects With Moderate to Severe Plaque Psoriasis Who Have Failed Therapy With Apremilast

Study Phase: 4

Indication: Plaque Psoriasis (PsO)

Primary Objective: To evaluate the efficacy of etanercept at week 12 as measured by a 75% improvement in Psoriasis Area and Severity Index (PASI 75) in adult subjects with moderate to severe plaque PsO who have failed therapy with apremilast (Otezla®)

Secondary Objectives: To evaluate the effect of treatment with etanercept on other efficacy endpoints (PASI, Static Physician's Global Assessment [sPGA], Body Surface Area [BSA]), and patient reported outcomes (PRO), including Psoriasis Symptom Inventory (PSI), Patient Assessment of Treatment Satisfaction, and Dermatology Life Quality Index (DLQI)

Safety Objective: To evaluate the safety and tolerability of etanercept in apremilast failures

Hypotheses: A formal hypothesis will not be tested in this study. This study will estimate the proportion of subjects with PsO who achieve a PASI 75 after 12 weeks of treatment with etanercept following failure of treatment with apremilast.

Primary Endpoint: PASI 75 at week 12

Secondary Endpoints:

- PASI 75 at all other visits
- PASI 50 and 90 at all visits
- Percent PASI improvement at all visits
- sPGA of 0 or 1 at all visits
- sPGA of 0, 1, or 2 at all visits
- sPGA at all visits
- One and two grade improvement in sPGA at all visits
- Percent BSA improvement at all visits
- PSI and component scores at all visits
- Patient Assessment of Treatment Satisfaction at week 12 and 24
- Improvement in DLQI at week 12 and 24

Safety Endpoints:

- Adverse events
- Laboratory assessments

Study Design: This is a multicenter, open-label, single-arm, phase 4, estimation study in subjects with PsO who have failed apremilast. Approximately 80 subjects will be enrolled in the study of which at least 10 subjects (and not to exceed 20) will be enrolled for reasons of intolerability to apremilast in the investigator's opinion. The remaining 60 to 70 subjects will be enrolled for reasons of primary or secondary failure to apremilast in the investigator's opinion. The study will consist of a screening period of up to 45 days, a 24-week treatment period with study visits every 4-weeks, and a 30-day follow-up period for safety. Etanercept dosing will follow the recommended label dosing for subjects with PsO.

Sample Size: Approximately 80 subjects will be enrolled in the study.

Summary of Subject Eligibility Criteria: The study seeks to enroll male and female subjects (≥ 18 years of age) with moderate to severe plaque PsO defined by BSA ≥ 10%, sPGA ≥ 3, and PASI ≥ 10 at screening and baseline who have failed therapy with apremilast either because of failure to achieve adequate response, loss of adequate response or intolerability in the opinion of

the investigator. Female subjects of childbearing potential must have a negative serum pregnancy test within 4 weeks from starting etanercept and a negative urine pregnancy test at baseline. For a full list of eligibility criteria, please refer to Section 4.1.1 through Section 4.1.2.

Investigational Product: Etanercept will be supplied in a single-use prefilled 1.0 mL syringe as a sterile, clear and colorless, preservative-free solution for subcutaneous injection. Each single-use prefilled syringe contains 0.98 mL of 50 mg/mL etanercept. Etanercept will be provided with 4 syringes to a pack.

Amgen Investigational Product Dosage and Administration: Etanercept dosing will follow the recommended label dosing for patients with PsO: 50 mg subcutaneously twice weekly for 12 weeks followed by 50 mg once weekly for the additional 12 weeks.

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 exam, vital signs, height and weight, tuberculosis testing, hepatitis testing, urinalysis, assessment of the sPGA score, PASI score and assessment of involved BSA. Blood samples will be collected for hematology, chemistry, and for all females (except those who have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy, or who are at least 2 years postmenopausal) to conduct a serum pregnancy test. The treatment period will be 24 weeks in duration with study visits every 4 weeks. Baseline evaluations will be performed on day 1 of treatment before subjects receive the first dose of etanercept. The following procedures will be performed at baseline (day 1) and during the treatment period: interim physical exam, vital signs, weight , PASI, BSA, sPGA, blood samples, urinalysis (day 1 only) and urine pregnancy tests when required per schedule of assessments. PROs will be collected at day 1 and during the treatment period. Adverse events, disease related events, serious adverse events and changes in concomitant medications will be recorded throughout the treatment period. Investigational product will be dispensed at baseline and every 4 weeks.up to week 20. Approximately 30 days after the last dose of etanercept, subjects will receive a final safety follow-up phone call to confirm the status of any ongoing and/or new disease related events or serious adverse events. The overall study design is described by a study schema at the end of this synopsis section. 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).

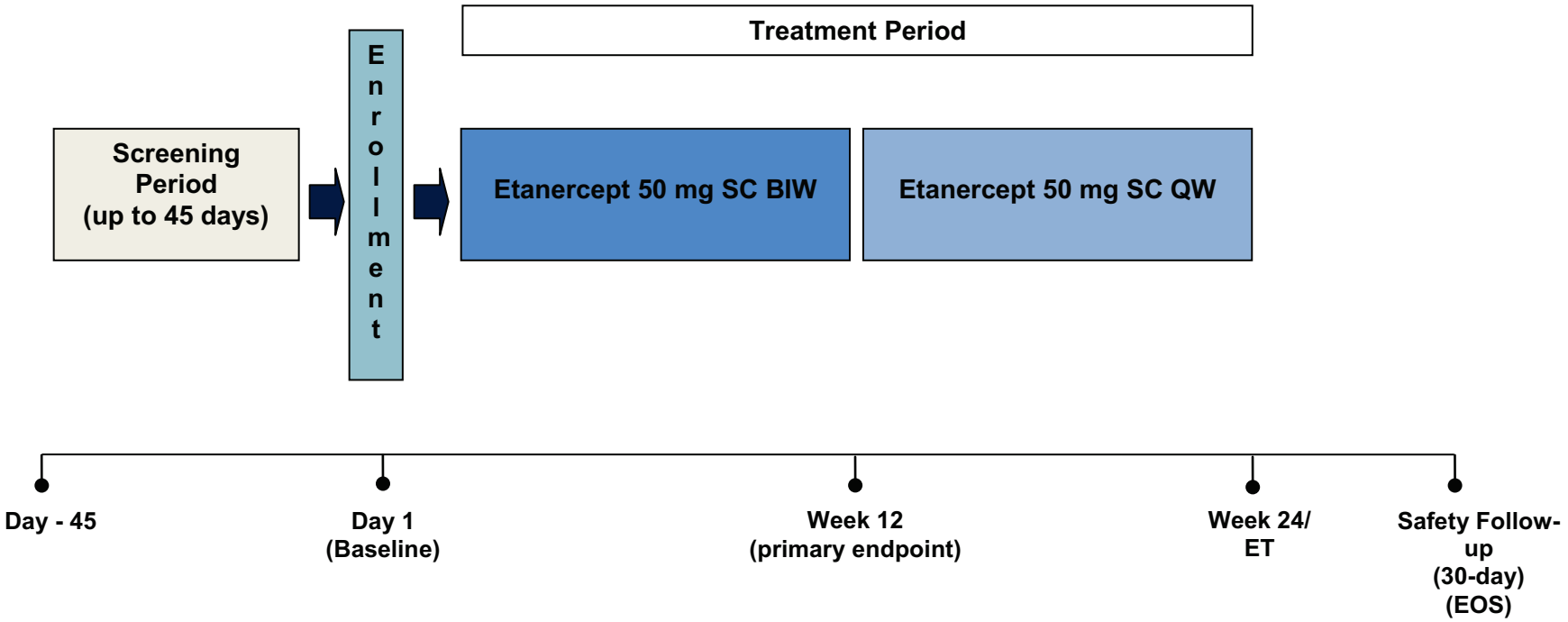
Statistical Considerations: This is an open-label single-arm study. Ninety five percent confidence intervals and p-values for estimated response rates will be generated for descriptive purposes only. The full analysis set includes all subjects who received at least one dose of investigational product during the study. All safety and efficacy endpoints will be analyzed using the full analysis set. For the primary analysis of all efficacy endpoints, missing efficacy data will be imputed using last observation carried forward method. A sensitivity analysis will be performed using observed cases. There will be no interim analysis.

For a full description of statistical analysis methods, refer to Section 10.

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s): 5: 20 March 2015

Study Design and Treatment Schema



SC: subcutaneous; BIW: twice a week; QW: once a week; ET: early termination; EOS: end of study

Study Glossary

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BIW	twice a week
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CI	confidence interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
Day 1	defined as the first day that protocol-specified investigational product is administered to the subject
DILI	Drug-induced liver injury
DLQI	Dermatology Life Quality Index
EDC	electronic data capture
ET	early termination
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
EOS	End of Study (for individual subject)
End of Study (end of trial)	defined as the time when the last subject is assessed or receives an intervention for evaluation in the study.
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
INR	International normalized ratio
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/ independent ethics committee
IVR	Interactive Voice Response, telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IWR	Interactive Web Response, web based technology that is linked to a central computer in real time as an interface to collect and process information.
kD	kilodalton
LT-α	lymphotoxin alpha
PASI	Psoriasis Area and Severity Index

Abbreviation or Term	Definition/Explanation
PDE4	phosphodiesterase 4
PPD	tuberculin purified protein derivative
PRO	Patient Reported Outcomes
PSI	Psoriasis Symptom Inventory
PsO	psoriasis
PUVA	Psoralen plus ultraviolet light A
Serum beta-HCG	Serum beta human chorionic gonadotropin
QW	Once a week
RA	rheumatoid arthritis
sPGA	Static Physician's Global Assessment
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
TBL	total bilirubin
TNF	tumor necrosis factor
ULN	upper limit of normal
UVA	ultraviolet light A
UVB	ultraviolet light B

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1. OBJECTIVES

1.1 Primary

To evaluate the efficacy of etanercept at week 12 as measured by a 75% improvement in Psoriasis Area and Severity Index (PASI 75) in adult subjects with moderate to severe plaque (PsO) who have failed therapy with apremilast (Otezla®).

1.2 Secondary

To evaluate the effect of treatment with etanercept on other efficacy endpoints (PASI, Static Physician's Global Assessment [sPGA], Body Surface Area [BSA]), and patient reported outcomes (PRO), including Psoriasis Symptom Inventory (PSI), Patient assessment of Treatment Satisfaction, and Dermatology Life Quality Index (DLQI).

1.3 Safety

To evaluate the safety and tolerability of etanercept in apremilast failures.

2. BACKGROUND AND RATIONALE

2.1 Disease

PsO is a chronic, often severe, autoimmune dermatologic condition that affects approximately 2% of the world's population (Menter et al, 2008). Moderate to severe plaque PsO is, for most patients, a chronic, life-long condition. Current therapies include topical agents (eg, corticosteroids, vitamin D3), phototherapy, oral systemic therapies (eg, apremilast, methotrexate, cyclosporine) and biologics (eg, etanercept, infliximab, adalimumab, ustekinumab and secukinumab). Many patients nevertheless remain untreated, fail to respond or lose response to therapy over time, or suffer from toxicities associated with systemic medication or phototherapy.

2.2 Apremilast (OTEZLA®) Background

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels. The specific mechanism(s) by which apremilast exerts its therapeutic action in psoriasis patients is not well defined. OTEZLA® (apremilast) is indicated for the treatment of patients with moderate to severe plaque PsO who are candidates for phototherapy or systemic therapy. Refer to the specific section of the product label for additional information.

The safety of apremilast was assessed in 1426 subjects with psoriasis in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque PsO who were candidates for phototherapy or systemic therapy. Subjects were

randomized to receive apremilast 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days. Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. Diarrhea (17%), nausea (17%), and upper respiratory tract infection (9%) were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking apremilast were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for subjects treated with apremilast 30 mg twice daily and 4.1% for placebo-treated subjects. Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with apremilast (Otezla® prescribing information, 2014).

Two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2) enrolled a total of 1257 subjects 18 years of age and older with moderate to severe plaque PsO. Study PSOR-1 enrolled 844 subjects and Study PSOR-2 enrolled 413 subjects. In both studies, subjects were randomized 2:1 to Otezla 30 mg BID or placebo for 16 weeks. Clinical Response at Week 16 in the PSOR-1 and PSOR-2 studies was as follows:

- PSOR-1
  - 33.1% achieved PASI 75 with apremilast vs. 5.3% with placebo
  - 21.7% achieved sPGA clear (0) or almost clear (1) with apremilast vs. 3.9% with placebo
- PSOR-2
  - 28.8% achieved PASI 75 with apremilast vs. 5.8% with placebo
  - 20.4% achieved sPGA clear (0) or almost clear (1) with apremilast vs. 4.4% with placebo

2.3 Amgen Investigational Product Background: Etanercept

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 PsO. Elevated levels of TNF are found in involved tissues and fluids of patients with rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, and PsO. Two distinct receptors for TNF, a 55 kilodalton (kD) protein (p55) and a 75 kD 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 kD TNF receptor linked to the Fc portion of human

immunoglobulin G1. Etanercept inhibits binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNF receptors, rendering TNF biologically inactive.

Etanercept is indicated in the United States for the treatment of : 1) moderately to severely active RA 2) moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 2 and older; 3) psoriatic arthritis; 4) active ankylosing spondylitis; and, 5) adult patients with chronic moderate to severe plaque PsO who are candidates for systemic therapy or phototherapy.

Refer to the specific section of the Investigator's Brochure, or the product label for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.4 Rationale

Limited data is available on the efficacy and tolerability of etanercept in patients with inadequate response to apremilast. This study will evaluate the use of etanercept in subjects with inadequate response to apremilast for reasons of either primary failure, secondary failure or intolerability. There is a current trend of Dermatologists adopting the use of apremilast as an oral therapy option for psoriasis. Despite the convenient administrative route, it is anticipated that there may be a growing population of active psoriasis patients who will need to be switched or require additional therapy for reasons of failure to respond to apremilast or intolerance to apremilast. This study aims to characterize the response to etanercept in this population. There is also a need to better understand patient oriented measures in psoriasis patients, and this study seeks to characterize PRO including a novel instrument termed the PSI, in response to etanercept treatment.

2.5 Clinical Hypotheses

A formal hypothesis will not be tested in this study. This study will estimate the proportion of subjects with PsO who achieve a PASI 75 after 12 weeks of treatment with etanercept following failure of treatment with apremilast.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, open-label, single-arm, phase 4 estimation study in subjects with PsO who have failed apremilast. Approximately 80 subjects will be enrolled in the study, among which at least 10 subjects (and not to exceed 20) will be enrolled for reasons of intolerability to apremilast in the investigator's opinion. The remaining 60 to 70 subjects

will be enrolled for reasons of primary or secondary failure to apremilast in the investigator's opinion. The study consists of up to a 45 day screening period, a 24-week treatment period with study visits every 4 weeks and a 30-day follow-up period for safety. Etanercept dosing will follow the recommended label dosing for patients with plaque PsO.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 20 sites in North America will participate in this study. 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". Approximately 80 subjects will be enrolled.

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 planned length of participation in the study for an individual subject is approximately 8 months. This includes up to a 45-day screening period, a 24-week treatment period and a safety follow-up phone call 30-days after the last dose of etanercept.

3.5.2 End of Study

The end of study (end of trial) 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). This log may be completed and updated via an Interactive Voice Response (IVR)/Interactive Web Response (IWR) system.

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 Male or female subject is ≥ 18 years of age at time of screening.

103 Subject is a candidate for systemic therapy or phototherapy in the opinion of the investigator.

104 Subject has moderate to severe plaque PsO with involved BSA ≥ 10%, PASI ≥ 10 and sPGA ≥ 3 at screening and baseline.

105 Subject is currently receiving treatment with apremilast for moderate to severe plaque PsO or subject has discontinued treatment with apremilast for PsO within the past 3 months prior to screening.

106 Subject has failed therapy with apremilast for moderate to severe plaque PsO defined as either (1) failure to achieve adequate clinical response in the opinion of the investigator, (2) loss of adequate clinical response in the opinion of the investigator or (3) intolerability to apremilast in the opinion of the investigator. A total of at least 10 and no more than 20 subjects may be enrolled for intolerability.

107 Subject has received at least 4 weeks of apremilast treatment for moderate to severe plaque PsO (this only applies for subjects who are qualifying by failure to achieve adequate clinical response or loss of adequate clinical response; this does not apply for subjects who are qualifying by intolerability to apremilast).

108 Subject has not had significant known weight increase or decrease (≥ 10%) during apremilast treatment.

109 Subject is < 264 lbs at screening and baseline.

110 Subject has a negative test for hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody.

111 Subject has no known history of tuberculosis.

112 Subject has a negative test for tuberculosis during screening defined as either:

- negative tuberculin 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 first dose of etanercept

- 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 etanercept

113 Subject if female and not at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, has a negative serum pregnancy test ≤ 4 weeks from starting etanercept and a negative urine pregnancy test at baseline (day 1).

114 Subject or designee must have the ability to inject etanercept subcutaneously.

4.1.2 Exclusion Criteria

Skin disease related

201 Subject has active erythrodermic, pustular, guttate psoriasis, or medication-induced psoriasis, or other skin conditions at the time of the screening visit (eg,eczema) that would interfere with evaluations of the effect of investigational product on PsO.

Other Medical Conditions

202 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
- liver disease
- anemia
- major chronic inflammatory disease or connective tissue disease other than psoriasis and/or psoriatic arthritis (eg, systemic lupus erythematosus with the exception of secondary Sjogren's syndrome)

203 Subject has active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma, Merkel cell carcinoma, or history of cancer (other than fully resected and surgically cured cutaneous basal cell and squamous cell carcinoma) within 5 years before the first dose of investigational product. If malignancy occurred more than 5 years ago, documentation of disease-free state since treatment is required.

204 Subject has known history of alcoholic hepatitis, non-alcoholic steatohepatitis or hepatitis B or C or immunodeficiency syndromes including Human Immunodeficiency Virus infection.

205 Subject has any condition that, in the opinion of the investigator, might cause the study to be detrimental to the subject.

206 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.

207 Subject has a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks before screening.

208 Subject has any condition that could, in the opinion of the investigator, compromise the subject's ability to give written consent and/or comply with the study procedures, such as a history of substance abuse or a psychiatric condition including suicidal ideation/attempt.

Washouts and Disallowed Medications

209 Subject has used any of the following therapies within 2-weeks prior to the first dose of etanercept:

- Ultraviolet light B (UVB) therapy
- Topical preparations of cyclosporine, a vitamin A or D analog, or a calcineurin inhibitor
- Topical steroids (exception: upper mid-strength or lower potency topical steroids are permitted on the scalp, axillae, and groin at the discretion of the investigator)

210 Subject has used any of the following therapies within 4-weeks prior to the first dose of etanercept:

- Ultraviolet light A (UVA) with or without Psoralen (PUVA) therapy
- Oral retinoids
- Intravenous or oral calcineurin inhibitors
- Anthralin
- Any other systemic psoriasis therapy (eg, cyclosporine, azathioprine, fumarates, hydroxyurea and thioguanine), including oral or parenteral corticosteroids
- Cyclophosphamide
- Sulfasalazine
- Methotrexate

211 Subject has used a biologic agent for PsO AND either:

- Did not have a documented satisfactory response as defined by sPGA 0 or 1 or clear or almost clear or the equivalent in the opinion of the investigator. Subjects who had a satisfactory response to a biologic for psoriasis and then lost satisfactory response are allowed, unless the biologic was etanercept.

OR

- Subject had a clinically significant adverse event (eg, serious infection, neurologic event, malignancy, hematologic event, or any other adverse event that the investigator feels might cause this study to be detrimental to the subject).

212 Subject has used interleukin 12/23 inhibitors within 6 months of the first dose of etanercept or has used other biologic therapies for psoriasis within 3 months prior to the first dose of etanercept.

213 Subject has used a biologic agent for PsO after discontinuing apremilast treatment.

214 While receiving apremilast treatment or after discontinuing apremilast, subject had a clinically significant adverse event (eg, serious infection, neurologic event, malignancy, hematologic event, psychiatric adverse event such as depression or suicidal ideation/attempt) or any other adverse event that the investigator feels might cause this study to be detrimental to the subject.

215 Subject has used a live vaccine within 1 month prior to the first dose of etanercept.

Laboratory Abnormalities

216 Subject has laboratory abnormalities at screening, including:

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 1.5x the upper limit of normal (ULN)
- Serum total bilirubin (TBL) ≥ 1.5 mg/dL
- Hemoglobin < 11 g/dL
- Platelet count < 125,000/mm^3
- White blood cell count < 3,000 cells/mm^3
- Absolute neutrophil count (ANC) < 1,500/mm^3
- Estimated creatine clearance < 50 mL/min (Cockroft-Gault formula, calculated value to be provided to sites)

217 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, will interfere with the interpretation of the study results, or might cause the study to be detrimental to the subject.

Other

218 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

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 Female subject is not willing to use acceptable method(s) of effective contraception during study treatment and for an additional 4 weeks after the last dose of etanercept (except those who have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy, or who are at least 2 years postmenopausal).

Note: Additional medications given during treatment with etanercept may increase the length of time that subjects must avoid becoming pregnant or breastfeeding after the last dose of study drugs. The investigator is to discuss these changes with the subject if applicable.

223 Subject is pregnant or breast feeding, or planning to become pregnant or breastfeed during the study treatment and through 4 weeks after the last dose of etanercept.

Note: Additional medications given during treatment with etanercept may increase the length of time that subjects must avoid becoming pregnant or breastfeeding after the last dose of study drugs. The investigator is to discuss these changes with the subject if applicable.

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 IRB/IEC and Amgen approved 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/on the enrollment case report form (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 will be assigned by IVR/IWR system. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen twice (see Section 7.2.2).

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Treatment Assignment

All subjects enrolled in the study will be assigned open-label etanercept treatment. The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

6. TREATMENT PROCEDURES

The Amgen Investigational Product(s) used in this study include(s): etanercept.

The investigational medical device used in this study include(s): prefilled syringe

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of etanercept.

6.1 Investigational Product

6.1.1 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 prefilled 1.0 mL syringe as a sterile, preservative-free solution for subcutaneous injection. The solution of etanercept is clear and colorless and is formulated at pH 6.3 $\pm$ 0.2. Each single-use prefilled syringe contains 0.98 mL of 50 mg/mL etanercept in a formulation consisting of 100 mM Sodium Chloride, 25 mM sodium phosphate, 25 mM L-Arginine-HCL, and 1% sucrose. Etanercept will be provided in packs with 4 syringes.

6.1.1.1 Dosage, Administration, and Schedule

Etanercept dosing will follow the recommended label dosing for patients with PsO: 50 mg subcutaneously, twice weekly for 12 weeks followed by 50 mg subcutaneously once weekly (for the additional 12 weeks).

Each dose of etanercept will consist of the complete contents of 1 pre-filled syringe. Injections should occur in the thigh, abdomen or outer area of the upper arm. The injection site should be rotated with each dose.

During the first 12 weeks of the study, subjects will receive 2 doses of etanercept per week (eg, on Monday and Thursday). During the second 12 weeks of the study, subjects will receive 1 dose of etanercept per week (scheduled approximately 7 days apart). Throughout the entire trial, administration of etanercept should occur on the scheduled 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. Subsequent doses of etanercept 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.

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 subject will be instructed in appropriate handling and storage of used and unused syringes.

The dose, start date, stop date, dose time and box number of etanercept are to be recorded on each subject's CRF.

The effects of overdose of etanercept are not known.

There may not be any adjustment of etanercept dosage other than the protocol-specified reduction from 50 mg twice weekly for the first 12 weeks of the study to 50 mg once weekly for the second 12 weeks.

Please refer to the US Prescribing Information or the Etanercept Investigator's Brochure for the most recent safety information.

6.2 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, TBL, and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis) as described below may meet the criteria for withholding or permanent discontinuation 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.

6.2.1 Criteria for Permanent Discontinuation of Amgen Investigational Product Due to Potential Hepatotoxicity

Etanercept should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

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

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

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including Steatohepatitis
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if etanercept should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.2.2 Criteria for Conditional Withholding of Amgen Investigational Product Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of etanercept outlined above and have no underlying liver disease, and eligibility criteria requiring

transaminases and TBL < 1.5x ULN at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

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

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Etanercept should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.2.3).

6.2.3 Criteria for Rechallenge of Amgen Investigational Product After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then etanercept should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.1) should never be rechallenged.

6.3 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 6.6.

Concomitant therapies are to be collected in the CRF from baseline (day 1) through the end of treatment.

For concomitant therapies being taken for PsO, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date. For other medications being taken, collect therapy name, indication, start date and stop date.

6.4 Medical Devices

The following medical device: prefilled syringe will be used in this study and provided by Amgen. Additional details for each medical device is to be provided in the IPIM.

Other medical devices, which are not considered test articles, may be used in the conduct of this study as part of standard care. These devices 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.

6.5 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 a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes etanercept and prefilled syringe.

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

6.6 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Proscribed medications during this study include the following:

- Any biologic immune modulator (other than etanercept), including but not limited to alefacept, anakinra, adalimumab, infliximab, secukinumab, ustekinumab
- Apremilast
- Azathioprine
- Cyclophosphamide
- Cyclosporine
- Fumarates
- Hydroxyurea
- Leflunomide
- Live vaccines (eg, measles, mumps, and rubella; varicella; intranasal flu)

- Methotrexate
- Mycophenolate mofetil
- Oral or parenteral corticosteroids including intramuscular or intra-articular administration (the use of otic, nasal, or inhaled corticosteroids within recommended doses is allowed)
- Oral retinoids
- Sulfasalazine
- Systemically administered calcineurin inhibitors
- Tofacitinib
- Any other systemic therapy for psoriasis
- Any investigational therapy
- Thioguanine
- Topical steroids (exception: upper mid-strength or lower potency topical steroids are permitted on the scalp, axillae, and groin at the discretion of the investigator)
- Topical vitamin A or D analog preparations, or anthralin
- Topical cyclosporine or other calcineurin inhibitors
- PUVA therapy
- UVA therapy
- UVB therapy

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 1 (Schedule of Assessments) 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 study visits should be scheduled from day 1 (date of the first dose of etanercept) of the study. It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated in Table 1. 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 in Table 1.

With the exception of the screening and re-screen visits, all study procedures for a visit should be completed on the same day. Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the CRFs. 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

	Screening	Treatment Period							Safety Follow-up Period
Study Visit	**Up to 45 days**	**Day 1 (baseline)**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24/ ET**	**30-day (phone call) (EOS)**
General and Safety Assessments									
Informed consent	X								
Medical history	X								
Medication history	X								
Physical exam[a]	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	
Height	X								
Concomitant medications		X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	
Disease related events		X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X
Disease Assessments									
PASI	X	X	X	X	X	X	X	X	
sPGA	X	X	X	X	X	X	X	X	
Involved BSA	X	X	X	X	X	X	X	X	
Patient Reported Outcomes									
PSI[b]		X	X	X	X	X	X	X	
Patient Assessment of Treatment Satisfaction		X			X			X	
DLQI		X			X			X	
Laboratory Assessments									
Hematology profile	X	X			X			X	
Chemistry profile	X	X			X			X	
Hepatitis C virus antibody	X								
Hepatitis B virus surface antigen and core antibody	X								
Urinalysis	X	X							
Pregnancy test[c]	X	X						X	
Tuberculosis testing	X								
Investigational Product									
Investigational product dispensation		X	X	X	X	X	X		
Subject Diary									
Subject diary dispensation/collection		X	X	X	X	X	X	X	

Footnotes defined on next page

PASI= Psoriasis Area and Severity Index; sPGA = Static Physician's Global Assessment; BSA = Body Surface Area; PSI = Psoriasis Symptom Inventory; DLQI = Dermatology Life Quality Index; ET: early termination; EOS: end of study

[a] Screening physical exam will be a full physical exam; subsequent exams will be interim exams to monitor for any changes.

[b] PSI to be completed at home at weeks 1, 2, and 3 as well as at each visit indicated.

[c] Pregnancy test to be performed for all women except those of non-reproductive potential (ie, those who have had a hysterectomy, bilateral salpingectomy or ophorectomy, or who are at least 2 years postmenopausal). Serum pregnancy test at screening must be performed ≤ 4 weeks from the first dose of etanercept; Urine pregnancy test will be performed at baseline and Week 24 or ET visit.

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, IVR/IWR system, 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 or discontinuation of standard therapy for any disallowed therapy. After signing the written informed consent form, site will register the subject in IVR/IWR and screen the subject in order to assess eligibility for participation. The screening window is up to 45 days. If a subject has not met all eligibility criteria at the end of the 45-day window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening twice as described in Section 7.2.2.

7.2.2 Re-screening

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen twice. Re-screen subjects must first be registered as screen failed in IVRS/IWRS system and subsequently registered as re-screened. Subjects will retain the same subject identification number assigned at the original screening. Once the subject is registered as re-screened, a new 45-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 less than 30 days after the original signing of the informed consent, then only those criteria that were originally failed are required to be repeated. The PPD test, chest X-ray, and Quantiferon will not need to be repeated for re-screen subjects if negative at the original screening. However, subjects screen-failing for and not meeting the tuberculosis testing inclusion criterion are not permitted to re-screen.

7.2.3 Treatment

Visits will occur per the Schedule of Assessments (Table 1) during the treatment period from day 1 (baseline) through week 24. On-study visits may be completed within ± 5 days of the target visit date. Prior to enrollment, subject eligibility must be confirmed with screening procedures. Subjects satisfying eligibility requirements will be enrolled. The date of the first dose of etanercept is defined as day 1 (baseline). All subsequent doses and study visits will be scheduled based on the day 1 date.

Etanercept is to be administered at the site after all assessments have been done for all visits that will include dosing. Subjects ending the study prior to week 24 will be asked to complete the unscheduled early termination (ET) visit assessments which are the same as those listed in the Schedule of Assessments under Week 24/ET.

7.2.4 Safety Follow-up/End of Study

Approximately 30 days (+ 7 days) after their last dose of etanercept, subjects will be contacted by phone by the study staff to follow-up on any continuing serious adverse events or disease related events and inquire about the emergence of any new serious adverse events or disease related events.

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures for required timepoints.

7.3.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study specific procedures are performed.

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.

7.3.3 Physical Examination and Medical History

Physical examination should be completed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event). Any clinically significant changes in physical exam throughout the study, per the investigator's opinion, should be recorded on the event CRF.

The Investigator or designee will collect a complete medical and surgical history that started within 5 years prior to enrollment through the first dose of etanercept. In addition to the medical history above, PsO history must date back to the original diagnosis. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.

7.3.4 Medication History

A complete history of psoriasis medications (including apremilast) starting at the time of diagnosis and up to screening will be recorded on the CRF. This information will include therapy name, indication, dose, unit, frequency, route, start date and stop date. All other

medications taken within 3 months prior to screening will be collected, including therapy name, indication, dose and start date and stop date.

7.3.5 Physical Measurements

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

7.3.6 Vital Signs

The following measurements must be performed: systolic/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 most recumbent position possible. The position selected for a subject should be the same throughout the study and documented on the vital signs CRF. The temperature location selected for a subject should be the same throughout the study and documented on the vital signs CRF. If abnormalities are found and they are considered an adverse event, record on the Event CRF.

7.3.7 Chest Radiograph

Subjects with a positive PPD test without a history of Bacillus Calmette-Guerin vaccination or subjects with a positive or indeterminate Quantiferon test will require a chest radiograph including posterior-anterior and lateral views performed within 3 months prior to the first dose of investigational product. The radiograph report should be read by a radiologist or per local requirement and the report must be reviewed by the investigator prior to enrollment of the subject.

7.3.8 Adverse Events and Disease Related Events

Adverse events, serious adverse events and disease related events observed by the investigator or reported by the subject will be collected as per Section 9.

7.3.9 Concomitant Medications

Concomitant medications are to be collected from baseline (day 1) through the end of treatment as described in Section 6.3.

7.3.10 Subject Diary for Study Drug Administration

7.3.10.1 Distribution and Instruction

All subjects should be able to complete entries in the subject diary in English or have a designee who can do so for the subject. All subjects will complete a diary which is dispensed per the schedule of assessments. Site staff must instruct the subject on accurate and complete documentation in the diary, which serves as a source document.

Subjects will complete the diary after each dose administered, including the first dose self-administered in the clinic. Subject is to record the date, time, dose of etanercept injection, injection site, etanercept box ID, any concomitant medications taken, and adverse events.

7.3.10.2 Collection and Review

Subjects will return the diary at each study visit. . Site staff will review the diary with the subject to confirm the subject accurately reported all required information, including adverse events and concomitant medications, and will clarify entries, as necessary. Site staff will enter the data into the CRF.

7.3.11 Disease Assessments

The assessor who performs the following assessments will be a licensed healthcare professional who has been certified as trained by Amgen standard training material for PASI, sPGA and BSA provided by Amgen OR who has been previously certified as trained with the standard training material provided by Amgen or by organizations such as Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) (documentation of certification must be provided to Amgen). If possible, each subject should have their assessments done by the same assessor throughout the study. If necessary, study visits may be rescheduled within the specified window "(± 3 days) to accommodate when the specific assessor will be available.

7.3.11.1 PASI

PASI score (0 to 72) is a calculation of plaque qualities, including induration, erythema, and desquamation, and the area involved with psoriasis. The assessor will score plaque qualities (0 to 4) and area of involvement (0 to 6) for each of 4 body areas: head and neck, upper extremities, trunk, and lower extremities. Higher scores indicate more severe and/or extensive psoriasis. The PASI worksheet will be signed and dated by the PASI assessor and maintained in the subject's source documents.

7.3.11.2 BSA Involvement

The involved BSA numerical score (0% to 100%) is completed by the same assessor performing the sPGA assessment and will be used to measure the physician's assessment of the proportion of the subject's total BSA involved with psoriasis.

7.3.11.3 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 to 5. It is important that each subject have their sPGA assessments done by the same assessor throughout the study.

7.3.12 Patient Reported Outcomes

7.3.12.1 Psoriasis Symptom Inventory

The subject will be asked to rate the severity of their psoriasis signs and symptoms on an 8-item questionnaire (itch, redness, scaling, burning, stinging, cracking, flaking, pain). Each item is scored from 0 (not at all severe) to 4 (very severe). A 7-day recall period will be utilized and the PSI will be completed by the subject on paper version at baseline and weeks 1, 2, 3 and then at each visit.

7.3.12.2 Patient Assessment of Treatment Satisfaction

The subject will be asked to check a box (from “very dissatisfied” to “very satisfied”) to indicate his or her level of satisfaction with the medication’s control of psoriasis. The response scale is adapted from the Medical Outcomes Study: Patient Satisfaction Survey.

7.3.12.3 Dermatology Life Quality Index

Health related quality of life will be evaluated using the DLQI, a skin disease-specific instrument that has been validated for use in patients with psoriasis (Finlay and Khan, 1994).

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 and PPD. The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, serum pregnancy, urinalysis, hepatitis C antibody, hepatitis B surface antigen and core antibody, and any other laboratory tests required. Urine pregnancy and PPD testing will be performed locally at each site. The results of this testing will be maintained in the source documents at the site.

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 etanercept administration (if etanercept is to be administered on the same day as a study visit) at the time points outlined in the Schedule of Assessments (Table 1). The date and time of sample collection will be recorded in the source documents at the site. Specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples are below (Table 2).

Table 2. Analyte Listing

Chemistry	Urinalysis	Hematology and Differential	Other Labs
Sodium	Specific gravity	Red blood cells	Serum beta hCG[b]
Potassium	pH	Red blood cell morphology	Hepatitis B surface antigen and Hepatitis B core antibody
Chloride	Blood	Hemoglobin	Hepatitis C virus antibody
Bicarbonate	Protein	Hematocrit	Quantiferon[c]
Total protein	Glucose	Platelets	
Albumin	Bilirubin	White blood cell Differential	
Adjusted calcium	Leukocyte esterase	• Bands/stabs	
Magnesium	Ketones	• Eosinophils	
Phosphorus	Microscopic (Reflex testing if abnormal)	• Basophils	
Glucose		• Lymphocytes	
BUN		• Neutrophils	
Creatinine[a]		• Monocytes	
Uric acid			
Total bilirubin			
Direct bilirubin			
Alkaline phosphatase			
AST (SGOT)			
ALT (SGPT)			

[a] Estimated creatine clearance will be calculated using the Cockroft-Gault formula.
[b] For all women, unless at least 2 years postmenopausal or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy. If a pregnancy is suspected, additional pregnancy testing may be performed at the discretion of the investigator.
[c] If applicable

7.4.1 Tuberculosis Testing

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

7.4.1.1 PPD

The PPD test must be read by a trained licensed healthcare professional 48 to 72 hours after the test material is placed intradermally under the skin. PPD test kits will not be provided by the sponsor and must be procured locally.

7.4.1.2 Quantiferon

If a subject does not receive a PPD test, then a Quantiferon test must be performed per the Inclusion Criteria. 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. All women, except those of non-reproductive potential (ie, those who have had a hysterectomy, bilateral

salpingectomy, or bilateral oophorectomy, or who are at least 2 years postmenopausal), must take a urine pregnancy test at baseline. The central laboratory will provide the urine pregnancy tests. Urine pregnancy tests must be given prior to dispensing investigational product.

7.5 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 the inflammatory conditions, the dose response and/or prediction of response to etanercept, 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 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 (or a legally acceptable representative) 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.

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

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

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

8.3 Reasons for Removal From 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, lost to follow-up)

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 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Disease related events for the purposes of this study include worsening of the skin symptoms associated with PsO. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition.

Disease Related Events and/or Disease Related Outcomes that do not qualify as Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event.
- Death due to the disease under study is to be recorded on the Event CRF.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

9.1.2 Adverse Events

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

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

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

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

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease Related Event as defined in Section 9.1.1):

- 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

A disease related event as described above is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

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 drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s)/study treatment/protocol-required therapies through the safety follow-up (ie, 30 days after the last dose of etanercept) are reported using the Event CRF. Additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF.

Events assessed by the investigator to be related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

9.2.2 Adverse Events

9.2.2.1 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 through the end of treatment period are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

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

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product. 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?

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.

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.

9.2.2.2 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 the 30-day safety follow-up period are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

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.

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 electronic Serious Adverse Event 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 /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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 Event CRF.

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs

in compliance with all reporting requirements according to local regulations and good clinical practice.

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.

9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them 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.

9.2.2.4 Serious Adverse Events That Are not to be Reported In an Expedited Manner

The study population involved will have an increased burden of comorbidities which are commonly associated with psoriasis and may lead to serious adverse events that do not need to be reported in an expedited manner. This includes any serious adverse event attributed to hypertension, obesity, type 2 diabetes, metabolic syndrome, myocardial infarction, angina, coronary artery disease, cerebrovascular accident, peripheral vascular disease, depression and anxiety. These serious adverse events will be monitored with routine pharmacovigilance on an ongoing basis.

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 after the last dose of protocol-required therapies through 4-weeks after the end of treatment with etanercept.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

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 after the last dose of protocol-required therapies through 4 weeks after the end of treatment with etanercept.

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- PASI 75 at week 12

10.1.1.2 Secondary Endpoints

- PASI 75 at all other visits
- PASI 50 and 90 at all visits
- Percent PASI improvement at all visits
- sPGA of 0 or 1 at all visits
- sPGA of 0, 1, or 2 at all visits
- sPGA at all visits
- One and two grade improvement in sPGA at all visits
- Percent BSA improvement at all visits
- PSI total and component scores at all visits
- Patient Assessment of Treatment Satisfaction at week 12 and 24
- Improvement in DLQI at week 12 and 24

10.1.1.3 Safety Endpoints

- Adverse events
- Laboratory assessments

10.1.2 Analysis Sets

The full analysis set is all subjects who received at least one dose of investigational product during the study. All safety and efficacy endpoints will be analyzed using the full analysis set.

10.1.3 Covariates and Subgroups

The following predictors and subgroup analyses may be performed to assess their influence on the primary endpoint:

- Body mass index (≤ 35 kg/m^2 or > 35 kg/m^2)
- Body Weight (≤ median, > median)
- Age (<65, ≥ 65)
- Gender (male vs. female)
- Race (white, non-white)
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
- Baseline PASI score (≤ median, > median)
- Baseline BSA with psoriasis involvement (%) (≤ median, > median)
- History of psoriatic arthritis (yes, no)
- Baseline sPGA score (3, 4 or 5)

10.2 Sample Size Considerations

This study will estimate the proportion of subjects with PsO who achieve a PASI 75 after 12 weeks of treatment with etanercept following failure of treatment with apremilast.

In recent etanercept studies, the 12-week PASI 75 response rate for etanercept was ~50 to 60%. The assumed response for a population with failure of treatment with apremilast is 40%. In placebo-controlled phase 3 studies, the PASI 75 placebo response rate was ~5% in subjects with moderate to severe plaque PsO. Therefore, in this single-arm study if the lower bound of the 95% confidence interval for the proportion of PASI 75 response is above 10%, we can safely conclude that in spite of limitations of a single-arm study (ie, regression to the mean and/or placebo effect), the etanercept effect is real.

The sample size of 80 is more than adequate to achieve a half-width of less than 15% for the 95% confidence interval for the proportion of subjects who achieve a PASI 75 response, assuming a sample proportion of 40% and a lower bound of the confidence interval above 10%.

In a phase 3, randomized, double-blind, placebo-controlled apremilast trial, 17% of subjects reported diarrhea and/or nausea. Of the 80 subjects enrolled, 60 subjects will be enrolled for reasons of primary or secondary failure to apremilast in the investigator's opinion. In addition, between 10 and 20 (up to 25%) will be enrolled for reasons of intolerability to apremilast in the investigator's opinion.

10.2.1 Planned Analysis

10.2.2 Primary Analysis

The primary analysis for all efficacy endpoints will be performed using the full analysis set. Missing values will be imputed using last observation carried forward method. Summary statistics will be generated as well as confidence intervals and p-values. No multiplicity adjustments will be made for the p-values.

No interim analysis is planned for this study.

10.2.3 Sensitivity Analysis

A sensitivity analysis will be performed using observed cases.

10.3 Planned Methods of Analysis

10.3.1 General Considerations

This is an open-label single-arm study. 95% confidence intervals and p-values for estimated response rates will be generated for descriptive purposes only.

The final analysis will be performed after all subjects have completed the week 24 assessments and all data through week 24 and the 30-day safety follow-up (EOS) have been finalized. Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively for all subjects.

10.3.2 Efficacy Endpoints

The primary analysis for all efficacy endpoints will be performed using the full analysis set. Missing values will be imputed using last observation carried foraward method. Summary statistics will be generated as well as confidence intervals and p-values.

For efficacy analyses, all categorical endpoints will be summarized using number and percentage of subjects. In addition to being summarized using number and percentage of subjects, ordinal categorical endpoints will also be summarized using number of observations, mean, standard error, standard deviation, median, minimum, and maximum. All continuous endpoints will be summarized using number of observations, mean, standard error, standard deviation, median, minimum, and maximum.

Subgroup analysis may be considered as described in Section 10.1.3.

10.3.3 Safety Endpoints

Safety endpoints will be summarized descriptively based on the full 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, and significant treatment-emergent adverse events will be provided.

Subject incidence of disease related events and fatal disease related events will be tabulated by system organ class and preferred term.

Laboratory parameters and vital signs will be summarized by study visit. Shift tables of the worst on-study laboratory toxicity based on CTCAE version 4.0 relative to baseline will be tabulated. Subject listings of grades 3 and 4 laboratory toxicities will be provided.

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 Clinical Study 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.
- 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 multicenter 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 IVR/IWR system captures the following data points and these are considered source data: subject ID, enrollment date, investigational product dispensation date and investigational product box number dispensed.

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, PROs noted in Schedule of Assessments will be considered as source document.

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 (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, 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 Amgen 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 (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 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 electronic data capture study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, 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.

12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors, 2013, updated 2014), which states:

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

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

12.7 Compensation

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

13. REFERENCES

Etanercept Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

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Menter A, Gottlieb A, Feldman SR et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58:826-50.

Otezla® Prescribing Information. Summit, NJ. Celgene Corporation.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is available at the following location:

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of drug induced liver injury (DILI), cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.2 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, 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 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product is withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.2.1 and 6.2.2 or who experience AST or ALT elevations > 3 x ULN are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

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

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

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia

- Obtain serum total immunoglobulin IgG, Anti-nuclear antibody, 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, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample Electronic Adverse Event Contingency Report Form

AMGEN Study # 20150252 Etanercept	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. ADVERSE EVENT

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

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

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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AMGEN Study # 20150252 Etanercept	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med 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? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test											
	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20150252 Etanercept	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20150252

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm / dd / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Etanercept				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm / dd / yyyy_____

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

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm / dd / yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy_____

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

If yes, provide date of delivery: mm / dd / yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20150252

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
Etanercept				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2.

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