

Title: A Multicenter, Randomized, Double-blind, Crossover Study to Assess the Injection Site Pain Associated With a Modified Etanercept Formulation in Adult Subjects With Either Rheumatoid Arthritis or Psoriatic Arthritis

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I have read the attached protocol entitled A Multicenter, Randomized, Double-blind, Crossover Study to Assess the Injection Site Pain Associated With a Modified Etanercept Formulation in Adult Subjects With Either Rheumatoid Arthritis or Psoriatic Arthritis, dated **30 March 2017**, and agree to abide by all provisions set forth therein.

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- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

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Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Multicenter, Randomized, Double-blind, Crossover Study to Assess the Injection Site Pain Associated With a Modified Etanercept Formulation in Adult Subjects With Either Rheumatoid Arthritis or Psoriatic Arthritis

Study Phase: 3b

Indication: Rheumatoid Arthritis (RA) or Psoriatic Arthritis (PsA)

Primary Objective:

- To assess the injection site pain associated with a modified formulation of etanercept compared to the currently marketed etanercept in adult subjects with either rheumatoid arthritis (RA) or psoriatic arthritis (PsA) as measured by a visual analog scale (VAS)

Secondary Objective:

- To describe the injection site pain by disease indication

Safety Objective:

- To evaluate the safety of etanercept

Hypotheses: The primary hypothesis of this study is that the modified etanercept formulation will be associated with less injection site pain compared to the currently marketed etanercept formulation.

Primary Endpoint:

- Change in injection site pain score between the current formulation and the modified formulation as measured by the VAS

Safety Endpoints:

- Adverse events

Study Design: This is a phase **3b**, multicenter, randomized, double-blind, 2-period, 2-sequence crossover study in subjects with RA or PsA who are naive to etanercept. The study will evaluate injection site pain associated with the current formulation of etanercept and the modified formulation of etanercept immediately after injection of each formulation.

Subjects will be randomized in a 1:1 ratio to receive each etanercept formulation in 1 of 2 crossover treatment sequences. Subjects randomized to the first treatment sequence (ie, sequence AB) will receive 1 dose of the current formulation during the first study period (ie, treatment A), followed by a second visit 1 week later during the second study period at which time subjects will receive 1 dose of the modified formulation (ie, treatment B). Subjects randomized to the second treatment sequence will undergo the same procedures but will receive investigational product in the opposite order (ie, sequence BA). Subjects who dropout after the first injection will not be replaced by new subjects. At each study visit, subjects will inject the blinded treatment and immediately (ie, within 30 seconds of injection) record the associated injection site pain using the VAS. A total of **112** subjects will be enrolled with **56** subjects in each treatment sequence, stratified by disease indication (RA or PsA). A minimum of 20 PsA subjects will be enrolled.

After study completion subjects may continue with commercially available etanercept. The study will consist of a screening period of up to 14 days, a treatment period of 2 weeks, and a 30-day safety follow-up period.

Sample Size: The proposed sample size of **112** (ie, **56** per sequence treatment arm with at least 10 subjects with PsA) would provide approximately **53** subjects for each sequence treatment arm at the completion of the study, assuming an early termination or dropout rate of 5% for each sequence treatment arm over the course of the study.

Summary of Subject Eligibility Criteria:

- Male or female subject is \geq 18 years of age at time of signing the informed consent form.
- Subject has a diagnosis of RA or PsA and indicated for treatment with etanercept per the current label, based on investigator judgment.
- Subject is naïve to etanercept.

For a full list of eligibility criteria, please refer to [Section 4.1](#).

Investigational Product

Amgen Investigational Product Dosage and Administration: All injections of etanercept will be administered by the subject as a subcutaneous injection at the study site on the scheduled dose day. The subject must demonstrate to the site staff that he or she is competent to correctly administer the subcutaneous doses. Supplies of etanercept will be dispensed to subjects during the study visit.

Each dose of etanercept will consist of the complete contents of 1 SureClick autoinjector. If the first injection site occurs on the **thigh**, the second injection site should be performed on the contralateral limb. If the injection occurs in the abdomen, the first injection should be on either the right or left half of the abdomen with the second injection occurring on the opposite side of the abdomen. Each dose will follow the recommended label dosing for subjects with RA and PsA: 50 mg weekly (scheduled approximately 7 days apart). Throughout the entire study, 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 3 days of the previous or next scheduled dose. If the dosing window is missed, that dose should be skipped. Etanercept is to be taken the day of a study visit in the presence of the investigator or designee.

Procedures: At specified time points outlined in the Schedule of Assessments subjects will undergo the following procedures: collection of informed consent form, medical/medication history, demographics, physical examination, height, weight, vital signs, and chest x-ray (if needed). Subjects will provide samples for hematology, blood chemistry, hepatitis B and C serologies, and tuberculosis testing. Females of childbearing potential will provide serum and urine pregnancy tests. Research staff will document the use of concomitant medications and all adverse events reported by the subject. Thirty days (+ 7 days) after the last dose of etanercept, subjects will undergo a safety follow-up visit. For a full list of study procedures, including the timing of each procedure, please refer to [Section 7](#) and the Schedule of Assessments ([Table 1](#)).

Statistical Considerations: The primary analysis set will include all subjects who received the dose of investigational product during each study period and who completed the injection site pain score during each study period. The primary endpoint will be evaluated based on this primary analysis set.

The safety analysis set will include all subjects who received at least 1 dose of investigational product during the study. All safety endpoints will be evaluated using the safety analysis set.

Analysis of covariance will be used to compare the difference in injection site pain score within subjects receiving etanercept in the currently marketed formulation and in the modified formulation, with the disease indication (RA or PsA) and the treatment as factors, adjusting for period effect and sequence effect.

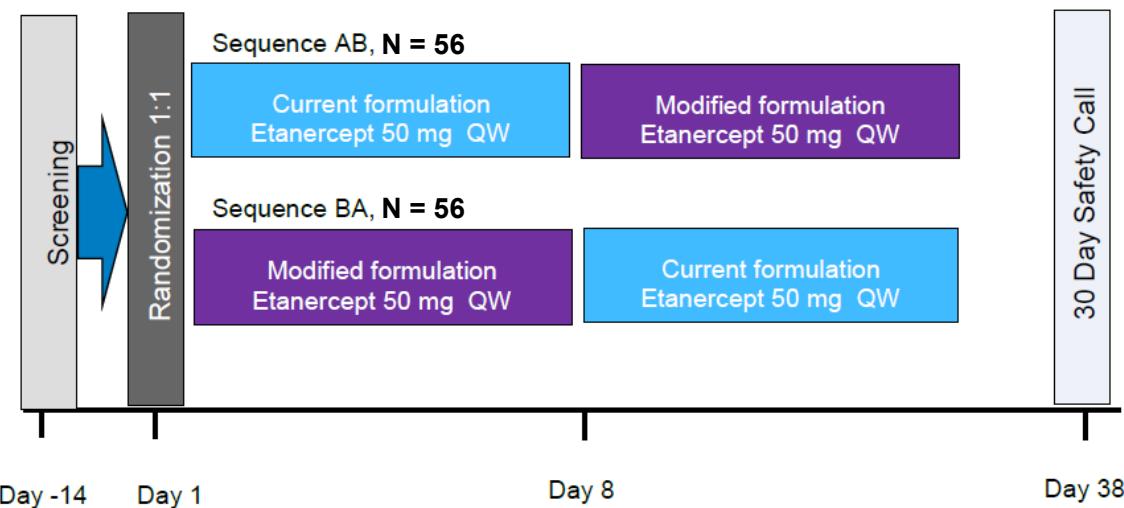
Descriptive statistics for continuous variables, consists of number of observations, mean, standard error and/or standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, maximum, and for categorical variables, the number of observations, frequency, and percentage will be presented. Subject disposition, demographics, baseline characteristics, and safety information will be summarized. There will be no adjustment for multiplicity and no imputation techniques for missing values. All analyses will be based on observed data.

For a full description of statistical analysis methods, please refer to [Section 10](#).

Sponsor: Amgen Inc.

Data Element Standards Version 5.0, 20 March 2015
Version(s)/Date(s):

Study Design and Treatment Schema



Abbreviations: QW = every week.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CRF	Case Report Form
DILI	drug-induced liver injury
EDC	electronic data capture
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End-of-Study (end of study)	defined as when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject completes safety follow-up)
End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie, last subject completes Study Visit 2)
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
Interactive Web Response (IWR)	web based technology that is linked to a central computer in real time as an interface to collect and process information.
IRB	institutional review board
PGA	Physician Global Assessment
PPD	purified protein derivative
PsA	psoriatic arthritis
PsO	psoriasis
RA	rheumatoid arthritis
SD	standard deviation

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Abbreviation or Term	Definition/Explanation
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 study necessary for the reconstruction and evaluation of the study. 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.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
TNF	tumor necrosis factor
TNF β	tumor necrosis factor beta
ULN	Upper limit of normal
US	United States
VAS	visual analog scale

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1. OBJECTIVES

1.1 Primary

- To assess the injection site pain associated with a modified formulation of etanercept compared to the currently marketed etanercept in adult subjects with either rheumatoid arthritis (RA) or psoriatic arthritis (PsA) as measured by a visual analog scale (VAS)

1.2 Secondary

- To describe the injection site pain by disease indication

1.3 Safety

- To evaluate the safety of etanercept

2. BACKGROUND AND RATIONALE

2.1 Disease

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

PsA is a chronic inflammatory disorder of the peripheral joints and axial skeleton that occurs in 7% to 34% of patients with psoriasis ([\[PsO\] Scarpa et al, 1984; Biondi et al, 1989; Espinoza et al, 1992; Shbeeb et al, 2000](#)), which in turn has a prevalence of 1% to 3% in the general population ([Biondi et al, 1989; Koo, 1996](#)). Articular involvement can vary widely from an isolated monoarthritis to a very destructive diffuse arthritis mutilans. Other symptoms associated with PsA include dactylitis, enthesitis, and nail changes. Typical nail changes include pitting of the nail, onycholysis, ridges, and thickening of the nail. Although most patients have associated PsO, PsA can present without skin changes. Radiographic features include joint erosions, joint space loss, osteolysis that may cause penciling of the phalanx, and periostitis. Psoriatic arthritis can lead to permanent destruction of joints and functional disabilities.

2.2 Amgen Investigational Product Background

Tumor necrosis factor (TNF) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays a role in the inflammatory process of RA and PsO. Elevated levels of TNF alpha (α) are found in involved tissues and fluids of

patients with RA, PsA, ankylosing spondylitis, and PsO. Two distinct receptors for TNF, a 55-kilodalton protein and a 75-kilodalton protein, exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF is dependent upon binding to either cell surface TNF receptor.

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75-kilodalton TNF receptor linked to the Fc portion of human immunoglobulin G1. Etanercept inhibits binding of TNF α and TNF beta ($[\beta]$ lymphotoxin alpha) to cell surface TNF receptors, rendering TNF biologically inactive. In the United States (US) and Canada, etanercept is currently indicated for the treatment of:

- 1) moderately to severely active RA, alone or in combination with methotrexate;
- 2) moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older in the US and 4 to 17 years in Canada; 3) PsA alone or in combination with methotrexate; 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 [Etanercept Investigators' Brochure](#), or the product label for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.3 Rationale

Injection-related pain can often contribute to the poor compliance of drug administration. It is believed that route of administration, physical and chemical attributes of injected drug products, and the physical attributes of needles used to administer these drugs play a role in injection pain associated with drug administration ([Flanagan et al, 2007](#); [Laursen et al, 2006](#); [Palmon et al, 1998](#); [Robb and Kanji, 2002](#)). Alleviation of injection site pain can occur through modification of the solution composition. An etanercept modified formulation with minor excipient changes has been developed in an attempt to reduce the injection site pain related to its administration. The modified etanercept 50 mg/mL liquid formulation designed for use in this study is similar to the currently marketed etanercept product and has been shown in a single dose study to reduce injection-related pain. This study is designed to investigate the injection site pain of the modified formulation in comparison with currently marketed formulation of etanercept.

This will be a multicenter, randomized, double-blind, 2-sequence, 2-period crossover study to assess the injection site pain associated with the etanercept modified formulation in RA and PsA subjects naïve to etanercept. Injection site pain will be

measured by a 100 mm VAS specifically designed to query these data. The VAS scores will be collected immediately (ie, within 30 seconds after injection) after subcutaneous administration to assess injection site pain. A difference of 13 to 16 mm on the VAS is considered to be clinically meaningful (Gallagher et al, 2002) in a setting of acute pain.

Both internal and published data on clinicaltrials.gov have demonstrated that patients with RA, in general, report injection site pain with lower intensity as compared to healthy volunteers. RA and PsA were the indications chosen for this study as prior studies with this formulation were in healthy volunteers. These are of the most common indications for which etanercept is prescribed. These populations use the same dosing interval of etanercept, which allows them both to be included in this study. Additionally, including both populations allows the results of this study to be applied in a broader context for the medical community.

Prior internal studies have demonstrated that attenuation of the injection site pain response occurs with repeated injection of investigational product. This study will collect data using 2 doses in a crossover design. This will leverage the efficiencies afforded by the cross over while minimizing the effects of long term attenuation.

These subjects are candidates for initiating etanercept for sustained treatment and will be able to initiate dosing in this study and then continue with commercially available etanercept treatment after completing the study. This is anticipated to mitigate the potential challenges with enrollment.

2.4 Clinical Hypotheses

The primary hypothesis of this study is that the modified etanercept formulation will be associated with less injection site pain compared to the currently marketed etanercept formulation.

3. EXPERIMENTAL PLAN

3.1 Study Design

The overall study design is described by a [study schema](#) at the end of the protocol synopsis section.

This is a phase **3b**, multicenter, randomized, double-blind, 2-period, 2-sequence crossover study in subjects with RA or PsA who are naive to etanercept. The study will evaluate injection site pain associated with the current formulation of etanercept and the modified formulation of etanercept immediately after injection of each formulation.

Subjects will be randomized in a 1:1 ratio to receive each etanercept formulation in 1 of 2 crossover treatment sequences. Subjects randomized to the first treatment sequence (ie, sequence AB) will receive 1 dose of the current formulation (ie, treatment A) during the first study period, followed by a second visit 1 week later during the second study period at which time subjects will receive 1 dose of the modified formulation (ie, treatment B). Subjects randomized to the second treatment sequence will undergo the same procedures but will receive investigational product in the opposite order (ie, sequence BA). At each study visit subjects will inject the blinded treatment and immediately (ie, within 30 seconds of injection) record the associated injection site pain using the VAS. A total of **112** subjects will be enrolled with **56** subjects in each treatment sequence, stratified by disease indication (RA or PsA). A minimum of 20 PsA subjects will be enrolled.

After study completion subjects may continue with commercially available etanercept. The study will consist of a screening period of up to 14 days, a treatment period of 2 weeks and a 30-day safety follow-up period.

The study endpoints are defined in [Section 10.1.1](#).

3.2 Number of Sites

Approximately 30 sites in the US 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".

A total of **112** subjects are expected to enroll in this study with **56** subjects in each treatment sequence. Subjects will be randomly assigned in a blinded manner to 1 of 2 crossover sequences. The sample size accounts for 5% withdrawal or dropout.

Refer to [Section 10.2](#) for sample size considerations.

3.4 Replacement of Subjects

Subjects who withdraw or removed from the study will not be replaced. Subjects who dropout after the first injection will not be replaced by new subjects.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

After signing the informed consent, subjects should be enrolled within 14 days. The planned length of participation in the study for an individual a subject is as follows:

- Up to a 14 day screening period
- 2-week treatment period
- 30 day post treatment safety follow-up

3.5.2 End-of-Study

Primary Completion: The time when the last subject is assessed for the purposes of final collection of data for the primary analysis (ie, last subject completes Study Visit 2).

End-of-Study: The time when the last subject is assessed for evaluation in the study (ie, last subject completes safety follow-up).

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 before initiation of any study-specific activities/procedures
- 102 Male or female subject is \geq 18 years of age at time of signing the informed consent form
- 103 Subject has a diagnosis of RA or PsA and indicated for treatment with etanercept per the current label, based on investigator judgment
- 104 Subject is naïve to etanercept
- 105 Subject is able to self-inject etanercept

4.1.2 Exclusion Criteria

RA Related

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

Skin Disease Related

202 Subject has active erythrodermic, pustular, guttate PsO, or medication induced PsO, or other skin conditions at the time of screening visit (eg, eczema) that would interfere with evaluations of the effect of investigational product on PsO for those subjects with PsA

Other Medical Conditions

203 Subject has a history of clinically significant skin allergies (eg, frequent rashes)

204 Subject has a history of alcoholic hepatitis, nonalcoholic steatohepatitis, or immunodeficiency syndromes, including Human Immunodeficiency Virus infection

205 Subject has any active infection (including chronic or localized infections) for which anti-infectives were indicated within 4 weeks before screening

206 Subject has had a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks before first dose of investigational product

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

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

209 Subject has positive hepatitis B surface antigen, hepatitis B core antibody (confirmed by hepatitis B DNA test) or hepatitis C virus antibody serology at screening, or a positive medical history for hepatitis B or C. (Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll)

210 Subject has any active malignancy, including evidence of cutaneous basal, squamous cell carcinoma, or melanoma.

211 Subject has a history of malignancy within the last 5 years EXCEPT for cases that have been treated and considered cured specifically involving cutaneous basal or squamous cell carcinoma (non-melanoma skin cancers), cervical carcinoma in situ or breast ductal carcinoma in situ

212 Subject has known history of active tuberculosis

213 Subject has a positive test for tuberculosis during screening defined as either:

- positive purified protein derivative ([PPD] \geq 5 mm of induration at 48 to 72 hours after test is placed)

OR

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

- Subjects with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have ALL of the following:
 - no symptoms per tuberculosis worksheet provided by Amgen
 - documented history of a completed course of adequate prophylaxis (completed treatment for latent tuberculosis) per local standard of care before the start of investigational product
 - no known exposure to a case of active tuberculosis after most recent prophylaxis

214 Subject has 1 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 before randomization
- uncontrolled hypertension
- severe chronic pulmonary disease (eg, requiring oxygen therapy)
- multiple sclerosis or any other demyelinating disease
- major chronic inflammatory disease or connective tissue disease other than RA or PsA (eg, fibromyalgia, systemic lupus erythematosus with the exception of secondary Sjögren's syndrome, etc.)

Excluded Medications

215 Subject has used biologic disease modifying agent \leq 3 months before screening

216 If subject is receiving continuous treatment with acetaminophen, non-steroidal anti-inflammatory drug or tramadol, hydrocodone, oxycodone, codeine, and/or propoxyphene and the dose is within 4 hours before study visit and dose is not stable for \geq 2 weeks before first dose of investigational product

217 For subjects not on continuous analgesics, subject has taken the following within 4 hours before screening: acetaminophen, non-steroidal anti-inflammatory drugs, hydrocodone, codeine, tramadol, propoxyphene, and/or oxycodone (unless in the form of OxyContin). For subjects not on continuous analgesics, subject has taken OxyContin within 24 hours before screening.

218 Subject has received live vaccines \leq 4 weeks before first dose of investigational product

Laboratory Abnormalities

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

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $> 1.5 \times$ the upper limit of normal (ULN)
- Platelet count $< 125,000/\text{mm}^3$ (or $125 \times 10^9/\text{L}$)
- White blood cell count $< 3000/\text{mm}^3$ (or $3.0 \times 10^9/\text{L}$)
- Absolute neutrophil count $< 1500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$)

220 Estimated creatinine clearance $< 50 \text{ mL/min}$ (Cockcroft-Gault formula, calculated value to be provided to sites)

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

Other

222 Subject is currently receiving treatment in another investigational device or drug study, or < 30 days since ending treatment on another investigational device or drug study(s).

223 Other investigational procedures while participating in this study

224 Females who are pregnant or breastfeeding, or planning to become pregnant or breastfeed during treatment and/or within 4 weeks after the last dose of etanercept

225 Females of child-bearing potential with a positive pregnancy test (assessed by a serum pregnancy test during screening and a urine pregnancy test at baseline)

226 Females of child-bearing potential who are unwilling to practice true sexual abstinence (refrain from heterosexual intercourse) or unwilling to use 1 of the following effective birth control methods during treatment and for an additional 4 weeks after the last dose of etanercept (refer to [Section 6.8](#) for specific contraception methods and definition of child-bearing potential):

- hormonal contraceptives in pill, implant, injection, or patch form;
- Intrauterine device
- Intrauterine hormonal-releasing system
- bilateral tubal ligation/occlusion
- male partner with confirmed vasectomy on semen analysis
- sexual abstinence
- two barrier method

227 Subject previously has enrolled in this study

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

- 229 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Patient Reported Outcomes) to the best of the subject's and investigator's knowledge
- 230 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.

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](#)).

Subjects must personally sign and date the IRB/IEC and Amgen approved informed consent form before commencement of study-specific activities/procedures.

Upon completion of the screening period the subject is evaluated by the investigator and providing the subject continues to meet the inclusion/exclusion criteria, the subject is subsequently eligible to be enrolled in the study and either randomized or assigned to a treatment regimen.

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 14-day screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IVR/IWR. 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. This number will not necessarily be the same as the randomization number assigned for the study. If a subject has not met all eligibility criteria at the end of the 14-day window, the subject will be registered as a screen fail. Screen failed subjects may be eligible for re-screening once.

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 Randomization/Treatment Assignment

Subjects will be randomized in a 1:1 ratio to receive each etanercept formulation in 1 of 2 crossover treatment sequences and will be stratified by indication. Subjects randomized to the first treatment sequence (ie, sequence AB) will receive 1 dose of the current formulation (ie, treatment A) during the first study period, followed by a second visit 1, week later during the second study period at which time subjects will receive 1 dose of the modified formulation (ie, treatment B). Subjects randomized to the second treatment sequence will undergo the same procedures but will receive investigational product in the opposite order (ie, sequence BA). At each study visit, subjects will inject the blinded treatment and immediately (ie, within 30 seconds of injection) record the associated injection site pain using the VAS.

The randomization will be performed via IVR/IWR system on-study day 1.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study.

Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Trial Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event (ie, unblinding).

6. TREATMENT PROCEDURES

6.1 Classification of Products and/or Medical Devices

The Amgen Investigational Products used in this study includes etanercept and SureClick auto injector device.

Note: Non-investigational medical device(s) (ie, medical device[s]not under study) or products will be described in [Section 6.5](#).

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product Etanercept

Etanercept will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. The solution of etanercept is clear and colorless. Etanercept will be supplied in a single-use SureClick autoinjector as a sterile, preservative-free solution for subcutaneous injection. Each single-use SureClick autoinjector contains 0.98 mL of 50 mg/mL etanercept in either the currently marketed formulation (Treatment A) or a modified formulation (Treatment B).

6.2.1.1 Dosage, Administration, and Schedule

All injections of etanercept will be administered by the subject as a subcutaneous injection at the study site on the scheduled dose day. The subject must demonstrate to the site staff that he or she is competent to correctly administer the subcutaneous doses. Supplies of etanercept will be dispensed to subjects during the study visit.

Each dose of etanercept will consist of the complete contents of 1 SureClick autoinjector. If the first injection site occurs on the **thigh**, the second injection site should be performed on the contralateral limb. If the injection occurs in the abdomen, the first injection should be on either the right or left half of the abdomen with the second injection occurring on the opposite side of the abdomen. Each dose will follow the recommended label dosing for subjects with RA and PsA: 50 mg weekly (scheduled approximately 7 days apart). Throughout the entire study, 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 3 days of the previous or next scheduled dose. If the dosing window is missed, that dose should be skipped. Etanercept is to be taken the day of a study visit in the presence of the investigator or designee.

The volume (full, partial, or none), dose date, and box number of etanercept are to be recorded on each subject's CRF.

The effects of overdose of etanercept are not known. Please refer to the US Prescribing Information or the [Etanercept Investigator's Brochure](#) for the most recent safety information.

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin [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).

6.3.1 Criteria for Permanent Discontinuation of Etanercept 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 > 2 x 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
< ULN	> 3 x 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, the investigator should determine (based on subject population and/or severity of the hepatotoxicity or event) if etanercept and other

protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.3.2 Criteria for Conditional Withholding of Etanercept 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 normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of etanercept:

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

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

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

Etanercept should be withheld pending investigation into alternative causes of DILI. If etanercept 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.

6.3.3 Criteria for Rechallenge of Etanercept 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 should never be rechallenged.

6.4 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 6.7](#).

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

For concomitant therapies being taken for RA and PsA, 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.

6.5 Medical Devices

The following medical device, SureClick, will be used in this study and provided by Amgen. Additional details for each medical device is to be provided in the Investigational Product Instruction Manual.

6.6 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), device(s) or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Concerns or irregularities about the packaging, appearance or usage of the SureClick or other Amgen provided protocol-required product (ie, etanercept) in this study are to be reported to Amgen within 24 hours of discovery or notification of the concern or irregularity.

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

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

Subjects are prohibited from receiving the following therapies during Treatment Phase of this study:

- Any other investigational agents
- Any commercially available biologic agent for treatment RA or PsA (other than investigational product)
- Analgesics including acetaminophen, non-steroidal anti-inflammatory drugs, hydrocodone, codeine, tramadol, propoxyphene (within 4 hours of study visit) and/or oxycodone (within 24 hours of study visit)
- Cytotoxic agents including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents
- Fumarates
- Hydroxyurea
- Live vaccines (eg, measles, mumps, and rubella; varicella; intranasal flu)

6.8 Contraceptive Requirements

6.8.1 Female Subjects

Female subjects of childbearing potential must agree to use an acceptable method of contraception during treatment and for an additional 4 weeks after the last dose of etanercept.

Acceptable methods of effective contraception include: Hormonal (Combined estrogen and progestogen or progesterone-only hormonal contraception given via oral, intravaginal, transdermal, injectable, or implantable route); Intrauterine device; Intrauterine hormonal-releasing system; Bilateral tubal occlusion/ligation; Vasectomized partner (provided that partner is the sole sexual partner of the female participant who is of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success); Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject). Two barrier methods (1 by each partner) and the female partner must use spermicide (if spermicide is commercially available) with the barrier method the male must use a condom (latex or other synthetic material) and the female may select either a diaphragm, cervical cap or contraceptive sponge. A female condom is not an option because there is a risk of tearing when both partners use a condom.

Females not of childbearing potential are defined as: Any female who has had a hysterectomy, OR bilateral salpingectomy, OR bilateral oophorectomy, OR is postmenopausal. Post-menopausal females are:

- Age > 55 years with cessation of menses for 12 or more months
- Age < 55 years but no spontaneous menses for at least 2 years
- Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with follicle-stimulating hormone levels > 40 IU/L, or postmenopausal estradiol levels < 5 ng/dL, or according to the definition of "postmenopausal range" for the laboratory involved.

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

6.8.2 Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical studies include: periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in [Table 1](#) will be performed after obtaining a signed informed consent form.

It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated below. When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit window as defined in the visit-specific section below.

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.

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

	Screening	Double-blind Treatment Period		Safety Follow-up/EOS
Days	-14 to -1	1 (\pm 3 days)	8 (\pm 3 days)	38 (\pm 7 days)^a
GENERAL & SAFETY ASSESSMENTS				
Informed consent	X			
Demographic data	X			
Registration via IVR/IWR	X			
Eligibility criteria	X			
Medical history	X			
Medication history	X			
Concomitant medications	X	X	X	
Adverse events ^b	X	X	X	
Serious adverse events ^b	X	X	X	X
Physical examination ^c	X	X	X	
Vital signs	X	X	X	
Weight	X			
Height	X			
Chest x-ray (if needed) ^d	X			
LABORATORY ASSESSMENTS				
Serum pregnancy test ^e	X			
Pregnancy test (urine) ^e		X		
Hematology profile	X			
Chemistry profile	X			
Tuberculosis testing ^f	X			
Hepatitis B and C serologies ^g	X			
DOSING				
Investigational product dispensation (etanercept)		X	X	
DISEASE ASSESSMENTS				
Physician global assessment of disease activity (VAS 0-100)	X	X	X	
SUBJECT ASSESSMENTS (Reported Outcomes)				
Injection site pain (VAS 0-100)		X	X	

Footnotes defined on next page.

EOS = end-of-study, IVR = interactive voice response, IWR = interactive web response, PPD = purified protein derivative, TNF = tumor necrosis factor, VAS = Visual Analog Scale

^a Thirty 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 and inquire about the emergence of any new serious adverse events.

^b Adverse events and serious adverse events are collected from signing the informed consent form. Adverse device effects are included in the collection of adverse events. Adverse events are collected through the end of treatment period.

^c A full physical examination will be completed at the screening visit. Subsequent physical examinations will be conducted per standard of care to monitor for any changes.

^d Only for subjects with a positive tuberculosis test (ie, positive PPD or positive or indeterminate Quantiferon).

^e For all females, unless at least 2 years postmenopausal or postmenopausal status has been confirmed or history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

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

^g Subjects positive for hepatitis B core antibody may require additional testing for hepatitis B DNA by polymerase chain reaction.

7.2 General Study Procedures

7.2.1 Screening Period

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, sites will register the subject in IVRS/IWRS and screen the subject in order to assess eligibility for participation. The screening window is 14 days. If a subject has not met all eligibility criteria at the end of the 14-day window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening one time.

7.2.2 Re-screening

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen once. Re-screen subjects must first be registered as screen failed in IVRS/IWRS 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 14-day screening window will begin. If the re-screening period begins more than 14 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 14 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 rescreen.

7.2.3 Treatment Period

Visits will occur per the Schedule of Assessments during the treatment period from screening through week 2. Study visits may be completed within \pm 3 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 investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date.

The procedures completed during the 2-week treatment period are those listed in **Table 1**. Etanercept is to be administered after all assessments have been done for all visits with the exception of the VAS subject injection site pain assessment.

7.2.4 Safety Follow-up/End-of-Study

Thirty 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 and inquire about the emergence of any new serious adverse 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 Medical History

The investigator or designee will collect a complete medical history from 5 years before enrollment through the first dose of etanercept, which will be recorded in the medical history CRF. Medical history will include information on the subject's concurrent medical conditions. Diagnosis dates for RA or PsA will also be collected.

7.3.4 Medication History

A complete history of RA or PsA medications starting at the time of diagnosis and up to screening will be recorded on the CRF. This information will include medication name, indication, dose, unit, frequency, route, start date and stop date. All other medications taken within 3 months before screening will be collected, including medication name, indication, dose, unit, frequency, route, start date and stop date.

7.3.5 Physical Examination

The screening physical examination will be a complete physical examination. Breast, genital, and rectal examinations are not required at any study visit unless specific evaluation is warranted. Physical examination findings at screening should be recorded in the medical and surgical history CRF.

The physical examination at subsequent study visits will consist of a musculoskeletal examination for RA and PsA subjects along with a skin examination for PsA subjects per standard of care. Examination findings should be recorded on the appropriate CRF (eg, medical history, event). Any clinically significant changes in musculoskeletal or skin

examinations throughout the study, per the investigator's opinion, should be recorded on the event CRF.

7.3.6 Physical Measurements

Height should be measured in inches without shoes. Weight should be measured in pounds without shoes.

7.3.7 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 summary page.

7.3.8 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 before 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 before enrollment of the subject.

7.3.9 Adverse Events and Serious Adverse Events

Adverse events and serious adverse events observed by the investigator or reported by the subject will be collected at all study visits.

7.3.10 Concomitant Medications

Concomitant medications are to be collected from baseline through the treatment period. For concomitant medications, collect therapy name, indication, dose, unit, frequency, route, start date and stop date. Concomitant medications include over-the-counter products and vitamins administered while the subject is on-study.

7.3.11 Injection Site Pain Score

The injection site pain score is an assessment of the severity of the subject's injection site pain and will be completed by the subject immediately after the administration of the

etanercept dose (ie, within 30 seconds) using a VAS ([Appendix D](#) [English version or [Appendix E](#) [Spanish version]]). The horizontal line is 100 mm in length with "0" and "No Pain At All" on the left end of the line and "100" and "Worst Pain Imaginable" on the right end of the line. This VAS has been specifically designed to capture injection site associated pain.

7.3.12 Physician Global Assessment of Disease Activity (PGA)

The global assessment of the subject's overall RA or PsA disease activity will be assessed by the principal investigator or sub investigator for the study by completion of a VAS. The PGA will be completed -at screening, and on day 1 and day 8 before investigational product administration. The VAS is 100 mm in length with "0" and "No Activity at All" on the left end of the line and "100" and "Worst Activity Imaginable" at the right end of the line.

7.3.13 Laboratory Assessments

All laboratory samples will be processed and sent to the central laboratory with the exception of urine pregnancy and PPD, which will be done by the site staff, and Quantiferon, which may be done by central or local laboratory. The central laboratory will be responsible for all screening and on-study serum chemistry, hematology, serum pregnancy, hepatitis C antibody, hepatitis B surface antigen and core antibody, and any other laboratory tests required. 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 investigational product administration. The date and time of sample collection will be recorded in the source documents at the site. Specific analytes for serum chemistry, hematology, and other testing to be conducted on blood and urine samples are listed below. Although not specifically listed, additional components, abnormal, and/or atypical cells will also be reported if present.

Table 2. Laboratory Analyte Listing

<u>Central Lab Chemistry</u>	<u>Central Lab Hematology</u>	<u>Central Lab Other Labs</u>	<u>Local Lab Other Labs</u>	<u>Local/Central Lab Other Labs</u>
Sodium	RBC	Hepatitis B	Urine	Tuberculosis
Potassium	RBC Morphology	surface antigen	pregnancy	testing ^b
Chloride	Hemoglobin	total		
Bicarbonate	Hematocrit	Hepatitis B core		
Total protein	Platelets	antibody		
Albumin	WBC	Hepatitis B virus		
Calcium	Differential	DNA by		
Adjusted calcium	<ul style="list-style-type: none">• Bands/stabs• Eosinophils• Basophils• Lymphocytes• Monocytes• Neutrophil ANC	polymerase		
Magnesium		chain reaction		
Phosphorus		Hepatitis C		
Glucose		antibody		
BUN or Urea		Serum beta		
Creatinine		hCG ^a		
Uric acid				
Total bilirubin				
Direct bilirubin				
Alkaline phosphatase				
AST (SGOT)				
ALT (SGPT)				

Abbreviations: ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BUN = blood urea nitrogen, hCG = human chorionic gonadotropin, PPD = purified protein derivative, RBC = red blood cell, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase, WBC = white blood count.

^aAll female subjects except those who are confirmed surgically sterile or at least 2 years postmenopausal or per the definition in [Section 6.8](#).

^b Subjects must receive either a PPD test or Quantiferon testing at screening.

7.3.14 Tuberculosis Testing

7.3.14.1 Purified Protein Derivative (PPD)

All subjects who have never received Bacillus Calmette-Guerin vaccination must receive a PPD test before enrollment in the study. The 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.

7.3.14.2 Quantiferon

Subjects with a positive PPD test and a history of Bacillus Calmette-Guerin vaccination will require Quantiferon testing. If testing is performed by central laboratory then refer to the central laboratory manual for instructions on sample collection, processing, and shipping of samples.

7.3.15 Urine Pregnancy Test

All females, except those who are confirmed to be of non-childbearing potential (refer to [Section 6.8](#) for this criteria), must have a negative urine pregnancy test at day 1, before administering the first dose of etanercept. Urine pregnancy tests will be performed locally at each site. The central laboratory will provide the urine pregnancy tests.

7.3.16 Hepatitis B and C Status

The following should be followed for the determination of hepatitis B and C status:

- if hepatitis B and/or hepatitis C status is known to be positive by serology no additional laboratory testing procedures are required
- if hepatitis B and/or hepatitis C status is not known to be positive by serology, the following laboratory testing is required:
 - hepatitis B surface antigen
 - if results are hepatitis B surface antigen positive, no additional testing is necessary
 - hepatitis B Core Antibody
 - if results are hepatitis B core antibody positive but negative for hepatitis B surface antigen, additional testing is necessary for hepatitis B virus DNA by polymerase chain reaction
 - hepatitis C virus antibody
- if results are hepatitis C virus antibody positive, no additional testing is necessary

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device 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, adverse events, disease related events, and device related events, as applicable. 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, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time before study completion.

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)
- disease flare requiring treatment not allowed in the protocol (eg, colitis, asthma)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical study 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 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. All adverse events will be summarized as described below based on the safety analysis set, overall, by indication, treatment arm, and by period.

9.1.2 Serious Adverse Events

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

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

A disease related event such as worsening of symptoms of RA or PsA 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 subject 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.

All adverse events of malignancies should be classified as serious adverse events.

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent form 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 SureClick device, study procedures/study activities, and
- Action taken.

The adverse event grading scale used will be the Common Toxicity Criteria. The grading scale used in this study is described in [Appendix A](#). **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 Event CRF.**

The investigator must assess whether the adverse event is possibly related to the etanercept and SureClick device. 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 etanercept and SureClick device?

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.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval or end-of-study, whichever is later are recorded in the subject's medical record and are submitted to Amgen. A shorter or longer safety follow-up interval can be utilized following consultation with the Amgen Global Safety Officer and 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.

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.

The investigator must assess whether the serious adverse event is possibly related to the etanercept and SureClick device. 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 etanercept and SureClick device?

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

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

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

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

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

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

9.2.1.3 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. 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 study cases for the purposes of expedited reporting.

9.2.1.4 Serious Adverse Events That Are Not To Be Reported By The Sponsors To Regulatory Agencies In An Expedited Manner

The study population involved will have an increased burden of comorbidities, which are commonly associated with PsA and RA 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 worsening of PsA and RA. These serious adverse events will be monitored with routine pharmacovigilance on an ongoing basis.

9.3 Pregnancy and Lactation Reporting

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

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

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

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

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

If a female breastfeeds while 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 report lactation cases that occur 4 weeks after the last dose of protocol-required therapies.

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

Notification Worksheet ([Appendix C](#)). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Change in injection site pain score between the current formulation and the modified formulation as measured by the VAS

10.1.1.2 Safety Endpoints

- Adverse events

10.1.2 Analysis Sets

The primary analysis set will include all subjects who received the dose of investigational product during each study period and who completed the injection site pain score during each study period. The primary endpoint will be evaluated based on this primary analysis set.

The safety analysis set will include all subjects who received at least 1 dose of investigational product during the study. All safety endpoints will be evaluated using the safety analysis set.

10.1.3 Covariates and Subgroups

The following subgroup analyses will be performed to assess their influence on the primary endpoint, overall, by indication, by randomization sequence, and by period:

- Age (< 65, \geq 65)
- Sex (male, female)
- Baseline PGA (< median, \geq median)
- Prior biologic use (yes, no)
- Other subgroups may be evaluated as necessary

10.1.4 Handling of Missing and Incomplete Data

Subjects who dropout after the first injection will not be replaced by new subjects.

Subjects will be included in the safety analysis, but not in the efficacy analysis as described in [Section 10.1.2](#).

10.2 Sample Size Considerations

The primary objective of the study is to compare the injection site pain from the modified formulation of etanercept with that from the currently marketed etanercept.

The proposed sample size of **112** (ie, **56** per sequence treatment arm with at least 10 subjects with PsA) would provide approximately **53** subjects for each sequence treatment arm at the completion of the study, assuming an early termination or dropout rate of 5% for each sequence treatment arm over the course of the study. Subjects who dropout after the first injection will not be replaced by new subjects.

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The sample population will be comprised of subjects with RA or PsA; the estimated injection site pain score for subjects with PsA is assumed to be similar to those with RA.

There are no data assessing injection site pain in subjects with either RA or PsA on any of the etanercept currently marketed or modified formulations. Given that RA subjects in non-etanercept studies have lower absolute injection site pain scores compared with healthy volunteers, the effect size between the formulations is expected to be smaller compared to that seen with healthy volunteers, in addition to expected attenuation at the second injection. Therefore, a conservative effect size of **8** mm was used for this study.

Therefore, the sample size of **53** per arm was calculated to have more than 90% power to detect a difference in means of **8** mm in the injection site pain score between the 2 formulations with corresponding SD of 25 using a t-test (crossover Analysis of Variance) with a 2-sided significance level of 0.05.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects before the study being formally

unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, [Section 5.2](#) and [Section 9.2.1.2](#)).

10.4 Planned Analyses

10.4.1 Primary Analyses

The primary analysis, will be conducted at the end of the study for the primary endpoint. The purpose will be to test the null hypothesis of no difference in injection site pain scores between the 2-etanercept formulations.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

The primary analysis of the primary endpoint will be conducted using the primary analysis set. Analysis of covariance will be used to compare the difference in injection site pain score within subjects receiving etanercept in the currently marketed formulation and in the modified formulation, with the disease indication (RA or PsA) and the treatment as factors, adjusting for period effect and sequence effect. Descriptive statistics will also be presented for the primary endpoint for the subgroups listed in [Section 10.1.1.1](#) and [Section 10.1.3](#).

Safety endpoints will be analyzed using the safety analysis set.

Descriptive statistics for continuous variables, consists of number of observations, mean, standard error and/or SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum, maximum, and for categorical variables, the number of observations, frequency, and percentage will be presented. Subject disposition, demographics, baseline characteristics, and safety information will be summarized. There will be no adjustment for multiplicity and no imputation techniques for missing values. All analyses will be based on observed data.

10.5.2 Primary Efficacy Endpoint

As state above, analysis of covariance will be used to compare the difference in injection site pain score between subjects receiving etanercept in the current marketed formulation and in the modified formulation, with the disease indication (RA or PsA) and the treatment as factors, adjusting for period effect and sequence effect. Sensitivity analyses may be performed for the primary endpoint for subjects who complete the injection site pain score per protocol. In addition, the difference in injection site pain score will be evaluated by disease indication, using descriptive statistics.

10.5.3 Safety Endpoints

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

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities version 19.0 or later. Events of interest and hospitalizations will be tabulated by treatment group. Subgroup analyses will be presented for all adverse events.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential subject 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 approval/IRB and IEC renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

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

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

In compliance with governmental/ International **Council for** Harmonisation (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

Amgen may amend the protocol at any time. After Amgen amends the protocol, Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. 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 and amended protocol Investigator's Signature page to Amgen before implementation of the protocol amendment at their site.

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 Clinical Trial Agreement. 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.

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 identification, enrollment date, investigational product dispensation date, and investigational product box number dispensed.

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

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- 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 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 Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study 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 study database. The Self-Evident Corrections will be documented in the CRF instructions available in the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subject's not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw before 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

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

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

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

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

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

http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in [Section 6.3](#) 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 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 9.2.1.2](#).

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in [Section 6.3](#) or who experience AST or ALT elevations $> 3 \times$ ULN or 2-fold increases above baseline values for subjects with elevated values before drug 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 $> 2 \times$ 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. The following are to be considered depending on the clinical situation:
 - Complete blood count (CBC) with differential to assess for eosinophilia

- Serum total immunoglobulin G, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- 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
- Viral serologies
- CPK, haptoglobin, LDH, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- 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 or considered stable by the investigator. 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 the corresponding CRFs.

Appendix B. Electronic Serious Event Contingency Form

Completion Instructions - Electronic Adverse Event Contingency Report Form (For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- Serious Adverse Events (regardless of causal relationship to IP)

1. Site Information

Site Number* – Enter your assigned site number for this study

Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. Subject Information

Subject ID Number* – Enter the entire number assigned to the subject

Age at event onset, Sex, and Race – Enter the subject's demographic information

End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. Serious Adverse Event

Provide the date the Investigator became aware of this Information

Serious Adverse Event Diagnosis or Syndrome* –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria) rather than the date of diagnosis or hospitalization. **This is a mandatory field.**

Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

Is event serious?* – Indicate Yes or No. **This is a mandatory field.**

Serious Criteria Code* – **This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. Hospitalization

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did

not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. IP Administration including Lot # and Serial # when known / available.

Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

6. Concomitant Medications

Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. Relevant Medical History

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. Relevant Laboratory Tests

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

9. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. Case Description

Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.

AMGEN Study # 20140339 etanercept	Electronic Serious Adverse Event Contingency Report Form <u>For Restricted Use</u>	
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Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

- Is not available due to internet outage at my site
- Is not yet available for this study
- Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country
-------------	--------------	---------

Reporter	Phone Number ()	Fax Number ()
----------	---------------------------	-------------------------

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex <input type="checkbox"/> F <input type="checkbox"/> M	Race	If applicable, provide End of Study date
-------------------	--------------------	--	------	--

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day Month Year		Check only if event occurred before first dose of IP	Is serious event Serious Criteria code (see codes below)	Relationship		Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
Date Started	Date Ended			Etanercept	SureClick Autoinjector		
Day Month Year	Day Month Year	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes				
		<input type="checkbox"/> Yes <input type="checkbox"/> No					
		<input type="checkbox"/> Yes <input type="checkbox"/> No					
		<input type="checkbox"/> Yes <input type="checkbox"/> No					
Serious Criteria:	01 Fatal 02 Immediately life-threatening	03 Required/prolonged hospitalization 04 Persistent or significant disability/incapacity			05 Congenital anomaly / birth defect 06 Other medically important serious event		

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

Date Admitted Day Month Year	Date Discharged Day Month Year
-------------------------------------	---------------------------------------

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

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event			Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
			Date of Dose Day Month Year	Dose	Route		
Etanercept		<input type="checkbox"/> blinded <input type="checkbox"/> open label					Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown
SureClick Autoinjector		<input type="checkbox"/> device open label					Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable /

AMGEN Study # 20140339 etanercept	Electronic Serious Adverse Event Contingency Report Form For Restricted Use								
--	--	--	--	--	--	--	--	--	--

									Unknown
--	--	--	--	--	--	--	--	--	---------

	Site Number	Subject ID Number						
--	-------------	-------------------	--	--	--	--	--	--

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

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No/ 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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information

Protocol/Study Number: 20140339

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm /dd /yyyy_____

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

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

Did the subject withdraw from the study? Yes No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ Unknown

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

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

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

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

Was the infant healthy? Yes No Unknown N/A

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

[Print Form](#)

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20140339

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

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

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

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

Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

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

If No, provide stop date: mm ____ / dd ____ / yyyy ____

Infant date of birth: mm ____ / dd ____ / yyyy ____

Infant gender: Female Male

Is the infant healthy? Yes No Unknown N/A

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

Form Completed by:

Print Name: _____ Title: _____

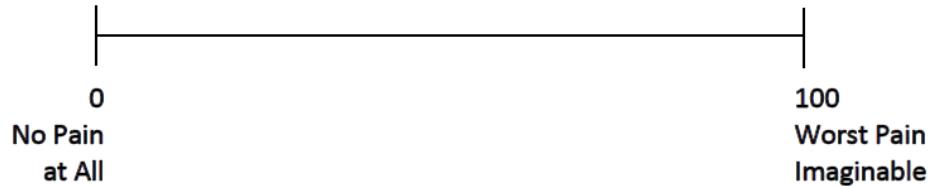
Signature: _____ Date: _____

Appendix D. Subject Injection Site Pain Perception Assessment (English Version)

Subject Injection Site Pain Perception Assessment

To be evaluated immediately following injection (i.e., within 30 seconds)

Place a single vertical line  on the scale below to indicate
the severity of your pain at the injection site during and after your most recent injection.



Appendix E. Subject Injection Site Pain Perception Assessment (Spanish Version)

Evaluación de la percepción del dolor en el lugar de la inyección según el/la paciente

Para ser evaluado inmediatamente después de la inyección (es decir, dentro de los 30 segundos)

Ponga una sola raya vertical |  en la siguiente escala para indicar

la intensidad de su dolor en el lugar de la inyección durante y después de su última inyección.



Amendment 1

**Protocol Title: A Multicenter, Randomized, Double-blind, Crossover Study to
Assess the Injection Site Pain Associated With a Modified Etanercept Formulation
in Adult Subjects With Either Rheumatoid Arthritis or Psoriatic Arthritis**

Amgen Protocol Number 20140339

Amendment Date: 30 March 2017

Rationale:

This protocol is being amended to:

- Recategorize study phase from phase 4 to phase 3b
- Update sample size based on 8 mm as an updated estimation of true effect size
- Make editorial updates and correct administrative errors throughout protocol

Description of Changes:

Section: Global

Change: Updated version date from 15 August 2017 to **30 March 2017**.

Section: Global

Change: Updated study phase from phase 4 to phase **3b**.

Section: Global

Change: Updated ICF definition from International Conference on Harmonisation to International **Council for Harmonisation**.

Section: Title Page, Key Sponsor Contacts

Replace:

PPD

One Amgen Center Drive

Thousand Oaks, CA 91320

PPD

With:

PPD

One Amgen Center Drive

Thousand Oaks, CA 91320

PPD

Section: Title Page

Add:

Date: 12 July 2016

Superseding 1: 15 August 2016

Amendment 1: **30 March 2017**

Section: Protocol Synopsis, Study Design, Paragraph 2

Replace:

A total of 90 subjects will be enrolled with 45 subjects in each treatment sequence, stratified by disease indication (RA or PsA). A minimum of 20 PsA subjects will be enrolled, therefore enrollment of RA subjects will be limited to 70 subjects.

With:

A total of **112** subjects will be enrolled with **56** subjects in each treatment sequence, stratified by disease indication (RA or PsA). A minimum of 20 PsA subjects will be enrolled.

Section: Protocol Synopsis, Sample Size

Replace:

The proposed sample size of 90 (ie, 45 per sequence treatment arm with at least 10 subjects with PsA) would provide approximately 42 subjects for each sequence treatment arm at the completion of the study, assuming an early termination or dropout rate of 5% for each sequence treatment arm over the course of the study.

With:

The proposed sample size of **112** (ie, **56** per sequence treatment arm with at least 10 subjects with PsA) would provide approximately **53** subjects for each sequence treatment arm at the completion of the study, assuming an early termination or dropout rate of 5% for each sequence treatment arm over the course of the study.

Section: Protocol Synopsis, Amgen Investigational Product Dosage and Administration, Paragraph 2

Replace:

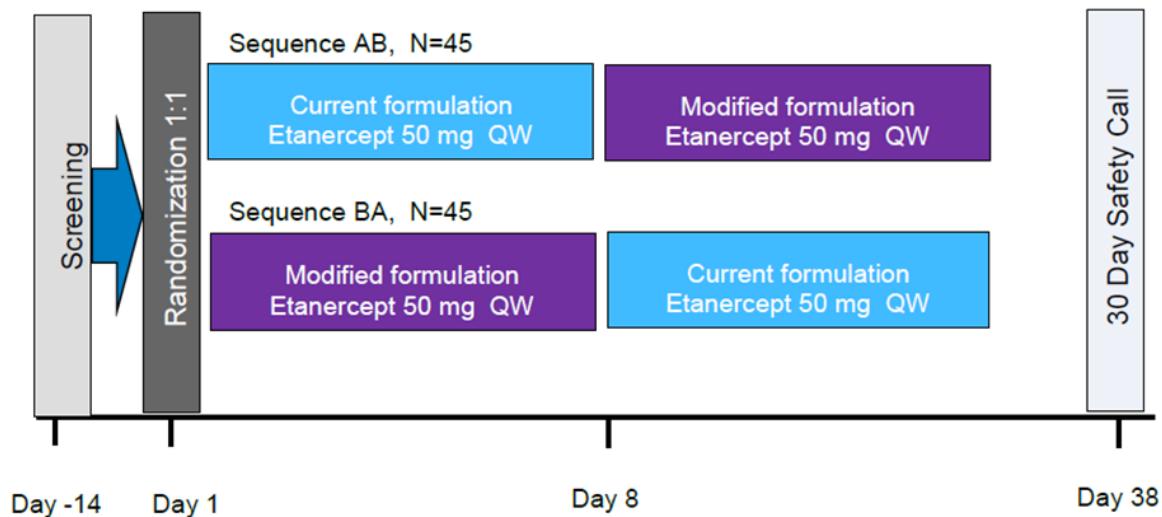
If the first injection site occurs on the arm or leg, the second injection site should be performed on the contralateral limb.

With:

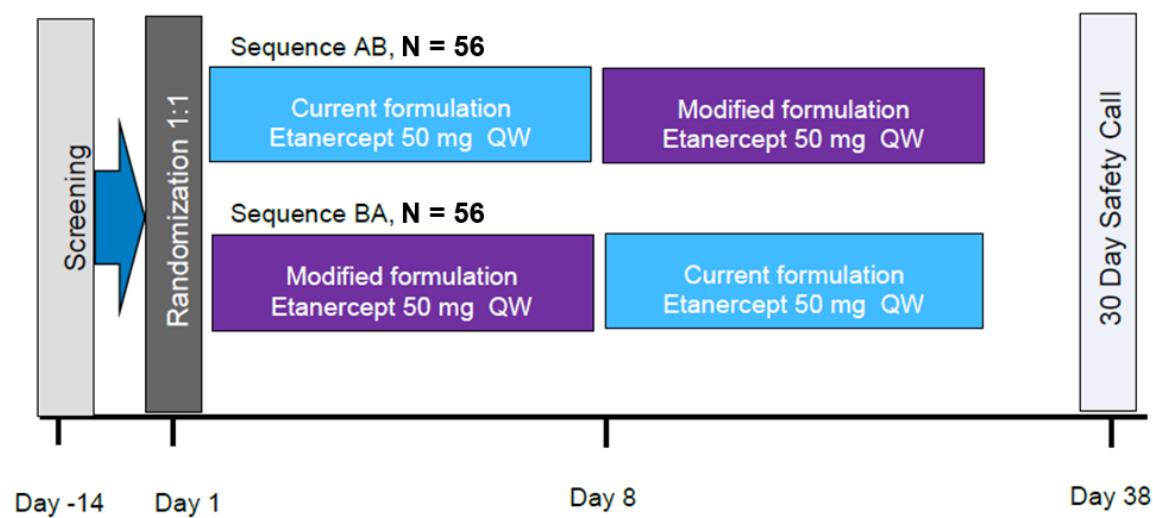
If the first injection site occurs on the **thigh**, the second injection site should be performed on the contralateral limb.

Section: Study Design and Treatment Schema

Replace:



With:



Section: 3.1 Study Design, Paragraph 3

Replace:

A total of 90 subjects will be enrolled with 45 subjects in each treatment sequence, stratified by disease indication (RA or PsA). A minimum of 20 PsA subjects will be enrolled, therefore enrollment of RA subjects will be limited to 70 subjects.

With:

A total of **112** subjects will be enrolled with **56** subjects in each treatment sequence, stratified by disease indication (RA or PsA). A minimum of 20 PsA subjects will be enrolled.

Section: 3.3 Number of Subjects, Paragraph 2

Replace:

A total of 90 subjects are expected to enroll in this study with 45 subjects in each treatment sequence.

With:

A total of **112** subjects are expected to enroll in this study with **56** subjects in each treatment sequence.

Section: 6.2.1.1 Dosage, Administration, and Schedule, Paragraph 2

Replace:

If the first injection site occurs on the arm or leg, the second injection site should be performed on the contralateral limb.

With:

If the first injection site occurs on the **thigh**, the second injection site should be performed on the contralateral limb.

Section: 6.2.1.1 Dosage, Administration, and Schedule, Paragraph 3

Delete:

The volume (full, partial, or none), dose date, ~~dose time~~, and box number of etanercept are to be recorded on each subject's CRF.

Section: 9.2.1.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria, Paragraph 3

Add:

The adverse event grading scale used will be the Common Toxicity Criteria. The grading scale used in this study is described in Appendix A. **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 Event CRF.**

Section: 10.2 Sample Size Considerations, Paragraph 2

Replace:

The proposed sample size of 90 (ie, 45 per sequence treatment arm with at least 10 subjects with PsA) would provide approximately 42 subjects for each sequence treatment arm at the completion of the study, assuming an early termination or dropout rate of 5% for each sequence treatment arm over the course of the study.

With:

The proposed sample size of **112** (ie, **56** per sequence treatment arm with at least 10 subjects with PsA) would provide approximately **53** subjects for each sequence treatment arm at the completion of the study, assuming an early termination or dropout rate of 5% for each sequence treatment arm over the course of the study.

Section: 10.2 Sample Size Considerations, Paragraph 6

Replace:

Therefore, a conservative effect size of 9 mm was used for this study.

With:

Therefore, a conservative effect size of **8** mm was used for this study.

Section: 10.2 Sample Size Considerations, Paragraph 7

Replace:

Therefore, the sample size of 42 per arm was calculated to have more than 90% power to detect a difference in means of 9 mm in the injection site pain score between the 2 formulations with corresponding SD of 25 using a t-test (crossover Analysis of Variance) with a 2-sided significance level of 0.05.

With:

Therefore, the sample size of **53** per arm was calculated to have more than 90% power to detect a difference in means of **8** mm in the injection site pain score between the 2 formulations with corresponding SD of 25 using a t-test (crossover Analysis of Variance) with a 2-sided significance level of 0.05.