Statistical Analysis Plan I9H-MC-FFAA

A Phase 1 Randomized, Placebo-Controlled Study of LY3316531 in Healthy Subjects and an Open-Label, Single-Dose Study in Patients with Psoriasis

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STATISTICAL ANALYSIS PLAN

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Clinical Phase I

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2. ABBREVIATIONS

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

ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
BSA	Body surface area
CGRP	Calcitonin gene-related peptide
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
HS-CRP	High Sensitivity-C Reactive Protein
ICH	International Council for Harmonisation
IP	Investigational product
IV	Intravenous
LY	LY3316531
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PASI	Psoriasis Area and Severity Index
PatGA	Patient's Global Assessment of Psoriasis
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic

Ps	Psoriasis
SAD	Single ascending dose
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
CCI	[redacted]
sPGA	Static Physician Global Assessment
SR	Safety review meeting
TBD	To be determined
TBL	Total bilirubin level
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
CCI	[redacted]
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 02 November 2017) and Protocol Amendment (a) (final version dated 18 January 2018).

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, PK and PD 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 objectives

The primary objectives of this study are:

- To explore the safety and tolerability of single and multiple doses of LY3316531 in healthy subjects
- To explore the safety and tolerability of a single dose of LY3316531 in patients with psoriasis

The secondary objectives of this study are:

- To characterize the PK of LY3316531 following intravenous (IV) and subcutaneous (SC) administration in healthy subjects
- To characterize the PK of LY3316531 following IV administration in patients with psoriasis

The exploratory objectives of this study are:

- To evaluate the injection tolerance after SC administration of LY3316531
- To evaluate the formation of antidrug antibodies (ADA) to LY3316531
- To evaluate the PD response (target engagement) of LY3316531 using total calcitonin gene-related peptide (CGRP)

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- To evaluate patient-reported outcomes, including measurement of disease activity of LY3316531 in patients with psoriasis
- To evaluate relationships between LY3316531 exposure and PD and clinical activity measures and safety endpoints

5. STUDY DESIGN

Study FFAA is a 3-part Phase 1, multicenter, randomized, sponsor unblind, subject- and investigator-blind (investigator will be partially blind for Cohorts 1 and 2 and unblind for Cohort 5 in Part A), placebo-controlled, parallel-dose group, single-ascending dose (SAD) design (Part A), and multiple-dose design (Part B) in healthy subjects. In addition, Part C of this study is an open-label, single dose design in patients with psoriasis. There are 3 parts to this study to explore the safety, tolerability, PK, and PD of LY3316531:

- Part A: SAD design in healthy subjects,
- Part B: Multiple-dose design in healthy subjects,
- Part C: Single-dose design in patients with psoriasis.

Table 1 provides a detailed description of subject/patient cohorts and planned doses for Parts A, B, and C. Figure 1 demonstrates the relationship among Parts A, B, and C. Part A will begin first and will trigger the initiation of Parts B and C, which will run in parallel.

Patients/subjects will be admitted to the clinical research unit (CRU) on Day -1 (Days -1, 28, and 56 in Part B) and fast overnight. Patients/subjects will receive a dose of study drug or placebo on Day 1 (Days 1, 29, and 57 in Part B) and will undergo the study assessments specified in the Schedule of Activities (Section 2 of the protocol). Patients/subjects may be discharged 24 hours after dose administration on Day 2 (Days 2, 30, and 58 in Part B). In case of safety concerns, patients/subjects will be required to stay in the CRU for a longer period at the discretion of the investigator. Patients/subjects will return to the CRU for outpatient visits for procedures specified in the Schedule of Activities (Section 2 of the protocol).

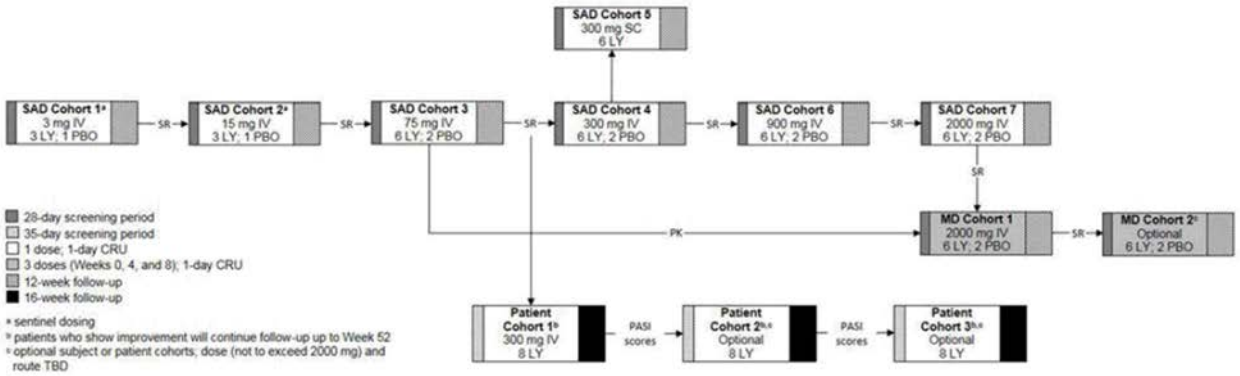
The decision to escalate to the next higher dose of LY3316531 will be based on safety data through Day 15 from at least 7 subjects (5 or 6 subjects will have received LY3316531 determined by randomization) from the preceding dose cohort. Exceptions will be for Cohorts 1 and 2, and Cohort 5 in if available at the time of decision in Part A, where safety data from all subjects through Day 15 will be required.

Table 1 Summary of Patient/Subject Cohorts

Cohort #	Planned Dose/ Administration Route	Number of Planned Subjects		Total Number of Planned Subjects
		LY	PBO	
Part A				
SAD Cohort 1[a]	3 mg/IV	3	1	4
SAD Cohort 2[a]	15 mg/IV	3	1	4
SAD Cohort 3	75 mg/IV	6	2	8
SAD Cohort 4	300 mg/IV	6	2	8
SAD Cohort 5	300 mg/SC	6	0	6
SAD Cohort 6	900 mg/IV	6	2	8
SAD Cohort 7	2000 mg/IV	6	2	8
Part B				
Multiple-Dose Cohort 1	2000 mg/IV	6	2	8
Multiple-Dose Cohort 2[b]	Route and dose TBD	6	2	8
Part C				
Patient Cohort 1	300 mg/IV	8	0	8
Patient Cohort 2[b]	Route and dose TBD	8	0	8
Patient Cohort 3[b]	Route and dose TBD	8	0	8

Abbreviations: IV = intravenous; LY = LY3316531; PBO = placebo; SAD = single-ascending dose; SC = subcutaneous; TBD = to be determined.
[a] Sentinel dosing will be used in this cohort.
[b] Optional subject or patient cohort. Actual dose and route of administration will be determined based on cumulative data from previous cohorts, but will not exceed 2000 mg of LY3316531 administered IV.

Figure 1 Illustration of study design



Abbreviations: IV = intravenous; LY = LY3316531; MD = multiple dose; PBO = placebo; PK = pharmacokinetic sampling; SAD = single-ascending dose; SC = subcutaneous; SR = safety review meeting; TBD = to be determined

5.1 Part A (SAD in Healthy Subjects)

Seven planned dose-escalation cohorts will be enrolled to receive either IV or SC administration of LY3316531 (3, 15, 75, 300, 900, or an additional dose not to exceed 2000 mg) or placebo. Sentinel dosing will be used in Cohorts 1 and 2 to minimize the risk to subjects receiving this novel antibody. Initially, 2 subjects (1 receiving LY3316531 and 1 receiving placebo) will be dosed in a blinded manner (sentinel subjects) and these subjects will be followed for at least 24 hours postdose before the remaining subjects in that cohort are dosed (subject blind only).

The remaining subjects may then be dosed on the same day or subsequent days (but not necessarily consecutive days), as determined by the investigator. Dose escalation to the next cohort can begin after a safety review of data from the preceding cohort. All 6 subjects in Cohort 5 will receive 300 mg of LY3316531 SC.

All subjects who meet eligibility criteria will be followed for 12 weeks post-treatment administration. A subject's participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 57. Subjects may be replaced if PK data are not collected up to and including Day 57.

5.2 Part B (Multiple-Dose Design in Healthy Subjects)

One planned multiple-dose cohort will be enrolled to receive IV administration of LY3316531 (2000 mg) or placebo. The dose and route of administration (IV or SC) for an optional second multiple-dose cohort would be determined after reviewing the data from the first IV cohort.

It is planned that a review of the safety data from Cohort 7 (Part A) and the preliminary PK data (maximum observed drug concentration [C_{max}] and area under the concentration versus time curve [AUC]) from Cohorts 1, 2, and 3 (through Day 29) in Part A will trigger enrollment to the first cohort in Part B.

All subjects who meet eligibility criteria will receive 3 doses of LY3316531 (1 dose every 4 weeks) and be followed for 12 weeks after the final treatment administration. A subject's participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 85. Subjects may be replaced if PK data are not collected up to and including Day 85.

5.3 Part C (Single-Dose Design in Patients with Psoriasis)

One planned single-dose cohort will be enrolled to receive IV administration of LY3316531 with the option of 2 subsequent cohorts where the dose levels and route of administration (SC or IV) would be determined after reviewing the data from the first IV cohort.

The first cohort is planned to receive 300 mg of LY3316531 pending the analysis of available safety data from Part A. The actual starting dose and expected exposure will not exceed the dose/exposure that is concurrently being evaluated in Part A. Any available preliminary PK data from Cohorts 1, 2, and 3 (through Day 29) in Part A will be considered in the decision to initiate Part C as well. Similarly, the dose for the optional cohorts will be determined based on cumulative data from previous cohorts, but will not exceed 2000 mg of LY3316531.

All patients who respond to LY3316531 treatment by exhibiting at least 50% reduction from baseline Psoriasis Area and Severity Index (PASI) score at Week 12 (Visit 11; Day 85) can enter an extended follow-up period for up to 52 weeks post-treatment administration. Other subjects who do not meet the above criterion for PASI reduction should be considered for discontinuation from the study at Week 16 (Visit 12; Day 113). Exceptions could be considered after a discussion between the sponsor and investigator.

A patient's participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 85. Patients may be replaced if PK or PD data are not collected up to and including Day 85.

6. TREATMENTS

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

Part	Cohort	Study Treatment Name	Treatment order in TFL
A	*	Pooled Placebo IV	1
	1	3 mg LY3316531 IV	2
	2	15 mg LY3316531 IV	3
	3	75 mg LY3316531 IV	4
	4	300 mg LY3316531 IV	5
	5	300 mg LY3316531 SC	6
	6	900 mg LY3316531 IV	7
	7	2000 mg LY3316531 IV	8
B	*	Pooled Placebo IV	9
	1	2000 mg LY3316531 IV	10
	2	XXX mg LY3316531 TBD	11
C	1	300 mg LY3316531 IV	12
	2	XXX mg LY3316531 TBD	13
	3	XXX mg LY3316531 TBD	14

* Placebo IV data will be pooled across all cohorts within each part

7. SAMPLE SIZE JUSTIFICATION

The sample size for each cohort is customary for first-in-human studies in which formal power analyses are not necessary to address the objectives associated with safety, tolerability, PK, and/or PD assessments. Approximately 86 patients/subjects are planned for enrollment; however, up to 102 subjects may be enrolled to allow for replacement of subjects and any additional dose cohorts (Parts A, B, and C).

Subjects/patients who withdraw from the study before completing the Day 57 (Part A) or Day 85 (Parts B and C) assessment may be replaced if necessary to have the planned number of subjects/patients complete a dose cohort. A replacement subject/patient will be assigned the same treatment as the subject/patient he or she replaces (Parts A, B, and C).

8. DEFINITION OF ANALYSIS POPULATIONS

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

PK/PD analyses (CGRP target engagement) will be conducted on data from all patients/subjects who receive at least 1 dose of the study drug and have evaluable data.

Clinical activity and PD analyses will be conducted for all patients with psoriasis who receive the study drug (Part C only).

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations prior to database lock and unblinding. Details of subject assignment to the analysis populations will be listed.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data in the database. 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, minimum, maximum, and number of data points (N). For log-normal data, the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts 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/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.

Furthermore, baseline disease characteristics (Psoriasis Area and Severity Index [PASI] score, static Physician Global Assessment [sPGA], and the percent total body surface area [BSA] of psoriasis) for patients in Part C will also be summarized and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK analysis and any associated TFLs will be the responsibility of Eli Lilly and Company. Pharmacokinetic parameter estimates for LY3316531 will be calculated using standard noncompartmental methods, and the primary parameters will be C_{max} and AUC of LY3316531. Refer to Section 10.3.2.1 of the protocol for additional details.

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 2 includes the description and derivation of the efficacy outcomes.

Table 2 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). 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. 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
		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

9.4.1.1 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 %BSA will be provided. The listing will include patient number, treatment, timepoint, %BSA and change from baseline in the %BSA.

9.4.1.4 Target Engagement Assay (Total Calcitonin Gene-Related Peptide [CGRP])

Total CGRP data and its change from baseline (Day 1 predose) will be summarized by treatment and listed.

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

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

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9.4.2 Pharmacodynamic Statistical Methodology

The PD biomarkers will be summarized by treatment and timepoint, and listed. The changes from baseline, and absolute percentage change from baseline, will also be summarized. Figures of mean values and mean changes from baseline will be presented by treatment. Individual profiles will also be plotted over time.

Analyses of PK-PD relationships will be the responsibility of Eli Lilly and Company. Refer to Section 10.3.3.1 of the protocol for additional details.

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 adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to 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 for Part B.

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 20.0 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 tabulated.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2017). Concomitant medication will be listed.

9.5.3 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.

9.5.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by treatment.

Furthermore, values for individual subjects will be listed.

9.5.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QTcB intervals, QRS duration and heart rate, where QTcB is the QT interval corrected using Bazett's formula. In addition, QTcF (the QT interval corrected using Fridericia's formula) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

The ECG data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of subjects with a maximum increase from baseline in QTcB and QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcB and QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

A plasma LY3316531 concentration-QT analysis will be performed to assess the changes from baseline (Day 1 predose) QTcF interval relative to plasma LY3316531 concentrations across all active treatments. The change from baseline adjustment will be based on individual subject's Day 1 predose value. The analysis will be performed by plotting change from baseline QTcF against LY3316531 concentrations, including all post Day 1 dosing timepoints. The plot will be produced separately for parts A, B, and C of the study. Each plot will include a simple linear regression.

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9.5.9 Immunogenicity

Immunogenicity data will be listed and frequency tables will be presented. The frequency of treatment-emergent ADAs will also be calculated. Treatment-emergent ADAs are those that are induced or boosted by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline or a titer 2-fold greater than the minimum required dilution (1:40) if no ADAs were detected at baseline.

To show the association of treatment-emergent ADAs with AEs, the frequency of treatment-emergent ADAs will be presented by MedDRA preferred term. Relationship between the presence of antibodies and the PK parameters of LY3316531 may be assessed graphically.

9.5.10 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.

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 a magnetic resonance elastography (MRE) scan and 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.

9.5.11 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS data will be listed.

9.5.12 Patient's Global Assessment of Psoriasis (PatGA) and Psoriasis Symptom Scale

The data will be listed and summarized by treatment.

9.5.13 Biopsy Assessment

The biopsy assessment data will be listed.

9.5.14 Other assessments

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

9.5.15 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

An interim analysis will occur when all patients/subjects in Parts A, B, and C have completed all requirements stated in the Schedule of Activities (Section 2; up to Day 85 for Part A, up to Day 141 for Part B, and up to Day 113 for Part C) or discontinued early from the study. Lilly employees and employees of any third-party organization involved in the interpretation of data collected during the study are authorized to evaluate unblinded data for the interim analyses. This interim analysis will include all planned analyses of available data. The data will be used for the development of a CSR. Results that are not available at the time the CSR is developed can be provided in a separate report or CSR addendum.

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 observed quantities 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 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.”

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