Statistical Analysis Plan I1F-MC-RHBU V3

Evaluation of the Effect of Ixekizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

NCT02993471

Approval Date: 31-May-2017

STATISTICAL ANALYSIS PLAN

Evaluation of the Effect of Ixekizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

Statistical Analysis Plan Status: Final V3
Statistical Analysis Plan Date: 22 May 2017

Study Drug: Ixekizumab (LY2439821)

Sponsor Reference: I1F-MC-RHBU
Covance CRU Study: 1000071-8342913

Clinical Phase I

Approval Date: 31-May-2017 GMT

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
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 zero to infinity
%AUC(t_{last}-∞)	Fraction of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
BSA	Body surface area
C_{last}	Last measurable drug concentration
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
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CRU	Clinical Research Unit
CV	Coefficient of variation
CYP	cytochrome P450
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantitation
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio calculated as AUC(0-∞) metabolite/AUC(0-∞) parent
PASI	Psoriasis Area Severity Index

PD	Pharmacodynamic
PK	Pharmacokinetic
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
sPGA	static Physicians Global Assessment
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
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organisation

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 25 August 2016 and Amendment [a] dated 08 December 2016).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) data from this study. A detailed description of the planned tables, figure and listings (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, PD 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 patient 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 Council 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 assess the effects of single and multiple doses of ixekizumab on the PK of a drug cocktail of cytochrome P450 (CYP) substrates in patients with moderate-to-severe psoriasis.

4.2   Secondary objective

To evaluate the tolerability of ixekizumab in patients with moderate-to-severe psoriasis.

4.3   Exploratory objectives

- To explore the effects of ixekizumab on the PK of a drug cocktail of CYP substrates in the subgroups of patients with moderate-to-severe psoriasis who respond to ixekizumab treatment at Week 12 and those who do not respond.

- To evaluate the effects of ixekizumab treatment over time on inflammatory biomarker concentrations in patients with moderate-to-severe psoriasis.
- To determine the PK of metabolites and metabolite to parent ratios where appropriate.

5. STUDY DESIGN

This is a 2-period, fixed-sequence, open-label, multi-center, Phase 1 study to assess the effects of single and multiple doses of ixekizumab on the PK of a drug cocktail of CYP substrates (midazolam, warfarin, dextromethorphan, omeprazole, and caffeine) in patients with moderate-to-severe psoriasis.

Patients will be admitted to the clinical research unit (CRU) on Day -1 of Period 1 and receive the drug cocktail, with single oral doses of 1 mg midazolam, 10 mg warfarin (+ 10 mg vitamin K), 30 mg dextromethorphan, 20 mg omeprazole, and 100 mg caffeine on the morning of Day 1. Patients will reside at the CRU until Day 2 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of PK samples and safety assessments, as applicable, on Day 3 (48 hours post-drug cocktail dose), Day 4 (72 hours post-drug cocktail dose), and Day 5 (96 hours post-drug cocktail dose).

Patients will attend the CRU as outpatients on Day 1 of Period 2 (3 to 7 days after Day 5 of Period 1) and receive a 160-mg dose of ixekizumab (administered as two 80-mg subcutaneous [SC] injections).

Patients will be admitted to the CRU on Day 7 (±2 days) of Period 2 and receive the drug cocktail on the following morning (Day 8; Week 1). Patients will reside at the CRU until Day 9 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of PK samples and safety assessments, as applicable, on Day 10 (48 hours post-drug cocktail dose), Day 11 (72 hours post-drug cocktail dose), and Day 12 (96 hours post-drug cocktail dose).

Patients will receive single 80-mg doses of ixekizumab on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), and Day 71 (Week 10) of Period 2. Patients will be admitted to the CRU on Day 84 (±2 days) and receive 80 mg ixekizumab and the drug cocktail on the following morning (Day 85; Week 12). Patients will reside at the CRU until Day 86 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of additional drug cocktail PK samples and safety assessments, as applicable, on Day 87 (48 hours post-drug cocktail dose), Day 88 (72 hours post-drug cocktail dose), and Day 89 (96 hours post-drug cocktail dose).

Blood sampling for assessment of inflammatory biomarkers (IL-1β, IL-6, IL-19, and Tumor Necrosis Factor α) and ixekizumab PK and immunogenicity will be conducted at prespecified visits. Concentrations of IL-17A will not be measured as it complexes with ixekizumab, and therefore correlates with the PK of ixekizumab. Interleukin-17A drives production of IL-19 in keratinocytes of psoriatic skin. C-reactive protein will also be used as an inflammatory biomarker and is collected as part of the clinical laboratory testing. Efficacy will be evaluated

using static Physicians Global Assessment (sPGA), Psoriasis Area Severity Index (PASI), and percentage of body surface area (BSA) assessments at prespecified visits.

All patients will attend a follow-up visit on Day 113 (±4 days; Week 16).

Figure RHBU.1 illustrates the study design.
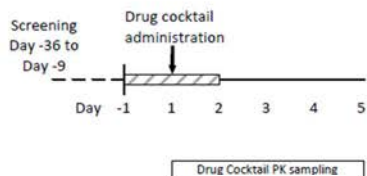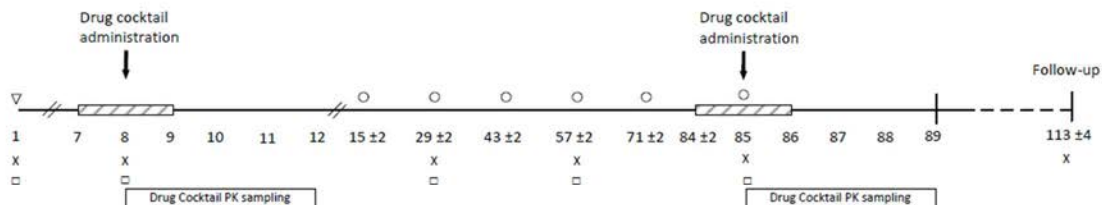
Abbreviations: BSA = body surface area; PASI = Psoriasis Area Severity Index; PK = pharmacokinetic; sPGA = static Physicians Global Assessment.

Figure RHBU.1. Illustration of Study Design for I1F-MC-RHBU

6. TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment order in TFLs
1 mg midazolam + 10 mg warfarin (+ 10 mg vitamin K) + 30 mg dextromethorphan + 20 mg omeprazole + 100 mg caffeine	Drug cocktail (Period 1)	1
160 mg ixekizumab	160 mg ixekizumab (Period 2)	2

160 mg ixekizumab + 1 mg midazolam + 10 mg warfarin (+ 10 mg vitamin K) + 30 mg dextromethorphan + 20 mg omeprazole + 100 mg caffeine	160 mg ixekizumab + Drug cocktail (Period 2)	3
80 mg ixekizumab Q2W	80 mg ixekizumab Q2W (Period 2)	4
80 mg ixekizumab Q2W + 1 mg midazolam + 10 mg warfarin + 30 mg dextromethorphan + 20 mg omeprazole + 100 mg caffeine	80 mg ixekizumab Q2W + Drug cocktail (Period 2)	5

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

Study Treatment Name	Treatment order in TFLs
1 mg midazolam	1
160 mg ixekizumab + 1 mg midazolam	2
80 mg ixekizumab Q2W + 1 mg midazolam	3
10 mg warfarin	4
160 mg ixekizumab + 10 mg warfarin	5
80 mg ixekizumab Q2W + 10 mg warfarin	6
30 mg dextromethorphan	7
160 mg ixekizumab + 30 mg dextromethorphan	8

80 mg ixekizumab Q2W + 30 mg dextromethorphan	9
20 mg omeprazole	10
160 mg ixekizumab + 20 mg omeprazole	11
80 mg ixekizumab Q2W + 20 mg omeprazole	12
100 mg caffeine	13
160 mg ixekizumab + 100 mg caffeine	14
80 mg ixekizumab Q2W + 100 mg caffeine	15

7. SAMPLE SIZE JUSTIFICATION

Approximately 30 patients will be enrolled with the assumption that 21 patients complete the study.

Midazolam

For midazolam AUC and C_{max}, the intrasubject variability coefficient of variation (CV%) was estimated to be 16.1% and 26.4%, respectively (derived from a previous study). Based on this assumption, 21 patients will provide a precision of 0.1 and 0.17 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% confidence interval (CI) of the ratio of the geometric means for AUC and C_{max} is no larger than 9.8% and 15.3%, respectively.

Warfarin

For S-warfarin AUC and C_{max}, the intrasubject variability CV% was estimated to be 7% and 8%, respectively (Steinijans et al. 1995). Based on these estimates, 21 patients will provide a precision of 0.045 and 0.049 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 4.4% and 4.8%, respectively.

Dextromethorphan

For dextromethorphan AUC and C_{max}, the intrasubject variability CV% was estimated to be 33.5% and 32.1%, respectively (derived from a previous study). Based on these estimates, 21 patients will provide a precision of 0.206 and 0.197 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 18.6% and 17.9%, respectively.

Omeprazole

For omeprazole AUC and C_{max}, the intrasubject variability CV% was estimated to be 21.8% and 29.8%, respectively (Public Assessment Report 1 Omeprazole "Copyfarm" Omeprazole). Based on these assumptions, 21 patients will provide a precision of 0.135 and 0.184 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 12.6% and 16.8%, respectively.

Caffeine

For caffeine AUC and C_{max}, the intrasubject variability CV% was estimated to be 21.0% (Blanchard and Sawers 1983) and 23.4% (Turpault et al. 2009), respectively. Based on these estimates, 21 patients will provide a precision of 0.13 and 0.148 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means is no larger than 12.2% and 13.8%, respectively.

8. DEFINITION OF ANALYSIS POPULATIONS

PK analyses will be conducted on the full analysis set. For drug cocktail PK, the full analysis set includes all data from all patients receiving at least one dose of drug cocktail, with evaluable PK data, according to the treatment the patients actually received.

For ixekizumab PK, the full analysis set includes all data from all patients receiving at least one dose of ixekizumab with evaluable PK data.

Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

PD (i.e. sPGA, PASI, percent BSA) and biomarker (e.g IL-1β, IL1-6, IL-19, tumor necrosis factor α, C-reactive protein) analyses will be conducted for all patients receiving at least one dose of ixekizumab with at least one postbaseline measurement in Period 2.

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

9. STATISTICAL METHODOLOGY

9.1   General

Data listings will be provided for all data that is 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: AUCs and Cmax) the geometric mean and geometric CV% will also be presented. Continuous data (such as PASI, sPGA, and %BSA) will be summarized in terms of the number of observations, mean, SD, minimum, median, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to 1 more decimal place than the raw data recorded in the database. The SD will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic. For categorical data, frequency count and percentages will be presented. Percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts. Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for patients included in the relevant analysis population.

Change from baseline will be calculated as the value at the visit of interest minus the baseline value. Baseline is defined as Day -1, Period 1, if this value is missing the screening value may be used. If all baseline values are missing for a particular variable, then the change from baseline and the percentage improvement from baseline will not be calculated.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

Age, sex, and race will be reported on all by-patient listings unless otherwise specified. Sex will be abbreviated as follows: female (F) and male (M). Race will be abbreviated as follows: American Indian or Alaska Native (AI), Asian (AS), Black or African American (BL), Native Hawaiian or other Pacific Islander (NH), White (WH), and Multiple (MU).

Data analysis will be performed using SAS$^{®}$ Version 9.3 or greater.

9.2   Demographics and Patient Disposition

Patient 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.

Baseline disease severity (PASI and sPGA score, and percentage of BSA), age of psoriasis onset, and previous psoriasis therapy type will also be summarized and listed.

9.3   Pharmacokinetic Assessment

9.3.1   Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program Phoenix WinNonlin (Pharsight Corporation, Version 6.4 or higher) to the plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam, S-warfarin, dextromethorphan and its metabolite dextrorphan, omeprazole and its metabolite 5-hydroxyomeprazole, and caffeine and its metabolite paraxanthine, respectively, and will be used to determine the following PK parameters, when possible:

midazolam, S-warfarin, dextromethorphan, omeprazole and caffeine

Parameter	Units	Definition
$AUC(0-\infty)$	h*ng/mL	area under the concentration versus time curve from zero to infinity
$\%AUC(t_{last}-\infty)$	%	fraction of $AUC(0-\infty)$ extrapolated
$AUC(0-t_{last})$	h*ng/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
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	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_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration

1-hydroxymidazolam, dextrorphan, 5-hydroxyomeprazole, paraxanthine

Parameter	Units	Definition
$AUC(0-\infty)$	h*ng/mL	area under the concentration versus time curve from zero to infinity
$\%AUC(t_{last}-\infty)$	%	fraction of $AUC(0-\infty)$ extrapolated
$AUC(0-t_{last})$	h*ng/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
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
MR	N/A	Metabolic ratio calculated as $AUC(0-\infty)$ metabolite/ $AUC(0-\infty)$ parent

Metabolic ratios will be corrected for the molecular weights of the parent and metabolite using the molecular weights.

Ixekizumab concentrations will be listed and summarized using descriptive summary statistics. Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

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. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- 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 plasma concentrations above the lower limit of quantitation (LLOQ), with at least one of these concentrations following C_{max}. $AUC(0-\infty)$ values where the percentage of the total area extrapolated is more than 20% will be flagged. Any $AUC(0-\infty)$ value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{1/2}$) 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 patient 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 plasma 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 $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ 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 <u>predicted</u> 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). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    o The compound is non-endogenous.

    o The samples are from the initial dose period for a patient or from a subsequent dose period following a suitable wash-out period.

    o 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 ± 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 multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.

- 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≥6, 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 $\pm 3*SD$ of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean $\pm 3*SD$, 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 $\pm 3*SD$, 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 $\pm 3*SD$ of the log-transformed values.

<u>Reporting of Excluded Values</u>
- 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

The PK parameter estimates of cocktail drugs will be evaluated to delineate the effects of drug interaction. Midazolam, warfarin, dextromethorphan, omeprazole, and caffeine administered in the absence of ixekizumab (Period 1, Day 1) will represent the reference treatments and will be analyzed separately. Each drug administered with ixekizumab will represent the test treatments (Period 2, Day 8 for single dosing and Period 2, Day 85 for multiple dosing). For the primary analysis, log-transformed C_{max} and AUC(0-∞) estimates of the parent drugs only will be evaluated in a linear mixed-effects analysis of variance model with a fixed effect for treatment and a random effect for patient. The treatment differences will be back-transformed to present ratios of geometric least squares means and the corresponding 90% CIs.

Example SAS code:

```
proc mixed data=pk;
    by parameter;
    class patient treatment;
    model log_pk = treatment / residual ddfm=kr;
    random patient;
    lsmeans treatment / alpha=0.1 cl pdiff;
    ods output lsmeans=lsmeans;
    ods output diffs=diffs;
run;
```

The AUC(0-t_{last}) will be analyzed using the same method described above.

The t$_{max}$ will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CI, and p-values will be calculated.

The same model used for the PK analysis will be applied to the subgroups of responders to ixekizumab and nonresponders at Week 12. This will be based on patients that have a Week 12 assessment. The treatment differences for each subgroup will be back-transformed to present ratios of geometric least squares means and the corresponding 90% CIs.

A responder to ixekizumab will be defined as a patient with a sPGA equal to 0 or 1 at Week 12. A nonresponder will be defined as a patient with sPGA >1 at Week 12.

Additional exploratory analyses may be conducted if needed.

9.4   Pharmacodynamic Assessment

9.4.1   Pharmacodynamic Analysis

The sPGA, PASI, and percent BSA are considered PD (efficacy) measures of disease activity in this study. Table 9.1 includes the description and derivation of the efficacy outcomes.

Table RHBU.9.1. Description and Derivation of Efficacy Outcomes (PD measures)

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
sPGA	Static Physician Global Assessment (sPGA): the physician's global assessment of the patient's psoriasis (Ps) lesions at a given time point (European Medicines Agency [EMA] 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	sPGA (0)	Score is clear (0)	Single item, missing if missing
		SPGA (0,1)	Score is Clear or Minimal (0 or 1)	Single item, missing if missing
PASI	Psoriasis Area and Severity Index (PASI): combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration (thickness, T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the	PASI 75	A clinically meaningful response; at least a 75% improvement in PASI score from baseline	Missing if baseline or observed value is missing
		PASI 90	Higher level of clearance; at least a 90% improvement in PASI score from baseline	Missing if baseline or observed value is missing
		PASI 100	Complete resolution of plaque Ps; a 100% improvement in PASI score from baseline	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	most severe disease (Fredriksson and Pettersson 1978). Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for very severe involvement): 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe The body is divided into four anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total body surface area affected is graded on a 0-6 scale (0 for no involvement; up to 6 for 90% - 100% involvement): 0 = 0% (clear) 1 = >0% to <10% 2 = 10% to <30% 3 = 30% to <50% 4 = 50% to <70% 5 = 70% to <90% 6 = 90% to 100% The various body regions are weighted to reflect their respective proportion of body surface area.	PASI total score	Sum the 3 scores for each body region to give a lesion score sum. Multiple the lesion score sum by the area score, for each body region to give 4 individual subtotals. Multiply each of the subtotals by amount of body surface area represented by that region, i.e., x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs. Add together each of the scores for each body region to give the final PASI score.	Missing if baseline or observed value is missing
		PASI change from baseline	Calculated as: observed PASI – baseline PASI	Missing if baseline or observed value is missing
		PASI percent improvement from baseline	Calculated as: $$100 \times \frac{\cdots\cdots}{=}$$ If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	Missing if baseline or observed value is missing
BSA	Percentage of Body Surface Area (BSA): The investigator will	BSA	Collected as a single scale as part of *PASI* electronic case report form (eCRF) page. Range from 0% to 100%.	Single item, missing if missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation [NPF] 2009).	BSA change from baseline	Calculated as: observed BSA – baseline BSA	Missing if baseline or observed value is missing

9.4.1.1   Static Physicians Global Assessment (sPGA)

The proportion of patients who achieve sPGA (0,1) and sPGA (0) will be summarized over time using descriptive statistics. A by-patient listing of sPGA scores and response rates will be provided. The listing will include patient number, treatment, timepoint, sPGA score and the sPGA response.

9.4.1.2   Psoriasis Area Severity Index (PASI)

The proportion of patients who achieve PASI 75 (at least a 75% improvement from baseline in PASI score), PASI 90 (at least a 90% improvement from baseline in PASI score) and PASI 100 (a 100% improvement from baseline in PASI score) will be summarized over time using descriptive statistics. In addition, the change from baseline and percent improvement from baseline will be summarized over time using descriptive statistics. A by-patient listing of PASI will be provided. The listing will include patient number, treatment, timepoint, PASI total score, change from baseline, percent improvement and the PASI response.

9.4.1.3   Percentage of Body Surface Area (%BSA) Assessment

The change from baseline in the %BSA will be summarized over time using descriptive statistics. A by-patient listing of sPGA will be provided. The listing will include patient number, treatment, timepoint, %BSA and change from baseline in the %BSA.

9.4.1.4   Exploratory biomarkers

Concentration of the exploratory biomarkers, IL-1β, IL-6, IL-19, tumor necrosis factor α and C-reactive protein, and their change from baseline will be summarized by treatment and listed.

9.5   Safety and Tolerability Assessments

9.5.1 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 patient 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. AEs by day of onset will be presented.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of patients experiencing an AE and the percentage of patients experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2016). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All laboratory parameters will be reported in both conventional and SI units.

All clinical chemistry and hematology data will be summarized over time, and listed. Baseline is defined as Day -1, Period 1. Urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual patient data listings.

9.5.4 Vital signs

Vital signs data and change from baseline will be summarized over time and listed. Baseline is defined as Day -1, Period 1.

9.5.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented.

9.5.6 Immunogenicity

Immunogenicity data will be summarized for treatment-emergent antidrug antibody (TE-ADA); definitions are documented in the ixekizumab program safety analysis plan (PSAP).

By-patient figures will also be provided which will include immunogenicity results, PK concentration and efficacy endpoints.

A by-patient listing of immunogenicity data will be provided, to include patient, treatment, visit, TE-ADA status, NAb (neutralizing antibody) status, titer and PK concentration.

Upon review of the data, additional analyses of immunogenicity data may be conducted.

9.5.7 Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16)

Data from the QIDS-SR16 questionnaire will be listed.

9.5.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS will be listed.

9.5.9   Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

9.5.10 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10.   INTERIM ANALYSES

No interim statistical analyses are planned.

11.   CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

The PASI 90% and PASI 100% response will be reported in addition to the PASI 75% response.

12.   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.

13.   DATA PRESENTATION

13.1   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.

13.2   Missing Data

Missing data will not be displayed in listings.

13.3   Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients 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."

Leo Document ID = 6cdf6f38-7a3a-4daa-ba35-9a2611e578ef

Approver: PPD
Approval Date & Time: 25-May-2017 08:33:45 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 30-May-2017 12:53:55 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 31-May-2017 07:09:36 GMT
Signature meaning: Approved