I1F-MC-RHCS Statistical Analysis Plan

A Randomized Study to Investigate Injection-Site Pain Following Subcutaneous Injections of 2 Ixekizumab Test Formulations Compared to the Commercial Formulation using a Pre-filled Syringe in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Conference on Harmonisation
ISR	Injection site reaction
HADS	Hospital Anxiety and Depression Scale
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
ULN	Upper limit of normal
VAS	Visual Analog Scale
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 29 October 2018 and amendment (a) dated 03 December 2018).

This SAP describes the planned analysis of the safety and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first subject administration for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Eli Lilly and Company and Covance EC Biometrics and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

Evaluate pain intensity on injection of ixekizumab with different formulations.

4.2 Exploratory Objective

To evaluate the safety and tolerability of a single 80 mg subcutaneous (SC) dose of ixekizumab Test Formulation 1 and Test Formulation 2 compared to the commercial formulation (Reference).

5. STUDY DESIGN

This will be a single-dose, subject-blind, 3-period, 3-formulation, randomized, crossover study in healthy subjects.

All subjects will be screened within 28 days prior to enrollment. Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and randomized 1:1:1 to 1 of 3 possible

formulation sequences (see Figure 1). On Day 1, subjects will receive a single 1-mL SC injection of 1 of the following formulations, according to the randomization schedule:

- 80 mg ixekizumab Commercial Formulation (Reference)
- 80 mg ixekizumab Test Formulation 1
- 80 mg ixekizumab Test Formulation 2

Subjects may be allowed to leave the CRU after completing the 4-hour safety assessments for Day 1, at the investigator's discretion. Subjects will be readmitted to the CRU on Days 7 and 14 to receive their second and third injections on Days 8 and 15, respectively, and may be allowed to leave the CRU after completing the 4-hour safety assessments at the investigator's discretion on Days 8 and 15, respectively. Subjects will return to the CRU as an outpatient on Days 21 (± 1 day) and 43 (± 3 days) for a safety check-up. A safety follow-up telephone call will be conducted on Day 71 (± 3 days). There will be a follow-up visit approximately 12 weeks after the last injection.

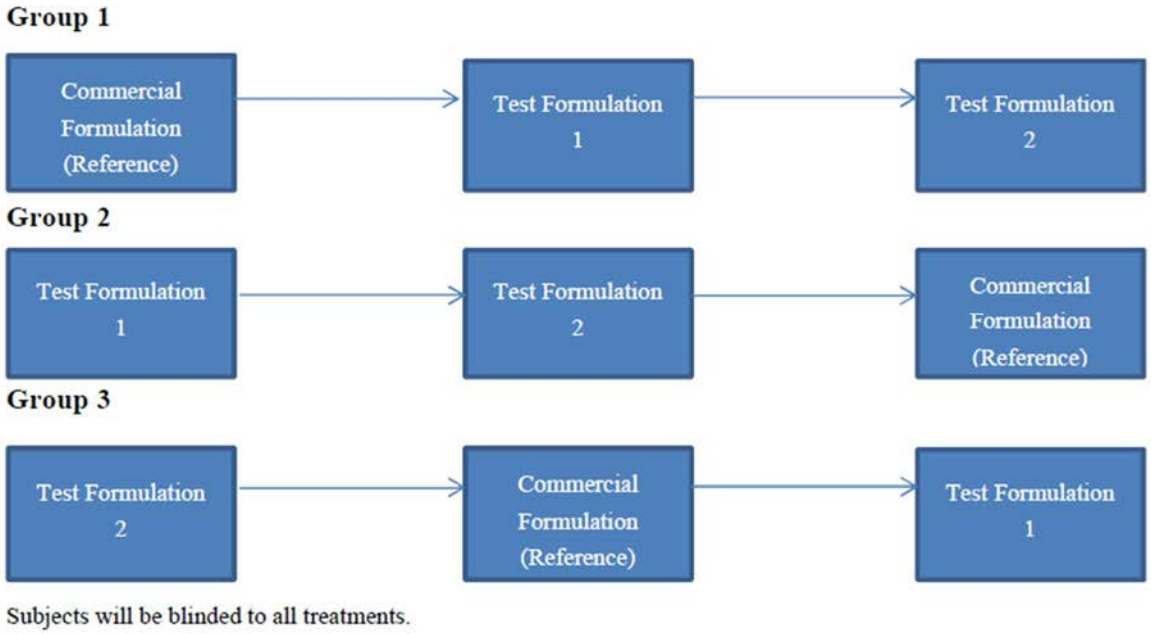

Figure 1. Illustration of study design.

6. FORMULATIONS

The following is a list of the study formulation abbreviations that will be used in the TFLs.

Study Formaulation Name	Abbreviation	Formulation order in TFL
80 mg ixekizumab Commercial Formulation	Reference	1
80 mg ixekizumab Test Formulation 1	Test Formulation 1	2
80 mg ixekizumab Test Formulation 2	Test Formulation 2	3

7. SAMPLE SIZE JUSTIFICATION

Up to 102 subjects may be enrolled to maximize the intent to have 78 subjects (26 subjects per formulation sequence) complete the study.

The objective of this study is to evaluate the injection pain immediately following dosing. Because of the crossover study design, each subject will have the opportunity to receive each formulation. [redacted]

8. DEFINITION OF ANALYSIS POPULATION

The "Safety" population will consist of all subjects who received at least one dose of study drug, whether or not they completed all protocol requirements.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to this analysis population.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that are databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic SD, median, min, max and N. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed.

9.3 Safety and Tolerability Assessments

9.3.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to the first dose. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by formulation and severity. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by formulation, Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities. Any serious AEs will be listed.

9.3.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2018). Concomitant medication will be listed.

9.3.3 Clinical laboratory parameters

Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

9.3.4 Vital signs

Vital signs data will be summarized by treatment.

Vital signs data will be listed for individual subjects.

9.3.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

9.3.6 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by formulation and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual subject data listings.

9.3.7 Columbia Suicide Severity Rating Scale (C-SSRS)/ Self-Harm Supplement

Given that few or no suicidal ideation or behaviours are anticipated, a listing of C-SSRS data will be produced by subject and visit. Only subjects that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be reviewed (i.e., if a subject's answers are all 'no' for the C-SSRS, then that subject will not be displayed). However, if a subject reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be reviewed, even if not positive.

9.3.8 Hospital Anxiety Depression Scale (HADS)

Data from the HADS assessment will be listed for individual subjects with HADS depression sub-scale ≥11 at any time.

9.3.9 Injection Site Assessments

Injection sites will be assessed for induration, swelling, pruritus, and erythema/redness. Data will be summarized in a frequency table by formulation, and listed for individual subjects.

9.3.10 Injection Site Pain Assessment

Pain measurements will be quantified using the 100-mm VAS pain score (100-mm line anchored by verbal descriptors, usually "no pain" and "worst imaginable pain) for all subjects, whether or not they report injection pain.

VAS pain score will be summarized using standard descriptive statistics. In addition, the severity of pain will be categorized by VAS pain score as: mild pain (≤30), moderate pain (>30 and ≤70), and severe pain (>70). The number and percentage of the subjects in each pain severity category will be summarized by formulation and time point. Figures of the continuous injection-site pain VAS score will also be presented, by formulation and measuring time point.

A mixed-effects repeated measures analysis model will be used to analyze the continuous injection-site pain VAS score by each time post-injection (0, 10, 20, 30, and 60 minutes). For measures at each time post-injection, the model will include formulation, period (Day 1, Day 8, or Day 15), formulation sequence, and formulation by formulation sequence as fixed effects. The covariance structure of the model will be unstructured. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least squares means will be used for the statistical comparison; formulation differences on every time point will be reported, along with the corresponding 95% confidence intervals for the differences. All pair-wise formulation comparisons by measuring time point will be evaluated and presented.

10. DATA REVIEW DURING THE STUDY

Data will be reviewed by the investigator throughout the course of the study to ensure subject safety.

11. INTERIM ANALYSES

One formal interim analysis is planned for this study. The interim analysis will include review of all subjects' safety data (AEs, VAS and injection site reaction [ISR] data) collected up to and including Day 21.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

14. DATA PRESENTATION

14.1 Derived Parameters

Individual derived parameters and appropriate summary statistics will be reported to three significant figures. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, “No serious adverse events occurred for this study.”