Statistical Analysis Plan Version 2

A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris

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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
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}-∞)	Percentage of AUC(0-∞) extrapolated
AUC_{τ}	Area under the concentration versus time curve during one dosing interval
BSA	Body surface area
BQL	Below the quantifiable lower limit of the assay
C_{last}	Last predicted concentration
C_{max}	Maximum observed drug concentration
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
EC	Early Clinical
e.g.	For example (Latin: *exempli gratia*)
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PK	Pharmacokinetic
PSAP	Program Safety Analysis Pllan
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report

Q2W	Every 2 weeks
Q4W	Every 4 weeks
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
SAP	Statistical Analysis Plan
sPGA	Static Physician's Global Assessment
SC	Subcutaneous
SD	Standard deviation
SDP	Single-dose phase
MDP	Multiple-dose phase
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TE-ADA	treatment-emergent antidrug antibody
t_{max}	Time of maximum observed drug concentration
t_{last}	Time of last observed drug concentration
V_{ss}/F	Apparent volume of distribution at steady state after extra vascular administration.
V_z/F	Apparent volume of distribution during the terminal phase 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 10 May 2016), Protocol Amendment (a) (final version dated 22 July 2016), Protocol Amendment (b) (final version dated 23 November 2016), and Protocol Amendment (c) (final version dated 20 June 2017).

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 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 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

The primary objective of this study is to assess the PK of ixekizumab after single and multiple subcutaneous (SC) doses in Chinese patients with psoriasis.

4.2 Secondary Objective

The secondary objective of this study is as follows:

- to assess the safety, tolerability, and immunogenicity of ixekizumab in Chinese patients with psoriasis.

4.3 Exploratory Objective

The exploratory objective of this study is as follows:

- to assess the efficacy endpoints of Psoriasis Area and Severity Index (PASI) and static Physician's Global Assessment (sPGA) of ixekizumab after single and multiple SC doses in Chinese patients with psoriasis.

5. STUDY DESIGN

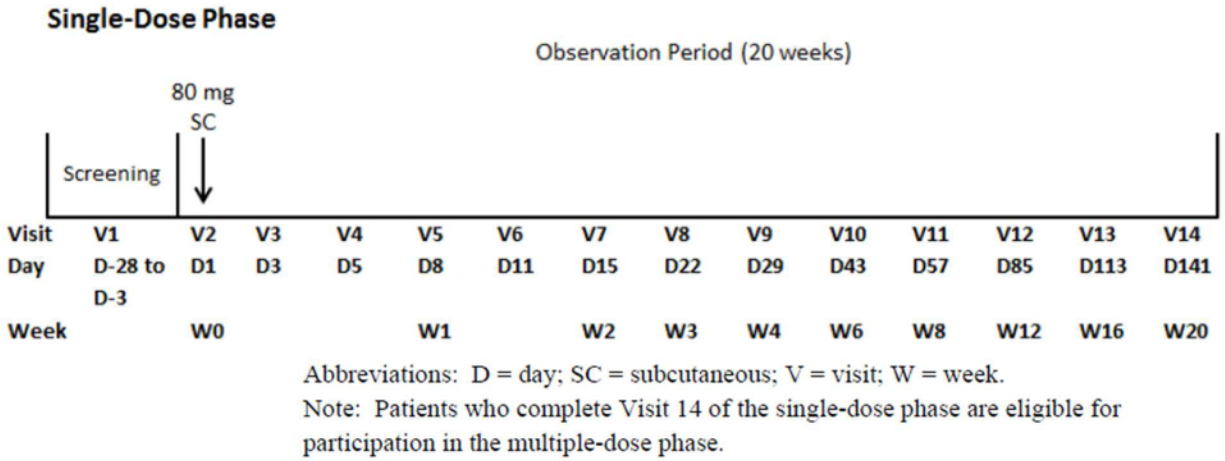
Study RHBN is a Phase 1, multicenter, open-label, single- and multiple-dose outpatient study in up to 45 patients with psoriasis. A 160 mg SC starting dose (Week 0) followed by an 80 mg SC dose Q2W or Q4W was evaluated as an induction dosing regimen over 12 weeks of treatment in global pivotal Phase 3 studies in patients with psoriasis (Studies RHAZ, RHBA, and RHBC). In this study, the PK profile and safety/tolerability of ixekizumab 80 mg will be assessed initially in the single-dose phase. Thereafter, the induction dosing regimens evaluated in the pivotal Phase 3 studies will be evaluated in the multiple-dose phase for this Phase 1 study in China.

For the single-dose phase, patients will receive a single dose of ixekizumab 80 mg SC on Day 1 and will be assessed at regular visits for 20 weeks. Patients completing the single-dose phase have the option of enrolling in the multiple-dose phase after completing the final visit in the single-dose phase. Patients will remain at the site for a minimum of 4 hours postdose.

The multiple-dose phase can be initiated once 6 patients have completed the Week 6 (Day 43) visit in the single-dose phase and safety data collected through 6 weeks postdosing from these patients have been reviewed. After review of these safety data, an agreement on initiation of the multiple-dose phase will be made by the investigator and sponsor.

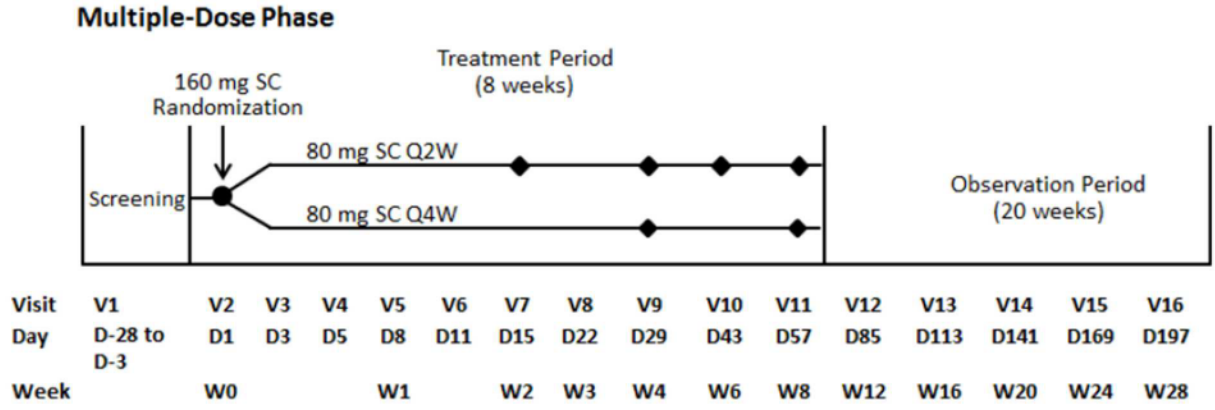
In the multiple-dose phase, patients will be administered a starting dose of ixekizumab 160 mg SC on Day 1 and will then be randomized into 1 of 2 dosing regimens for the 8-week treatment period: (1) 80 mg SC Q2W (at Weeks 2, 4, 6 and 8) or (2) 80 mg SC Q4W (at Weeks 4 and 8). After Week 8, patients will be assessed at regular visits for an additional 20 weeks. Patients will remain at the site for a minimum of 4 hours after the first dose and for 2 hours after subsequent doses.

Figure 1 and Figure 2 illustrate the study design for the single-dose phase and multiple-dose phase, respectively.



Abbreviations: D = day; SC = subcutaneous; V = visit; W = week.
Note: Patients who complete Visit 14 of the single-dose phase are eligible for participation in the multiple-dose phase.

Figure 1. Study design for the single-dose phase of Study I1F-MC-RHBN



● = 160 mg SC starting dose (open label) administered to both treatment arms at randomization
◆ = 80 mg SC dose (open label) administered to treatment arm on visit day indicated
Abbreviations: D = day; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.

Figure 2. Study design for multiple-dose phase of Study I1F-MC-RHBN

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
Ixekizumab 80 mg Single Dose	1
Ixekizumab 160 mg Starting Dose /80 mg Q2W	2
Ixekizumab 160 mg Starting Dose /80 mg Q4W	3

7. SAMPLE SIZE JUSTIFICATION

Up to 45 patients (15 patients for the single-dose phase and 30 patients for the multiple-dose phase) will be enrolled to target that 8 patients complete the single-dose phase and 20 patients (10 for each dosing regimen) complete the multiple-dose phase.

This study has been designed to meet the primary objective of assessing the PK of a single dose and multiple doses of ixekizumab in Chinese patients with psoriasis. The sample size was chosen to meet Chinese regulatory requirements and to provide sufficient data to evaluate the objectives and is not intended to achieve any prior statistical requirements.

8. DEFINITION OF ANALYSIS POPULATIONS

For the single-dose phase the "Safety" population will consist of all enrolled patients who received at least one dose of study drug during the single-dose phase, whether or not they completed all protocol requirements. For the multiple-dose phase, this population will consist of all enrolled patients who received at least one dose of study drug during the multiple-dose phase.

For the single-dose phase the "Pharmacokinetic" population will consist of all patients who received at least one dose of study drug during the single-dose phase and have evaluable PK data. For the multiple-dose phase, this population will consist of all enrolled patients who received at least one dose of study drug during the multiple-dose phase and have evaluable PK data.

For the single-dose phase the "Pharmacodynamic" population will consist of all patients who received at least one dose of study drug during the single-dose phase and have at least one postbaseline measurement. For the multiple-dose phase, this population will consist of all enrolled patients who received at least one dose of study drug during the multiple-dose phase and have at least one postbaseline measurement.

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, including PASI, sPGA, and % body surface area (BSA), 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 versus time curve [AUCs] and maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. 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. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient'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 9.3 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 at baseline will be summarized and listed. If a patient only participates in the single-dose phase (SDP) or multiple-dose phase (MDP), baseline is defined as the screening visit; if a patient participates in both SDP and MDP, the baseline for SDP and MDP will be the screening visit in SDP.

Baseline clinical measures such as sPGA score, PASI total score and body surface area at baseline (Day 1, predose) will be summarized and listed. If a patient participates in both the single-dose and multiple-dose phase of the study, the baseline for SDPwill be the baseline visit (Day 1, predose) from SDP, and the baseline for MDP will be the baseline visit (Day 1, predose) from MDP. If the baseline Day 1, predose value is missing, the screening value may be used.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Noncompartmental methods will be applied using a validated software program (Phoenix WinNonlin Version 6.4 or later) to analyze the serum concentrations of ixekizumab and determine the PK parameters of ixekizumab.

Single-Dose Phase

Following the 80 mg in the single dose phase, the following PK parameters will be determined, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	µg.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(0-∞)	µg.day/mL	area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	day	time of maximum observed drug concentration
t_{last}	day	time of last observed drug concentration
$t_{1/2}$	day	half-life associated with the terminal rate constant (λz) 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
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration

Multiple-Dose Phase

Serum concentrations of ixekizumab following single dosing of 160 mg on Day 1 (i.e. up to 14 days post the first dose and prior to the second ixekizumab dose), will be used to determine the single dose PK parameters and will be a subset of the parameters listed above that can be calculated based on only 14 days worth of sampling. Serum concentrations of ixekizumab from Week 8 following the last dose of repeated dosing of ixekizuamb will be used to determine the following multiple-dose PK parameters, when possible:

Parameter	Units	Definition
AUCτ	µg.day/mL	area under the concentration versus time curve during one dosing interval
C_{max}	µg/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 (λz) 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
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration

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 serum concentrations above the lower limit of quantificati on (LLOQ), with at least one of these concentrations following C_{max}.

- 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 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 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 last predicted 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 quantification (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 patient or from a subsequent dose period following a suitable wash-out period.
  - For patients who participate in the single-dose phase and move to the multiple-dose phase a review of the data for measurable predose.
  - 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.

  Quantifiable predose concentrations observed on Day 1 of the multiple dose phase will be evaluated for impact on derived PK parameters. If this occurs, the method of dealing with it will be documented in the study report.

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 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 $n\geq6$, 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

Descriptive statistics of PK parameters will be presented for each dose regimen (single-dose, Q2W multiple-dose, and Q4W multiple-dose) separately.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Clinical outcome measure PASI and sPGA are considered the PD measures in this study.

9.4.2 Pharmacodynamic Statistical Methodology

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

Descriptive statistics will be presented for overall PASI scores and sPGA scores (for both the single-dose and multiple-dose phases of the study) by dose regimen and study day. 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 will be provided. The listing will include patient number, treatment, timepoint, sPGA score and the sPGA response. 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 percent change in PASI scores 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, percent change from baseline and the PASI response.

Additional analyses may be conducted as deemed appropriate.

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: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$ 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

9.5 Pharmacokinetic/Pharmacodynamic Analyses

Exploratory exposure-response relationship analyses for PASI scores and sPGA scores may be conducted, if deemed appropriate.

9.6 Safety and Tolerability Assessments

9.6.1 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 patient has provided the first 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 within the defined phase, or which is present prior to the first dosing and becomes more severe postdose within the defined phase. Treatment-emergent AEs will be assigned to the phase to which it's considered treatment-emergent. Note that for patients who participate in both phases, (i) if AEs start and end during the gap (after the end of SDP and before the start of MDP), or if AEs start during the gap and continue to the multiple-dose phase without worsening in severity, such AEs will not be considered as treatment-emergent or be analyzed, but may be noted in CSR; (ii) if AEs start in SDP and continue to MDP without worsening in severity, it will be considered as treatment-emergent in SDP, but not treatment-emergent in MDP. AEs by week of onset will be presented.

All AEs will be listed. Treatment-emergent AEs will be summarized by phase, dose regimen, 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 dose regimen, Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 (use the latest version of MedDRA when an updated version becomes available) 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.

9.6.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version September 2016 [use the latest version if an updated version becomes available]). Concomitant medication will be listed. If a patient participates in both single-dose phase and multiple-dose phase, the concomitant medication starting after the end of SDP and before the start of MDP, will be listed separately and may be noted in CSR.

9.6.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by dose regimen and parameter, and listed. 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.

9.6.4 Vital signs

Vital signs data will be summarized by dose regimen together with changes from baseline, where baseline is defined as Day 1 predose. If a patient participates in both single-dose phase and multiple-dose phase, the baseline for the single-dose phase is defined as Day 1 predose in the single-dose phase, and the baseline for the multiple-dose phase is definded as Day 1 predose in the multiple-dose phase. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by dose regimen. Furthermore, values for individual patients will be listed.

9.6.5 Immunogenicity

A by-patient listing of immunogenicity data will be provided, to include patient, treatment, visit, treatment-emergent antidrug antibody (TE-ADA) status, NAb (neutralizing antibody) status, titer and PK concentration. A by-patient listing of AEs for patients who are TE-ADA positive will be provided along with their immunogenicity data. Definitions are documented in a separate ixekizumab program safety analysis plan (PSAP).

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

Additional analyses of immunogenicity data will be conducted as deemed appropriate.

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

Data from the QIDS-SR16 questionnaire will be listed for individual patients.

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

Data from the C-SSRS will be listed for individual patients.

9.6.8 Other assessments

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

9.6.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

Interim access to data may be conducted to support comparisons of PK data from Chinese patients in this study to PK data observed in non-Chinese patients from global studies, to enable planning for future studies. No changes to this study design are planned based on these PK analyses. Additionally, interim access to safety data may occur if deemed necessary or appropriate.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

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."