Statistical Analysis Plan I6T-MC-AMBP

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

NCT03718884

Approval Date: 04-Sep-2018

STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 29-August-2018

Study Drug: Mirikizumab (LY3074828)

Sponsor Reference: I6T-MC-AMBP
Covance CRU Study: 1000071-8388871

Clinical Phase I

Approval Date: 04-Sep-2018 GMT

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2. ABBREVIATIONS

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

%AUC(t_{last}-∞)	percentage of AUC(0-∞) extrapolated
ADA	antidrug antibody
AE	adverse event
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
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
BP	blood pressure
BQL	below the lower limit of quantitation
BSA	body surface area
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
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
CV	coefficient of variation
CYP	cytochrome P450
EC	Early Clinical
ECG	electrocardiogram
e.g.	for example (Latin: *exempli gratia*)
HS-CRP	High Sensitivity-C Reactive Protein
ICH	International Council on Harmonisation
IL	interleukin
LLOQ	lower limit of quantification
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities

MR	metabolic ratio
MW	Molecular weight
NA	not applicable
PASI	Psoriasis Area Severity Index
PK	pharmacokinetic
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report (16 items)
SAP	Statistical Analysis Plan
SD	standard deviation
sPGA	static Physicians Global Assessment
TE ADA	treatment-emergent antidrug antibody
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
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 27 June 2018) and Protocol Amendment (a) (final version dated 09 August 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 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

- To assess the effects of multiple doses of mirikizumab on the PK of a drug cocktail of cytochrome P450 (CYP) substrates in patients with moderate-to-severe psoriasis.

4.2 Secondary

- To evaluate the tolerability of mirikizumab in patients with moderate-to-severe psoriasis.
- To determine the PK of metabolites where appropriate.

4.3 Exploratory

- To explore the effects of mirikizumab on the PK of a drug cocktail of CYP substrates in the subgroups of patients with moderate-to-severe psoriasis who respond to mirikizumab treatment at Week 16 and those who do not respond.

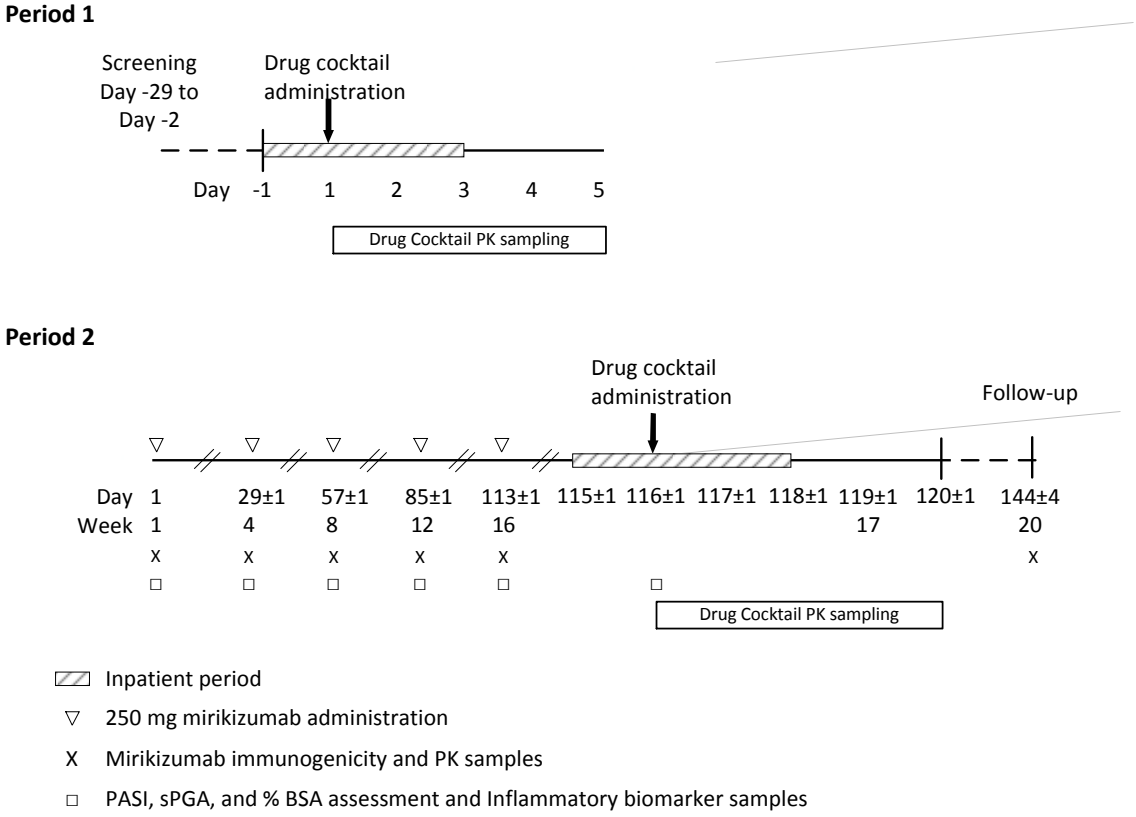
- To evaluate the effects of mirikizumab treatment over time of inflammatory biomarker concentrations in patients with moderate-to-severe psoriasis.

5. STUDY DESIGN

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

Blood sampling for assessment of PK of the CYP substrates (and metabolites, as appropriate), inflammatory biomarkers, and mirikizumab PK and immunogenicity will be collected at prespecified visits. 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. Safety will be monitored throughout the study by recording of adverse events (AEs), clinical laboratory parameters, vital signs, physical examination, Quick Inventory of Depressive Symptomatology-Self Report (16 items) (QIDS-SR16), Columbia-Suicide Severity Rating Scale (C-SSRS), Lilly Self-Harm Supplement, and electrocardiograms (ECGs).

Figure AMBP.1. Illustration of study design.



Abbreviations: BSA = body surface area; PASI = Psoriasis Area Severity Index; PK = pharmacokinetic; sPGA = static Physicians Global Assessment.
Note: In Period 2, drug cocktail will be administered 48 to 96 hours after the final mirikizumab dose.

6. TREATMENTS

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

Study Treatment Name	Abbreviation	Treatment order in TFL
1 mg Midazolam + 10 mg Warfarin (plus vitamin K) + 30 mg Dextromethorphan + 20 mg Omeprazole + 100 mg Caffeine (Period 1)	Drug Cocktail (Period 1)	1
250 mg Mirikizumab SC Q4W (Period 2)	250 mg Mirikizumab SC (Period 2)	2
1 mg Midazolam + 10 mg Warfarin (plus vitamin K) + 30 mg Dextromethorphan + 20 mg Omeprazole + 100 mg Caffeine (Period 2)	Drug Cocktail (Period 2)	3

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

Study Treatment Name	Abbreviation	Treatment order in TFL
1 mg Midazolam (Period 1)	1 mg Midazolam (Period 1)	1
10 mg Warfarin (plus vitamin K) (Period 1)	10 mg Warfarin (Period 1)	2
30 mg Dextromethorphan (Period 1)	30 mg Dextromethorphan (Period 1)	3
20 mg Omeprazole (Period 1)	20 mg Omeprazole (Period 1)	4
100 mg Caffeine (Period 1)	100 mg Caffeine (Period 1)	5
250 mg Mirikizumab SC Q4W (Period 2)	250 mg Mirikizumab SC (Period 2)	6
1 mg Midazolam (Period 2)	1 mg Midazolam (Period 2)	7
10 mg Warfarin (plus vitamin K) (Period 2)	10 mg Warfarin (Period 2)	8
30 mg Dextromethorphan (Period 2)	30 mg Dextromethorphan (Period 2)	9
20 mg Omeprazole (Period 2)	20 mg Omeprazole (Period 2)	10
100 mg Caffeine (Period 2)	100 mg Caffeine (Period 2)	11

7. SAMPLE SIZE JUSTIFICATION

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

Midazolam

For midazolam area under the concentration versus time curve (AUC) and maximum observed drug concentration (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[3]. 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[4]. 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%[5] and 23.4%[6], 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

Pharmacokinetic 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 mirikizumab PK, the full analysis set includes all data from all patients receiving at least one dose of mirikizumab with evaluable PK data. For patients with serum mirikizumab concentrations that are less than the drug exposure range expected after multiple doses, the drug cocktail PK results for Period 2 may be excluded from the analysis and the rationale will be provided in the study report.

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

Biomarker analyses will be conducted for all patients receiving at least one dose of mirikizumab 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 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: AUCs and C_{max}) the geometric mean and geometric 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 timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

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

9.2 Demographics and Subject Disposition

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

Furthermore, baseline disease characteristics (PASI score, sPGA score, percent total BSA of psoriasis, age of psoriasis onset, and previous psoriasis therapy type) will also be summarized and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined by standard non-compartmental procedures using a validated software program (Phoenix WinNonlin Version 6.4 or later).

Plasma concentrations of midazolam, 1'-hydroxymidazolam, S-warfarin, dextromethorphan, dextrorphan, omeprazole, 5'-hydroxyomeprazole, caffeine and paraxanthine will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
C_{max}	ng/mL[a]	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
AUC(0-∞)	ng.h/mL[a]	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ng.h/mL[a]	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(0-∞) extrapolated
$t_{1/2}$	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 (midazolam, S-warfarin, dextromethorphan, omeprazole and caffeine only)
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (midazolam, S-warfarin, dextromethorphan, omeprazole and caffeine only)
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration (midazolam, S-warfarin, dextromethorphan, omeprazole and caffeine only)
MR		metabolic ratio

Metabolic ratios (MR) will be calculated as follows for AUC(0-∞). If for any reason the AUC(0-∞) is not calculable then an alternative AUC such as AUC(0-t_{last}) may be used:

$$\mathrm{MR} = \frac{\mathrm{AUC}(0-\infty)\ (\mathrm{metabolite})}{\mathrm{AUC}(0-\infty)\ (\mathrm{parent})} \times \frac{\mathrm{MW}\ (\mathrm{parent})}{\mathrm{MW}\ (\mathrm{metabolite})}$$

Parent	MW*	Metabolite	MW*
Midazolam	325.77	1'-hydroxymidazolam	341.77
Dextromethorphan	271.40	Dextrorphan	257.38
Omeprazole	345.42	5'-hydroxyomeprazole	364.42
Caffeine	194.19	Paraxanthine	180.17

Abbreviation: MW = Molecular weight.
* Molecular weights obtained from PubChem[7]

Serum concentrations of mirikizumab (LY3074828) will be listed and summarized using descriptive 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 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.

- 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 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 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 predicted minimum observed 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). Plasma 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 or from a subsequent dose period following a suitable wash-out period.
    - 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 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

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 mirikizumab (Period 1) will represent the reference treatments and will be analyzed separately. Each drug administered after multiple dosing of mirikizumab (Period 2) will represent the test treatments and will be analyzed separately. For the primary analysis, log-transformed C_{max} and AUC(0-∞) estimates 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 derive ratios of geometric least squares (LS) means and the corresponding 90% CIs. The MR and AUC(0-t_{last}) will also be analyzed using this method.

Example SAS code:

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

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.

A sensitivity analysis will also be performed including only subjects with evaluable PK data in both treatment periods. Subject will be fitted as a fixed effect for this analysis.

The inter- and intra-subject variability, expressed as a CV, will be reported for each drug (using the statistical model from the primary analysis).

9.3.3 Pharmacokinetic Exploratory Statistical Methodology

The same model used for the primary PK analysis will be applied to the subgroups of responders to mirikizumab and nonresponders. A responder to mirikizumab will be defined as a patient with an sPGA equal to 0 or 1 at Day 116 in Period 2. A nonresponder will be defined as a patient

with sPGA >1 at Day 116 in Period 2. The treatment differences for each subgroup will be back-transformed to present ratios of geometric LS means and the corresponding 90% CIs.

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, severity and relationship to the study drug. 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 and those considered related to the study drug. Any serious AEs will be listed. In Period 2, AEs by day of onset will be presented.

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

All clinical chemistry and hematology data will be summarized by parameter and treatment, 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 subject data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day -1 in Period 1 and Day 1 predose in Period 2. Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram

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

9.4.6 Injection-site Reaction

If an AE of injection site reaction is reported, then the investigator will complete a supplemental injection site reaction form. The injection site reaction form documents the presence of erythema, induration, pain (mild, moderate, or severe), pruritus, and edema.

Injection-site reaction data will be listed and summarized in frequency tables.

9.4.7 Columbia-Suicide Severity Scale (C-SSRS) and Self-Harm Supplement

The C-SSRS and self-harm supplement data will be listed and summarized by treatment.

9.4.8 Quick Inventory of Depressive Symptomatology-Self Report (16 items) (QIDS-SR16)

The QIDS-SR16 scores will be listed and summarized by treatment.

9.4.9 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.

9.4.10 Other assessments

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

9.4.11 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9.5 Efficacy Assessments

9.5.1 Static Physicians Global Assessment (sPGA)

The proportion of patients who achieve sPGA (0,1) and sPGA (0) will be summarized by treatment and timepoint, and listed. The following table details the derivation for these 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 lesions at a given time point. 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

9.5.2 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 by treatment and timepoint, and listed. The following table details the derivation for these measures:

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
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 most severe disease[8]. 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	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
		PASI total score	Sum the 3 scores for each body region to give a lesion score sum. Multiply 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

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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 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

9.5.3 Percentage of Body Surface Area (%BSA) Assessment

The change from baseline in the %BSA will be summarized by treatment and timepoint, and listed. The following table details the derivation:

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
BSA	Percentage of Body Surface Area (BSA): The investigator will 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)[9].	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
		BSA change from baseline	Calculated as: observed BSA – baseline BSA	Missing if baseline or observed value is missing

9.6 Immunogenicity Analyses

Treatment-emergent antidrug antibodies (TE ADAs) are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution (1:10) if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of patients with preexisting ADAs and with TE ADA+ to mirikizumab will be listed and summarized. The frequency of neutralizing antibodies will also be tabulated for TE ADA+ patients.

The relationship between the presence of antibodies and the PK parameters and other responses, including safety and efficacy to mirikizumab, may be assessed.

9.7 Biomarker Analyses

Exploratory biomarkers, including concentrations of interleukin (IL-19), will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose of Period 2. Individual values will be listed.

9.7.1 High Sensitivity-C Reactive Protein (HS-CRP)

HS-CRP data and its change from baseline (Day 1 predose of Period 2) will be summarized by treatment and listed.

10. INTERIM ANALYSES

An interim analysis may be performed after all enrolled subjects have completed the outpatient visit and PK sample collection on Day 120 in Period 2. The purpose of this interim analysis is to provide PK results to support a regulatory submission. No changes to the study design are planned. The PK analyses detailed in Section 9.3.1 may be deemed final after this interim analyses (as all scheduled PK samples are included) and may not be repeated.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

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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. Unless otherwise stated, there are no plans to impute missing data.

13.3 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."

Leo Document ID = e810f0f1-e35b-49ec-ab7f-a0e2f365e08d

Approver: [redacted]
Approval Date & Time: 29-Aug-2018 13:18:27 GMT
Signature meaning: Approved

Approver: [redacted])
Approval Date & Time: 29-Aug-2018 19:08:11 GMT
Signature meaning: Approved

Approver: [redacted]
Approval Date & Time: 03-Sep-2018 11:48:08 GMT
Signature meaning: Approved

Approver: [redacted]
Approval Date & Time: 04-Sep-2018 19:48:13 GMT
Signature meaning: Approved