STATISTICAL ANALYSIS PLAN

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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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
CRF	Case Report Form
EDC	Electronic Data Capture
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.
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
VAS	Visual Analog Scale
PGA	Physician Global Assessment
SD	standard deviation
Q1	Quartile 1, 25th Percentile
Q3	Quartile 3, 75th Percentile
MedDRA	Medical Dictionary for Regulatory Activities
CTCAE	Common Terminology Criteria for Adverse Events

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for Etanercept Phase 3b Study 20140339 dated 30 March 2017. The scope of this plan includes the final analysis that is planned and will be executed by the Biostatistics department.

2. Objectives

2.1 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)

2.2 Secondary

- To describe the injection site pain by disease indication

2.3 Safety

- To evaluate the safety of etanercept

3. Study Overview

3.1 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.

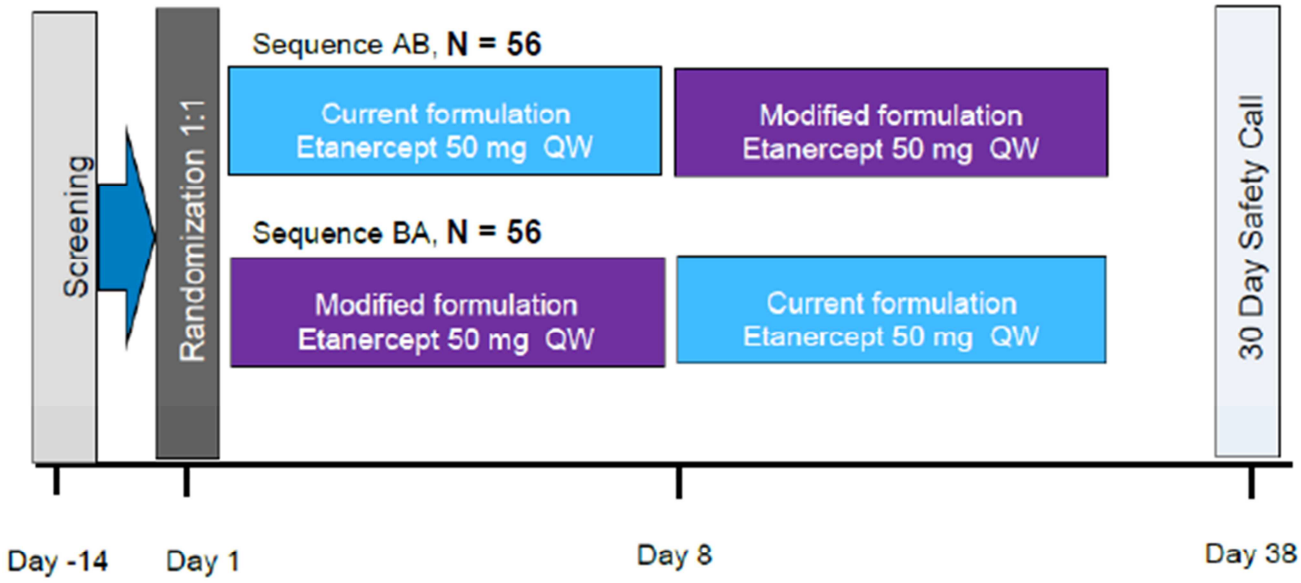
Subjects will be randomized in a 1:1 ratio to receive each etanercept formulation in 1 of 2 crossover treatment sequences. Subjects randomized to the first treatment sequence (ie, sequence AB) will receive 1 dose of the current formulation (ie, treatment A) during the first study period, followed by 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, therefore enrollment of RA subjects will be limited to 92 subjects.

After study completion subjects may continue with modifiedly 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.

3.1.1 Study Schema

The overall study design is described as follows:

Study Design and Treatment Schema



Abbreviations: QW = every week

3.2 Sample Size

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 formulation of 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 drop out 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 2-sided t-test (crossover analysis of variance) with a significance level of 0.05.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

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

4.1.2 Safety Endpoint

- Adverse events

4.2 Planned Covariates and Subgroups

The disease indication will be adjusted as the straitification factor when analyzing the primary endpoint.

The following subgroup analyses will be performed to assess their influnce on the primary endpoint:

- Age (< 65, ≥ 65)
- Sex (male, female)
- Baseline PGA (< median, ≥ median)
- Baseline PGA (< 66.7 mm, ≥ 66.7 mm)
- Prior biologic use (yes, no)
- Other subgroups may be evaluated as necessary

5. Hypotheses and/or Estimations

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.

6. Definitions

Injection Site Pain Visual Analog Scale (VAS)

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 visual analog scale. 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.

The 100 mm VAS is commonly used in such studies and has been shown to correlate well with categorical pain scales. 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.

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.

Enrollment

A subject is considered enrolled once randomized to treatment.

Randomization Date

The date the subject was assigned a randomization number.

Study Day 1

Study day 1 is defined as the first day of administration of investigational product after enrollment. The day prior to Study Day 1 is considered Day -1. For subjects that is not dosed, Study Day 1 is defined as the randomization date.

Study Day

Post-study day 1: study day = (date – date of Study Day 1) + 1

Pre-study day 1: study day = (date – date of Study Day 1)

End of Follow-up

When the last subject completes the last protocol-specified assessment in the study

End of Study (EOS)

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)

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)

Investigation Product

The term 'investigational product' is used in reference to etanercept, either the modified formulation or the modified formulation

Serious Adverse Event

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria: Serious Adverse Event (SAE)

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

An adverse event would meet the criterion of "requires in-patient hospitalization" if the event necessitated an in-patient admission to a health care facility. If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury (see Appendix A in protocol for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention. Since the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 "life threatening" CTCAE grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the subject's medical record.

Treatment Emergent Adverse Event

A treatment-emergent adverse event is any adverse event that begins or worsens after the initial dose of investigational product and before the end of study. The severity of each adverse event will be graded using the CTCAE version 4.0 criteria, to be consistent with the version used for all etanercept studies. Adverse events will be coded using MedDRA (version 19.0 or later).

7. Analysis Subsets

7.1 Primary Analysis Set

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 using the primary analysis set.

7.2 Safety 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.

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

9.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required: Incomplete dates for adverse event and concomitant medication will be imputed as described in Appendix A.

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

These subjects will be included in the safety analysis set, but not in the primary analysis set.

9.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each treatment group. The clinical study team will identify and document the criteria for important protocol deviations.

9.5 Outliers

Outlier data will not be excluded, unless for any specific reason(s) that could be justified.

9.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example the SAS System.

10. Statistical Methods of Analysis

10.1 General Principles

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.

10.2 Subject Accountability

A summary of subject disposition with discontinuation reasons, and etanercept completion and discontinuation will be provided. A list of subjects who withdraw early will be provided. It will include the reason and timing of the withdrawal. Similarly, the reason any subject is excluded from an analysis set will also be provided. In addition, significant known protocol deviations will be noted for individual subjects.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. Eligibility deviations are defined

in the protocol. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

10.4 Demographic and Baseline Characteristics

Age, race, sex, height, weight, baseline PGA, prior biologic use and indication will be summarized for all the subjects enrolled.

10.5 Primary Analyses

A mixed effects analysis of variance model will be used for the primary endpoint. Treatment, period, sequence and disease indication (RA or PsA) will be evaluated as fixed effects, and subject nested within sequence will be included as a random effect. The modified formulation of etanercept will be used as the test treatment and current formulation of etanercept as the reference treatment.

The null hypothesis that there is no difference of injection site pain between the current and modified formulation will be tested and p-value will be provided. The least square mean of the injection site pain score and the difference between the formulations will be estimated and the corresponding 2-sided 95% CI will be provided..

10.6 Other Analyses

The descriptive statistics will be provided for the injection site pain score for overall and by indication and formulation.

Sensitivity analyses will be performed for the primary endpoint for subjects in the primary analysis set, excluding the subject(s) with injection(s) administrated without warming the investigation product to the required temperature.

Subgroup analyzes will be conducted for the primary endpoint with the subgroups defined in Section 4.2.

10.7 Safety Analyses

10.7.1 Adverse Events and Disease Related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term. The severity of each adverse event will be graded using CTCAE version 4.0 criteria.

The subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, fatal AEs.

Subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade in descending order of frequency.

Adverse events (such as injection site reactions) occuring during different periods of the treatment may be examined to evaluate the safety and tolerability of a current formulation versus the modified formulation of etanercept.

10.7.2 Laboratory Test Results

Drug-induced liver injury will be assessed by evaluating subjects for Hy's Law in the study period. Hy's law lab value criteria is defined as aspartate amino transferase or alanine amino transferase > 3 times upper limit of normal (ULN), total bilirubin > 2 times ULN, and alkaline phosphatase < 2 times ULN assessed within 7 days. Subjects who meet these criteria on study will be further evaluated to assess whether there exist underlying conditions or concomitant medications which can explain the elevation in laboratory analytes.

Individual chemistry, hematology laboratory data will not be listed unless any safety issue arises.

10.7.3 Physical Examination

The physical examination results will not be listed unless any safety issue arises.

10.7.4 Vital Signs

The vital signs results will not be listed unless any safety issue arises.

10.7.5 Exposure to Investigational Product

The formulation, period, administration site, laterality, quantity and reason of dose change/withheld (if available) of each investigational product administration will be listed for each subject. In addition a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

10.7.6 Exposure to Concomitant Medication

All medications will be coded using the WHOdrug dictionary. Concomitant medication will not be listed or summarized unless any safety issues arise.

11. Appendices

Appendix A. Imputation Rules for Partial or Missing Stop Dates

We are using the following imputation rules:

1. For the start date
    a. If the month is missing, impute Janurary
    b. If the day is missing, impute the 1
    c. If both the month and day are missing, impute Janurary 1.
2. For the stop date
    a. If the month is missing, impute December
    b. If the day is missing, impute the last day of the month
    c. If both month and day are missing, impute December 31.
3. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or concomitant medication stopped and the stop date will be imputed, if partial.

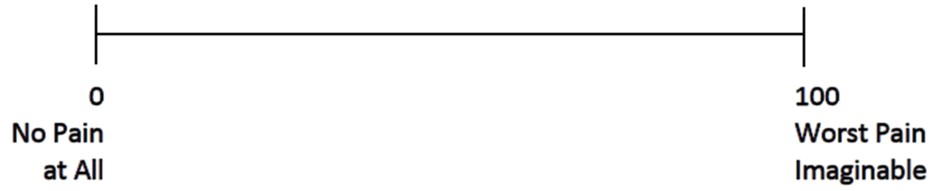
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month. If an imputed stop date based on abive rule is on or after the end of study (EOS) date, the EOS date should be used as the imputed stop date.

Appendix B. Visual Analog Scale

Subject Injection Site Pain Perception Assessment

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

the severity of your pain at the injection site during and after your most recent injection.



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)

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

Appendix C. Code Fragment

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