I1F-MC-RHCT Statistical Analysis Plan

Relative Bioavailability of 2 Ixekizumab Test Formulations Compared to the Commercial Formulation in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

Relative Bioavailability of 2 Ixekizumab Test Formulations Compared to the Commercial Formulation in Healthy Subjects

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Study Drug: Ixekizumab (LY2439821)

Sponsor Reference: I1F-MC-RHCT
Covance CRU Study: 1000071-8391838

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ADA	Anti-drug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
BQL	Below the quantifiable lower limit of the assay
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PK	Pharmacokinetic

SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
VAS	Visual Analog scale
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 19th September 2018 and amendment a dated 15 November 2018).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) 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 and PK 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

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

4.2 Secondary Objective

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

4.3 Exploratory Objective

To evaluate the effect of ixekizumab on immunogenicity.

5. STUDY DESIGN

Study I1F-MC-RHCT is a Phase 1, subject-blind, 3-arm, randomized, parallel-design study in healthy subjects.

Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and randomized 1:1:1 to 1 of 3 possible treatments. On Day 1, subjects will receive a single SC dose of one of the following treatments, according to the randomization schedule:

- 80 mg ixekizumab Commerical 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 on Day 1, at the investigator's discretion, and will return for PK and immunogenicity sampling and safety assessments at predefined times up to 12 weeks postdose.

6. TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment order in TFL
80 mg ixekizumab Commercial Formulation (Reference)	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 99 subjects may be enrolled to ensure that 78 subjects (26 for each treatment) complete the study.

[redacted]

Subjects who are randomized but not administered treatment may be replaced to ensure that 78 subjects (26 for each treatment) complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received one dose of ixekizumab and have evaluable PK data.

All protocol deviations and adverse events (AEs) that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

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 standard deviation (SD), median, min, max and N; for log-normal data (e.g. the PK parameters: area under the concentration time curve [AUC] and maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. 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 time point. 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. All other demographic variables will be listed if applicable.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 6.4 or later):

Serum concentrations of ixekizumab and will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-∞)	ug.day/mL	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ug.day/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(t_{last}-∞)	%	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	ug/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
$t_{1/2}$	day	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration

Weight normalized PK parameters will be calculated. Additional PK parameters may be calculated where appropriate.

Any exceptions or special handling of data will be clearly documented within the final study report.

PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero.
- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.
- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The

minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive serum concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table. If AUC(0-∞) cannot be determined for all subjects an alternative AUC measure, such as AUC to a fixed time point, may be used in the assessment exposure between dose groups.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on the last observed quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Serum concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a subject.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile
A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values
Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

PK parameters will be evaluated to estimate the relative bioavailability of Test Formulation 1 and Test Formulation 2 compared to the commercial formulation (Reference).

Log-transformed $C_{max,}$ AUC(0-∞) and AUC(0-t_{last}) will be evaluated in a linear mixed-effects model with a fixed effect for formulation and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

Example SAS code:

```
proc mixed data=xxx;
   by parameter;
   class formulation subject;
   model log_pk = formulation / residual;
   lsmeans formulation / alpha=0.1 cl pdiff;
   random intercept / subject=subject;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
run;
```

The t_{max} will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference based on the observed medians, 90% CIs and p-values from the Wilcoxon rank sum test will be calculated.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the 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 dosing. 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 treatment 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 treatment, 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.

9.4.2 Concomitant medication

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

9.4.3 Clinical laboratory parameters

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

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the Day 1 predose assessment.

Vital signs data will be listed for individual subjects.

9.4.5 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.

9.4.6 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 treatment 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.

9.4.7 Injection-Site Assessments

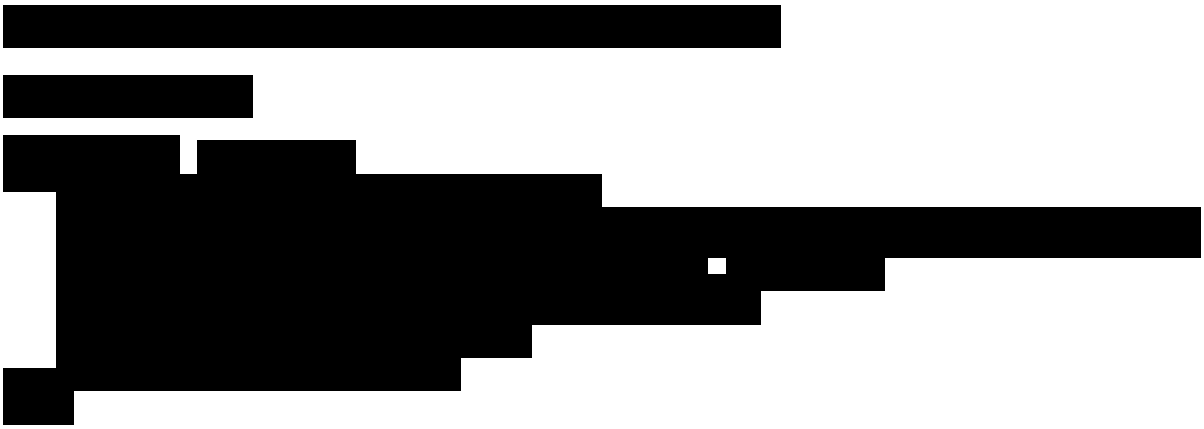
Injection sites will be assessed for induration, swelling, pruritus, and erythema/redness. Data will be summarized in a frequency table by treatment, and listed for individual subjects.

9.4.8 Injection-Site Pain

Visual analog scale (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 summarized by formulation and time point.

A mixed model for the repeating measures analysis model will be used to analyze the continuous injection-site pain VAS score. The model will include formulation and time post injection (0, 10, 20, 30, and 60 minutes) and formulation by time as fixed factors. The covariance

structure of the model will be unstructured. Other covariance matrices may be explored if needed. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least squares (LS) means will be used for the statistical comparison; the treatment differences along with their corresponding 95% CIs will also be reported.



9.4.9 Columbia-Suicide Severity Rating Scale (C-SSRS) / Self-Harm Supplement / Hospital Anxiety Depression Scale (HADS)

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.

HADS item scores will be listed for subjects with HADS depression subscale ≥11 at any time.

9.4.10 Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and with treatment emergent ADA+ to ixekizumab will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold increase in titer compared to baseline, if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA+ subjects the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in TE ADA+ subjects.

The relationship between the presence of antibodies and the PK parameters of ixekizumab may be assessed.

9.4.11 Safety and Tolerability Statistical Methodology

Inferential statistical analyses is planned for the pain VAS score, using a mixed repeated measures model.

10. DATA REVIEW DURING THE STUDY

Review of the PK and safety data may be conducted during the conduct of this study to inform internal Chemistry, Manufacturing, and Control processes with respect to the new ixekizumab formulation development.

11. INTERIM ANALYSES

No interim statistical analyses are planned.

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 (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. 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.”