Statistical Analysis Plan Version 1 J1P-MC-KFAC

# A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous LY3471851 in Patients with Psoriasis

NCT04119557

Approval Date: 06-Aug-2020

# Statistical Analysis Plan

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| **Sponsor:** | Eli Lilly and Company |
| **Protocol:** | J1P-MC-KFAC(a) |
| **PRA Project Id:** | J1P-MC-KFAC |
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|---|---|
| **Title:** | A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous LY3471851 in Patients with Psoriasis |
| **CRF Version No./Date:** | 2.0/12-Jun-2020 |

## 1.0 Approvals

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|---|---|
| **Sponsor** | |
| **Sponsor Name:** | Eli Lilly and Company |
| **Representative/ Title:** | PPD |
| **Signature /Date:** | |
| CCI | |
| **Project Manager/Title:** | PPD |
| **Signature /Date:** | |
| **Biostatistician / Title (Owner):** | PPD |
| **Signature /Date:** | |

## Table of Contents

## 2.0 Statistical Analysis Plan

The statistical analysis plan (SAP) describes the statistical methods for reporting and analyses of data collected under Protocol J1P-MC-KFAC.

This plan is a living document that will be created during the trial start-up. Each version of the SAP will require sign off from the Project Manager and the sponsor prior to programming starting or being updated as a result of an amended version of the SAP. The Statistical Analysis Plan will be signed before the unblinding occurs for the interim analysis.

The Statistical Analysis Plan outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse events handling, laboratory data and physical examinations

## 3.0 Introduction

Study J1P-MC-KFAC is a Phase 1 study designed to evaluate the safety, tolerability, and pharmacokinetic (PK) of multiple subcutaneous (SC) doses of LY3471851 (also known as NKTR-358) in patients with psoriasis (PsO).

LY3471851 is recombinant human interleukin 2 (rhIL-2) with stable covalently attached polyethylene glycol (PEG) moieties. IL-2 has pleiotropic immunoregulatory functions and has a role in the control of the proliferation and survival of regulatory T cells, which are impaired in various autoimmune diseases and inflammatory skin diseases, including PsO.

### 3.1 Changes from Protocol

Not applicable

## 4.0 Study Objectives

- To evaluate the safety and tolerability of multiple SC doses of LY3471851 administered to adult patients with chronic plaque psoriasis (PsO).
- To quantify LY3471851 plasma concentrations following multiple SC doses in patients with PsO.

## 5.0 Study Design

This is a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, PK, and PD effects of multiple doses of LY3471851 in up to 2 cohorts of patients with plaque PsO involving ≥10% body surface area (BSA) in the affected skin and a Psoriasis Area and Severity Index (PASI) score of ≥12 at screening.

Patients will receive either LY3471851 or placebo every 2 weeks over a treatment period of 12 weeks. Patients will receive SC injection(s) of LY3471851 (n=16) or placebo (n=4). The planned dose for Cohort 1 is 10 µg/kg. Last safety follow-up will be 50 days after the last dose (Week 19), with additional visits up to Week 48 for PASI 50 (patient's PASI score reduced by at least 50% relative to their baseline score) responders at Week 19.

Cohort 1 stopped enrolling new subjects CCI [redacted] at the time of the coronavirus disease 2019 (COVID-19) pandemic CCI [redacted]

When the study is restarted, enrollment will begin in Cohort 2 with a dose of 24 µg/kg every 2 weeks. The initiation of Cohort 2 is supported by emerging safety, PK, and PD data from the MAD study at the highest dose level of 24 µg/kg [Study J1P-MC-KFAB] and longer-term toxicology studies.

### 5.1 Sample Size Considerations

Approximately 20 patients with PsO will be enrolled in each cohort for a maximum of 2 cohorts (40 patients). The sample size is customary for Phase 1 studies evaluating safety and PK and is not powered on the basis of statistical hypothesis testing.

Patients who discontinue the study before completing the Day 85 assessment may be replaced at the discretion of the sponsor. The replacement patient should be assigned to the same treatment allocation as the discontinued patient.

A key clinical assessment is the percentage change from baseline in PASI at Week 12. With a sample size of 20 patients per cohort, randomized in a 4:1 ratio to LY3471851 or placebo, the half-width of the 95% confidence interval of the percentage change from baseline in PASI between LY3471851 and placebo will be within 22% with a standard deviation assumption of 20%.

### 5.2 Randomization

On Day 1 of each cohort period, the patients who meet all screening and eligibility criteria will be randomized in a 4:1 ratio to either LY3471851 or placebo. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

The block sizes will not be known to the investigator.

### 5.3 Blinding

The investigator, patients, and all study site and Lilly personnel involved in study activities will be blinded, with the following exceptions:

- those involved in drug preparation and accountability

- the Statistical Analysis Center (individuals from the statistical and PK group [which may include both Lilly and CRO personnel]) who will produce tables, figures, and listings for the interim analysis, and
- the assessment committee

The individuals or functional groups who are planned to be unblinded will be identified in the study unblinding plan.

## 5.4 Objectives and Endpoints

The following objectives and endpoints listed in the table below are defined in the protocol:

| Objectives | Endpoints |
|---|---|
| **Primary**<br>• To evaluate the safety and tolerability of multiple SC doses of LY3471851 administered to adult patients with chronic plaque PsO | Incidence of adverse events, treatment-emergent adverse events, and serious adverse events |
| **Secondary**<br>• To quantify LY3471851 plasma concentrations following multiple SC doses in patients with PsO | $C_{max.}$, $T_{max}$, and AUC after the first dose and trough concentrations after repeated dosing |
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Abbreviations: AUC = area under the plasma concentration versus time curve; CCI $C_{max}$ = maximum observed plasma concentration; CCI CCI PsO = psoriasis; CCI CCI SC = subcutaneous; CCI $T_{max}$ = time to maximum observed plasma concentration; CCI

## 5.5 Safety Endpoints

### 5.5.1 Adverse Events

Treatment-emergent adverse events will be used for the presentation of adverse events. Treatment-emergent adverse events are those which first occur or increase in severity or relationship to study drug after the first dose of study drug up to study discontinuation for that patient (up to 48 weeks). In reality, all adverse events which change in severity or relationship to study drug are assigned a new start date and captured as a new record.

AEs will be graded as mild, moderate, or severe using the following definitions:

- Mild: Condition does not interfere with activities of daily living. Use of a concomitant therapy can still be consistent with a mild severity as long as the patient is able to carry out activities of daily living.
- Moderate: Condition interferes with activities of daily living, but patient is able to compensate and do the daily activities that must be done (e.g., go to work, school, shop for groceries, etc.)
- Severe: Condition prevents patients from completing activities of daily living, confined to bed or must miss work or school

### 5.5.2 Laboratory Tests

Clinical laboratory tests consist of hematology, chemistry, and urinalysis (clean catch). Hepatic function (including AST, ALT, gamma-glutamyl transferase, ALP, lactate dehydrogenase, and TBIL) were tested as part of the chemistry panel. Blood and urine samples were collected at the times specified in the Schedule of Activities. A list of tests that were performed is displayed in Appendix 2.

### 5.5.3 Vital Signs

Vital sign measurements, including respiratory rate (RR; breaths/minute), HR (bpm), and BP (mm Hg), were recorded while the patient was in supine position, and has been resting for at least 5 minutes, and body temperature (°C) was recorded at the times specified in the Schedule of Activities of the protocol. On days when the study drug was administered, vital sign measurements were taken predose and at 2 hours ±15 minutes postdose.

Following criteria will be used for determining the out-of-range for vital signs.

- RR: <16 or >20 breaths/minute
- HR: <40 or >100 bpm
- BP systolic: >140 or <90 mm Hg
- BP diastolic: >90 or <50 mm Hg
- Fever: >38°C (100.4°F).

### 5.5.4 Electrocardiograms

Single ECGs were performed on a calibrated digital 12-lead machine at the times specified in Schedule of Activities of the protocol. Electrocardiograms should be recorded before collecting any blood for safety or PK tests. Patients had to be resting quietly in a supine position for at least 5 minutes prior to each ECG and had to remain supine and awake during ECG collection.

### 5.5.5 Injection-Site Assessments

According to the Schedule of Activities of the protocol, injection-site assessments were performed at the end of each visit on Day 1 through Day 99. The investigator had to ask the patient if she/he had any injection-site concern since the preceding visit or, when assessed on Day 1, since the first injection. If more than one injection is given per occasion, then each injection site will be evaluated. Patient's responses were recorded per the Injection Site Assessment and Pain visual analog scale tools to capture specific information relating to an injection site. CCI [redacted]

### 5.5.6 Physical Examination

Physical examinations included an examination of all major organ systems. Prior to the dose of study drug on Day 1, clinically significant findings that were present had to be documented as medical history in the eCRF. After the dose of study drug on Day 1, clinically significant findings that met the definition of an AE had to be recorded as an AE in the eCRF.

## 5.6 Efficacy Endpoints

### 5.6.1 Disease Activity Endpoints

The following disease activity measures described below were collected at the times shown in the Schedule of Activities of the protocol.

**Psoriasis Area and Severity Index:** The PASI scores the severity of disease on a scale from 0 to 72 (where a score of 72 indicates extreme disease severity) by combining assessments of the

extent of body surface involvement in the head, trunk, arms, and legs together with the severity of desquamation, erythema, and lesion induration/infiltration (thickness) in each region. The PASI percent improvement at a visit was defined as (baseline value – visit value)/(baseline value)x100%. A PASI 75 response is defined as a 75% or greater improvement from baseline. PASI 25, PASI 90 and PASI 100 are similarly defined.

**Percentage of BSA** affected by PsO was derived as part of the PASI assessment. The percentage of BSA was evaluated as the percentage involvement of PsO on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the patient's hand (including the palm and fingers).

**Target Lesion Total Sign Score:** Target lesion assessments were performed to measure the redness, thickness, and scaliness of target lesions using the Target Lesion Score (TSS), (Fowler et al. 2016). The TSS is the sum of erythema, scaling, and lesion elevation scores, each on a 4-point scale (0 to 3, with 0 indicating a grade of clear and 3 indicating a grade of severe to very severe).

**Static Physician's Global Assessment (sPGA):** The sPGA provides the physician's determination of the patient's PsO lesions, overall, at a given time point. Overall lesions were graded for induration, erythema, and scaling (range 0 to 4). The sPGA score (range 0 to 4) at a visit was defined as the sum of 3 scores divided by 3. For the analysis of responder rate, the sPGA scores were rounded to the nearest whole number and was assessed as clear (0), almost clear (1), mild (2), moderate (3), and severe (4).

An sPGA (0,1) response is defined as a postbaseline sPGA score of 0 or 1. An sPGA (0) response is defined as a postbaseline sPGA score of 0 (remission).

## 5.7 Other Endpoints and Variables

### 5.7.1 Patient-Reported Outcome/Quality-of-Life Measures for Patients with Psoriasis

The following patient-reported outcomes/quality-of-life measures described will be collected at the times shown in the Schedule of Activities.

**Itch Numerical Rating Scale (Itch NRS):** The Itch NRS is a patient-administered, 11-point, horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching from PsO is indicated by circling the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016).

**Patient's Global Assessment of Disease Severity:** In the Patient's Global Assessment of Disease Severity, patients are asked to rank, on a 0 to 5 NRS, the severity of their PsO "today" from 0 (clear; no PsO) to 5 (severe; worst their PsO has ever been).

### 5.8 Covariates and Prognostic Factors

Pre-determined covariates or prognostic factors are not planned for the analysis but may be explored as deemed meaningful.

## 6.0 **Definitions**

**Baseline** is defined as the last measurement prior to the first injection of study drug.

**Change from baseline** (CFBL) is defined as (value at post-baseline visit – value at baseline). In summary tabulations, unscheduled post-baseline values will be excluded. All assessments, planned or unscheduled are included in listings. If the baseline value is missing for a subject the change from baseline is not defined and excluded from the table or listing.

**Percent change from baseline**, when needed, is the CFBL divided by the baseline value multiplied by 100%. Patients with a value of 0 at baseline cannot have percent CFBL calculated.

**Body mass index (BMI)** will be calculated based on weight and height using the following formula:

$$BMI = Weight\ (kg) / Height^2\ (m)$$

**Age group** will be categorized into the following groups:< 65 years old, 65 - 75 years old and > 75 years old.

**Concomitant medications** are all medications taken and treatments applied (eg, IV solution, blood transfusion for AEs and SAEs) from the day of the first injection or ongoing from prior to first injection through the Last Study Visit (Day 134 for PASI 50 non-responders and Day 169 for PASI 50 responders).

**Prior medications** are all medications with a start date prior to the date of the first injection and may be ongoing at the date of first injection.

**End of treatment** is defined as the last value for a given patient, whenever it occurred.

**Discontinuation of Study:** A patient will be considered discontinued from the study when a End of Study CRF page is completed indicating primary reason for discontinuation.

### 6.1 Handling of Missing Data

Missing data will be handled differently depending on the parameter and analysis. Note that analyses done on 'observed cases' will not follow any imputation rules below. See below for considerations:

- Missing baseline values will not be imputed in any situation.
- An LOCF approach will also be used for efficacy analyses on the mITT 12-Week Parallel Group population, meaning the last non-missing post-baseline observation will be carried forward to each visit.

- For any safety assessments of patients without a Week 12 safety endpoint assessment, the last non-missing post-baseline observation will be used as the end of treatment value.
- Missing data for AE relationship will be imputed as "Related."
- Rules for partial dates are described in Appendices 2 and 3. These will apply to AE and concomitant medications when applicable.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

- Missing onset day (where UK and UKN indicate unknown or missing day and month respectively) UK-MMM-YYYY:
  - If the month and year are different from the month and year of the infusion, assume 01-MMM-YYYY;
  - If the month and year are the same as the infusion month and year, and the end date (after any imputation) is on or after the infusion, then assume the date of the infusion;
  - If the month and year are the same as the infusion and the end date (after any imputation) is prior to the infusion, then assume the end date for the onset date.
- Missing onset month DD-UKN-YYYY/UK-UKN-YYYY:
  - If the year is different from the year of the infusion, assume 01-JAN-YYYY of the collected year;
  - If the year is the same as the infusion, and the end date (after any imputation) is on or after the infusion, then assume the date of the infusion;
  - If the year is the same as the infusion, and the end date (after any imputation) is prior to the infusion, then assume the end date for the onset date.
- Missing end dates:
  - UK-MMM-YYYY: assume the last day of the month;
  - DD-UKN-YYYY/UK-UKN-YYYY: assume DD-DEC-YYYY/31-DEC-YYYY.

### 6.2 Summary Statistics

Quantitative displays will be summarized using descriptive statistics. The mean, standard deviation, median, minimum, and maximum will be provided. Decimal precision will be based on the mean value. The median contains the same number of decimal places as the mean, the standard deviation contains one more decimal place, and the minimum and maximum contain one less decimal place. The mean will typically have one more decimal place than the raw values but if necessary, decimal precision for the mean will be provided in the table specifications.

### 6.3 Data Listings

Unless otherwise specified, data listings will be provided on observed values. Efficacy listings will be flagged for imputations. In addition, the analysis visit will be displayed if it is important for the corresponding summary. Listings are generally sorted by treatment, subject, variable to display and visit (if different sort order is used it is specified in the listing. Listings will be provided to serve as support for all summary tables or figures.

### 6.4 Graphical Displays

Supporting figures may be used for some efficacy or safety analyses in addition to the summary tables. Details regarding the content, layout, and structure of figures will be provided in the table specifications.

## 7.0 Analysis Populations

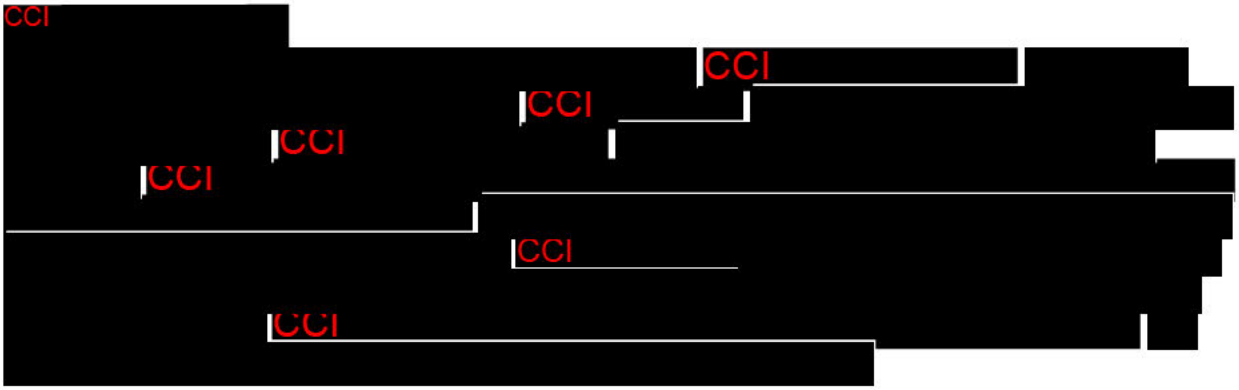
**Intent to treat population (ITT)**
All randomized patients, even if patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow protocol.

**Safety analysis population**
All randomized patients who receive at least 1 dose of study drug will be included according to the randomized treatment, regardless of whether they have completed all protocol requirements. This includes also patients who terminated early and were replaced.

**Per-Protocol analysis population**
The per-protocol population (PP) will be a subset of the safety population. Subjects may be completely excluded or data points will be excluded after an important protocol deviation from this population. Important protocol deviations are deviations or violations that could affect efficacy endpoints of the study. All decisions to exclude subjects or data points from this population to form the per-protocol population will be made prior to the unblinding of the study.

**PK analysis population**
The PK analysis population will consist of all randomized patients who receive LY3471851 and have adequate PK data to permit a meaningful analysis.

**PD analysis population**
Pharmacodynamic analyses will be conducted on the full analysis set, which includes all evaluable data from all patients receiving at least 1 dose of study drug according to the randomized treatment. Pharmacodynamics, immunogenicity, cytokine, and disease activity measures will be analyzed on this population.



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Additional interim access to the data may be performed as needed. The AC may be consulted by the study team for a recommendation if discontinuation from study treatment is considered when stopping rules are met (see Section 8.1 of the study protocol).

## 9.0 **Data Review**

Final data for analysis should always be cleaned prior to receipt by Clinical Programming. The purpose of this section is to indicate the history of the data and the process used to ensure that the data are acceptable for statistical analysis prior to database lock.

### 9.1 Data Handling and Transfer

The data handling and the data transfers from vendors are described in the Data Management Plan.

### 9.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word "Problem" and extracted from the logs by a SAS macro and sent to Data Management.

A TFL dry-run allows for further data screening and that the planned outputs are adequate to summarize the data. The PRA statistician and the sponsor must approve database lock.

# 10.0 Statistical Methods

## 10.1 Patient Disposition

The number and percentage of patients randomized and treated in the study and patients included in each analysis set will be presented, together with the number and percentage of patients who were replaced and withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal.

## 10.2 Important Protocol Deviations

Per PRA processes, important protocol deviations data will be entered into PRA's Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS. The deviation criteria may be adjusted throughout the study, as deemed appropriate. The final list of important protocol deviations will be used to create the PP population, and hence must be finalized prior to database lock at the post-freeze data review meeting (or earlier).

Important protocol deviations or violations (PDVs) for each subject will be reviewed on blinded data prior to database lock to evaluate whether the patient has been protocol compliant. Important PDVs were assessed as to whether or not they have a significant impact on the assessment of efficacy or safety.

Important protocol violations include, but are not limited to the following:

- Dosing non-compliance
- Prohibited concomitant medications/therapy
- Violation of Inclusion/Exclusion Criteria
- Blind has been compromised
- Those who developed withdrawal criteria but were not withdrawn
- Those who received the wrong treatment or incorrect dose

The number of patients with each type of important PDV will be tabulated and by deviation type for all patients in the safety population. A listing of all PDVs including deviation date, deviation category, and deviation description will be generated.

## 10.3 Treatments

### 10.3.1 Extent of Study Drug Exposure

The weekly treatment duration (days) of study drug (length of treatment week) and the percent compliance with study medication will be calculated for each patient at each visit as follows:

- Treatment duration (days) = date of last dose– date of the first dose + 1.
- Percent compliance = 100 x Total number of injections / expected number of injections
- Expected number of injections = largest integer less or equal (treatment duration / 14)

Summary statistics will be calculated for duration and percent compliance by treatment administered for the safety population.

The placebo treated patients of the cohorts will be pooled for the analysis if more than one cohort is analysed.

All dosing, compliance and drug administration will be provided as data listings.

### 10.3.2 Prior and Concomitant Medications

Medications received concomitantly with study drug, categorized by medication group and subgroup according to WHODRUG (Current Version or higher), will be summarized. The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each medication group and subgroup. ATC codes are merged to the medications and if possible will programmatically select one ATC code according the indication and route of administration.

## 10.4 Demographic and Baseline Characteristics

Subject demographic and baseline characteristic information listed as follows will be summarized descriptively and provided as listing:

**Demographics:**

- Sex (Female, Male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age (years)
- Baseline Weight (kg) and Height (cm)
- Baseline BMI ($kg/m^2$)

**Baseline characteristics:**

- PASI
- BSA
- sPGA
- Itch NRS
- PatGA
- TSS

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## 10.5 Efficacy Analysis

Clinical efficacy endpoints over time will be summarized by treatment. Treatment comparisons of continuous clinical endpoints will be explored using mixed-effects model for repeated measures. For binary/categorical clinical data, endpoints will be explored by logistic regression models for repeated measures and Fisher exact test.

CCI No formal statistical inference based on efficacy is planned to be made. No adjustment of Type I error will be performed.

### 10.5.1 Multiplicity

No adjustments will be made to adjust the performed efficacy analysis for multiplicity.

### 10.5.2 Pooling of Sites

Sites will be pooled for the statistical analysis.

### 10.5.3 Sensitivity Analyses

No sensitivity analyses are planned to explore the missing data mechanism for the primary analysis and any alternate analyses relaxing other assumptions.

### 10.5.4 Sub-group Analyses

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## 10.6 Pharmacokinetic Analyses

### 10.6.1 Pharmacokinetic Variables

Concentrations of LY3471851 will be collected in plasma over a dosing interval after the first dose and trough concentrations after repeat dosing.

PK parameters of LY3471851 will be calculated for plasma after the first dose.

### 10.6.2 Plasma Pharmacokinetic Summaries

#### 10.6.2.1 Plasma Concentrations

Plasma concentrations for LY3471851 below the quantifiable limit (BQL) will be set to 0 in the computation of summary statistics. Descriptive statistics (n, arithmetic mean, geometric mean, SD, coefficient of variation, median, min, and max) will be used to summarize the plasma concentrations at each scheduled timepoint and for each dose group. If the mean at a given timepoint is BQL, then the descriptive statistics will not be presented and will instead display as BQL for the mean and min. With the exception of number of subjects and max (unless also BQL, then BQL will be presented), all other statistics will be missing.

Linear (+/- SD) and semi-logarithmic (+ SD) plots of the arithmetic mean plasma concentrations by scheduled sampling time will be provided by dose group after the first dose (time in hours) and separately for all concentration data included (time in days)

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by subject (one subject per page). These plots will show time in hours/days as defined above for mean plots. Individual plots will use the BQL handling procedure described below for “Plasma Pharmacokinetic Parameters”.

All individual subject plasma concentration data will be listed by subject.

#### 10.6.2.2 Plasma Pharmacokinetic Parameters

Plasma PK parameters for LY3471851 will be estimated using non-compartmental methods with WinNonlin® after the first dose including data from day 1 (pre-dose) up to day 15 (sample prior to the second dose). The plasma PK parameters will be estimated from the concentration-time

profiles, and AUCs will be calculated using linear up / log down. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

It is expected that the terminal elimination phase will not be calculable with a sampling period of 15 days after the first dose. However the data will be reviewed to confirm this and if calculated the points to be included in the λz range will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used. The Cmax data point will not be included.

The pharmacokinetic analysis will estimate the pharmacokinetic parameters Cmax, Tmax, and AUC after the first dose as shown below and will quantify LY3471851 plasma concentrations following multiple SC doses in patients with PsO.

| Parameter | Description | CCI [redacted] |
|---|---|---|
| Cmax | Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units | CCI [redacted] |
| Tmax | Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units. | CCI [redacted] |
| AUClast | Area under the concentration-time curve (time 0 to time of last quantifiable concentration). | CCI [redacted] |
| AUCinf | Area under the plasma concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 20% is required to obtain a reliable AUCinf. | CCI [redacted] |
| λz | Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three points and an $r^2$ greater than 0.80 are required to obtain a reliable λz. | CCI [redacted] |
| t1/2 | Terminal phase half-life expressed in time units. Percent extrapolation less than or equal to 20% and $r^2$ greater than 0.80 is required to obtain a reliable $t_{1/2}$. | CCI [redacted] |
| AUC%extrap | Extrapolation area portion in AUCinf, expressed as percentage of AUCinf. | CCI [redacted] |
| $R^2$ | Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-time profile identified by least-squares linear regression and adjusted for the number of points | CCI [redacted] |
| Lz_Start | Lz_Start is the start time used in the regression for the determination of λz. | CCI [redacted] |
| Lz_End | Lz_End is the end time used in the regression for the determination of λz. | CCI [redacted] |
| Lz_N | Lz_N is the number of points used in the regression for the determination of λz. | CCI [redacted] |

If the WNL model approach cannot be applied parameters will be estimated by applying a non-compartmental analysis.

Descriptive statistics (number of subjects, mean, geometric mean, SD, %CV, geometric %CV, median, min, and max) will be used to summarize the calculated PK parameters by dose group. For Tmax, only median, min, and max will be presented.

In addition, trough plasma LY3471851 concentrations will be summarized after repeat dosing using descriptive statistics.

A mixed-effect modeling approach may be applied to all LY3471851 concentration-time data to develop a compartmental PK model in which parameters such as clearance and volume of distribution will be estimated.

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## 10.7 Other Efficacy Analyses

#### 10.7.1.1 Disease Activity Measures

The following continuous and binary disease activity clinical endpoints will be analyzed over time and summarized by treatment:

Continuous variables:

- PASI
- PASI %CFB
- TSS
- Itch NRS
- sPGA
- BSA
- PatGA

Categorical variables:

- PASI50
- PASI75,
- PASI90,
- sPGA(0,1)

Treatment comparisons of continuous clinical endpoints will be explored using mixed-effects for repeated measures.

The analysis will be applied for all subjects including data up to Day 134, In addition the analysis will be repeated for subject who are sustained PASI responders and met the criteria to enter the follow-up period.

P-values, LS mean differences and associated confidence intervals are presented for each treatment arm minus placebo treatment arm.

CCI No adjustment of Type I error will be performed.

Logistic regression models will be used for PASI50, PASI75, and PASI90 with treatment and the baseline PASI value as independent variable. The logistic regression model for sPGA(0,1) includes treatment and baseline sPGA as independent variable.

For responder analyses, repeated measures over time will be fit using generalized estimating equations using the procedure for generalized linear models in SAS (Proc GENMOD). Factors included in the model are treatment, visit, treatment-by-visit interaction, and baseline PASI or baseline sPGA.

#### 10.7.1.2 Evaluation of Immunogenicity

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples were collected to determine antibody production against LY3471851. A blood PK sample was collected at the same time points to determine the plasma concentrations of LY3471851. All samples for immunogenicity during the treatment period were taken predose.

Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3471851.

The frequency and percentage of patients with preexisting ADAs and with TE-ADAs to LY3471851 will be tabulated.

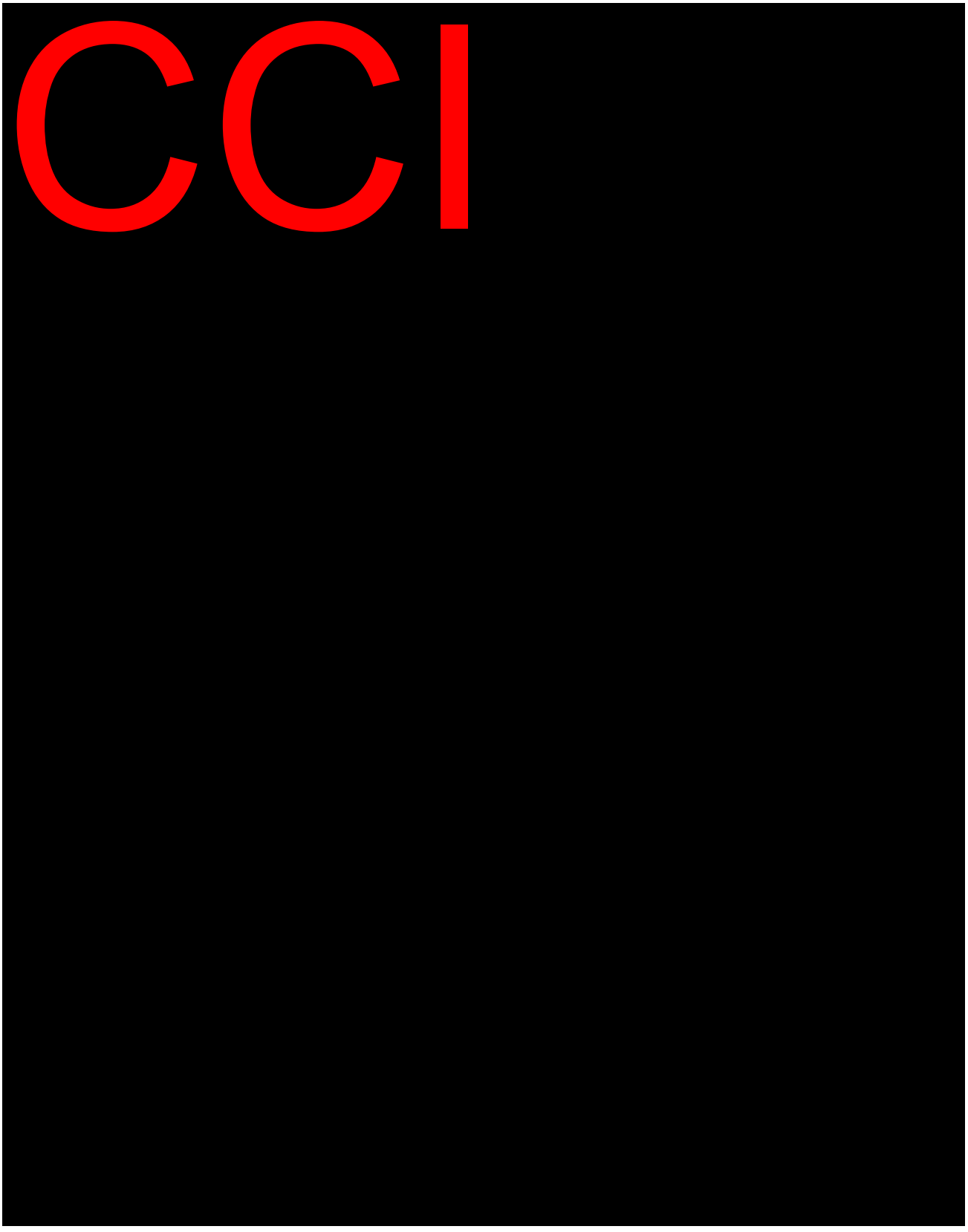
Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA) CCI The frequency of neutralizing antibodies will be tabulated in TE-ADA+ patients if assessed.

CCI

### 10.7.2 Pharmacodynamics

The PD parameters include changes in T-cell subsets, disease relevant cytokines and other immune cells.

Blood and tissue for PD analysis will be collected as shown in the Schedule of Activities.



Summaries over time for each of these will be provided along with line plots of mean observed values over time.

CCI [redacted]

[redacted]

CCI [redacted]

## 10.9 Safety Analyses

### 10.9.1 Adverse Events

A summary of treatment-emergent adverse events (TEAE), the number and percentage of patients reporting at least one TEAE, the number and percentage of patients discontinuing due to an adverse event, the number and percentage of patients with at least one serious adverse event, and the number and percentage of deaths will be presented.

A breakdown of the number and percentage of patients reporting each adverse event, categorized by body system and preferred term coded according to the MedDRA dictionary, will be presented. Note that counting will be by patient and patients are only counted once within each body system or preferred term.

A further tabulation of these data, categorized by relationship to study drug, will be presented. patients with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that body system or preferred term. Relationship to study drug is categorized as "related" or "not related" as recorded on the CRF. Adverse events with missing relationship will be counted as "related".

All summaries of TEAEs will consist of the number of events and the numbers and percentages of patients who had the events being summarized. For each SOC (System Organ Class) and PT (Preferred Term), patients are included only once, even if they experience multiple events in that SOC or PT.

TEAEs will also be summarized by maximum severity. For each event, patients are summarized corresponding to the most severe event among the events of that preferred term type reported. A patient who had a mild and a severe event of the same preferred term type would be summarized as severe for that event. If the severity is missing for an event, the event will be categorized as severe.

A separate summary table will be presented for the following categories of TEAEs:

- All TEAEs (by SOC, PT, and maximum severity)
- Serious TEAEs (by SOC, PT, and maximum severity)
- Treatment-related TEAEs (by SOC and PT)
- TEAEs leading to study discontinuation (by SOC and PT)
- TEAEs leading to death (as listings only)

TEAEs will be classified by SOC and PT using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AEs (including non-treatment-emergent events) recorded in the CRF will be listed for any patients with informed consent. No inferential statistics are planned.

Patients with multiple events within a particular body system or preferred term will be counted under the category of their most severe event within that body system or preferred term.

A further tabulation presenting the preferred terms for the events in descending order of frequency for the LY3471851 treatment group will also be presented.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

### 10.9.2 Deaths and Serious Adverse Events

Summaries of serious TEAEs and deaths will be presented by treatment and by MedDRA SOC and PT.

All data for serious adverse events (SAEs) and deaths will be listed.

### 10.9.3 Adverse Events of Special Interest

Clinical manifestations of cytokine release syndrome (CRS), defined by a constellation of symptoms including fever, nausea, chills, hypotension, tachycardia, rash, headache, chest discomfort, fatigue/generalized weakness, and dyspnea/shortness of breath, which typically occur in close temporal relationship with study drug administration in the absence of another obvious cause (e.g. infection) will be presented as adverse events of special interest in a separate frequency table.

### 10.9.4 Injection Site Assessment and Pain VAS scale

According to the Schedule of Activities, injection-site assessments were performed at the end of each visit on Day 1 through Day 99. The investigator asked the patient if she/he had any injection-site concern since the preceding visit or, when assessed on Day 1, since the first

injection. Patient's responses will be recorded per the Injection Site Assessment and Pain Visual Analog Scale tools to capture specific information relating to an injection site. CCI

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A summary table with number of subjects (frequencies) with any post-baseline injection site reaction, the number of events, and maximal severity categories as defined above will be presented by treatment.

An analysis will be provided using the total number of injections as denominator with the actual severity grading for each ISR associated with the injection.

Summary statistics will be calculated for all injection site reactions and the pain VAS scale for all injections.

These summaries will be provided by treatment for the safety population. No inferential statistics are planned.

A listing for the injection site reactions including anatomical site, onset time after the last injection, and duration will be presented sorted by treatment, subject ID and visit.

### 10.9.5 Laboratory Data

Clinical laboratory tests consist of hematology, chemistry, and urinalysis. Hepatic function (including AST, ALT, gamma-glutamyl transferase, ALP, lactate dehydrogenase, and TBL) will be summarized by descriptive statistics over time. A complete list of tests is provided in Appendix 2.

Summary statistics will be calculated for all hematology, serum chemistry, and urinalysis parameters for the screening visit, all study visits and early termination, and for change from baseline for continuous variables. These summaries will be provided by treatment for the safety population.

Low, normal, and high classifications will be applied to determine whether the laboratory test value was below (low), within (normal), or above (high) the reference range for that test. The number and percentage of subjects with shifts in their results from classification of baseline (low, normal, high) to classification of the minimum/maximum post-baseline (low, normal, high) will be presented.

Plots of average clinical laboratory parameters will be presented over time. Listings will be provided for hematology, serum chemistry, immunochemistry, urinalysis, urine drug screen, urine pregnancy, human immunodeficiency virus (HIV), and serology.

Liver function test data will also be provided in separate listings for:

- Subjects who possibly met Hy's Law criteria (ie, had any elevated ALT or AST of >3xULN, and increase in total bilirubin >=2xULN, and ALP <2xULN at the same visit)
- Subjects who met any one or more of the following criteria at any post-baseline visit (list laboratory parameters ALT, AST, ALP and total bilirubin only)
    - Either ALT or AST or both >=3xULN
    - ALP >1.5xULN
    - Total bilirubin >2xULN
- Subjects who had any elevated ALT or AST of >3xULN, and an increase in total bilirubin >1.5xULN at the same visit

A summary table will also be provided for number of subjects who met any of the criteria specified above at any post-baseline visit.

Additional safety data were collected, as per the July 2009 FDA "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation" documentation, if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests

- patient discontinued from treatment due to a hepatic event or abnormality of liver tests

### 10.9.6 Vital Signs

The observed data at baseline and change from baseline for each measurement visit will be summarized for each parameter with descriptive statistics. Plots of mean vital signs values (and standard error bars) over the treatment period and follow-up will be produced.

No inferential statistics are planned. Physical Examinations, ECGs, and Other Observations Related to Safety

### 10.9.7 Electrocardiogram Results

For each patient, a single 12-lead digital ECG was collected according to the Schedule of Activities. ECGs had to be recorded before collecting any blood for safety or PK tests. Unscheduled ECGs could be obtained at additional times, when deemed clinically necessary.

Digital ECGs were electronically transmitted from the investigator sites to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory conducted a full overread on ECGs (including all intervals). All data from the overreads were placed in the Lilly database for analytical and study report purposes.

Results for each ECG parameter will be summarized by treatment group at each visit for the observed data and for changes from baseline.

The overall ECG assessment as determined by the investigator will be reported as "Normal" or "Abnormal – not clinically significant", or "Abnormal – clinically significant" and summarized by visit and across visits. A shift table of overall ECG assessment from baseline to the most extreme post-baseline value will be presented.

Additionally, the highest post-baseline value for QTc interval (using Fridericia's correction) will be summarized descriptively as a categorical variable. Each QTcF value for a given subject will be grouped into 3 categories:

- QTcF interval ≥ 450 - <480 msec
- QTcF interval ≥ 480 - <500 msec
- QTcF interval ≥ 500 msec

The largest post-baseline change in QTcF measures will also be analyzed as categorical variables. The change in QTcF in a given subject will be grouped into 2 categories:

- QTcF interval increases from baseline ≥ 30 msec
- QTcF interval increases from baseline ≥ 60 msec

Relevant ECG data will also be displayed in separate listings for:

- Subjects who shifted from normal or abnormal not clinically significant at baseline to abnormal clinically significant during the treatment period

- Subjects who had an abnormal clinically significant assessment at any time during the study
- Subjects who ever had a QTcF interval increase from baseline ≥ 30 msec during the treatment period
- Subjects who ever had any value of QTcF interval ≥ 450 msec at any visit

### 10.9.8 Suicidality

#### 10.9.8.1 Columbia Suicide Severity Rating Scale

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred.

For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories. A listing will be provided for the C-SSRS.

#### 10.9.8.2 Self-Harm Supplement and Follow-up Forms

Suicide-related events (behavior and/or ideations) will be assessed and evaluated with each administration of the C-SSRS. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or non-suicidal self-injurious behaviors. If the number of behavioral events is greater than zero, it will lead to the completion of the Self-Harm Follow-up Form. The Self-Harm Follow-up form is a series of questions that provides a more detailed description of the behavior cases. Results will be listed for subjects who who completed the form.

### 10.9.9 Pregnancies

Any reported positive pregnancy results or reported pregnancies will be listed.

## 11.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

## 12.0 References

Kimball AB, Naegeli AN, Edson-Heredia E, Lin CY, Gaich C, Nikai E, Wyrwich K, Yosipovitch G. Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2016;175(1):157-162.

Naegeli AN, Flood E, Tucker J, Devlen J, Edson-Heredia E. The Worst Itch Numeric Rating Scale for patients with moderate to severe plaque psoriasis or psoriatic arthritis. Int J Dermatol. 2015;54(6):715-722.

## Appendix 1 Glossary of Abbreviations

| Abbreviation | Definition |
|---|---|
| **AC** | assessment committee |
| **ADA** | antidrug antibody |
| **AE** | adverse event |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **AST** | aspartate aminotransferase |
| **AUC** | area under the plasma concentration versus time curve |
| **BP** | blood pressure |
| **$C_{max}$** | maximum observed plasma concentration |
| **CRO** | clinical research organization |
| **CRS** | cytokine release syndrome |
| **C-SSRS** | Columbia Suicide Severity Rating Scale |
| **ECG** | electrocardiogram |
| **eCRF** | electronic case report form |
| **FDA** | Food and Drug Administration |
| **HCV** | hepatitis C virus |
| **HIV** | human immunodeficiency virus |
| **HR** | heart rate |
| **IL-2** | interleukin-2 |
| **IV** | intravenous |
| **IWRS** | interactive web-response system |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **NK** | natural killer |
| **NRS** | Numeric Rating Scale |
| **PASI** | Psoriasis Area and Severity Index |
| **PASI 50** | PASI score reduced by at least 50% relative to the baseline score |
| **PD** | pharmacodynamic(s) |
| **PEG** | polyethylene glycol |

| | |
|---|---|
| **PK** | pharmacokinetic(s) |
| **PP** | per-protocol |
| **PsO** | psoriasis |
| **PT** | preferred term |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **SC** | subcutaneous |
| **SOC** | system organ class |
| **sPGA** | static Physician's Global Assessment |
| **TBIL** | total bilirubin level |
| **Tcon** | conventional T |
| **TE-ADA** | treatment-emergent antidrug antibody |
| **TEAE** | treatment emergent adverse event |
| **Treg** | regulatory T |
| **TSS** | Total Sign Score |
| **ULN** | upper limit of normal |
| **WBC** | white blood cell |

## Appendix 2 Clinical Laboratory Tests

| Hematology | Chemistry | Serology |
|---|---|---|
| • Hemoglobin[a]<br>• Hematocrit[a]<br>• RBC<br>• WBC[a]<br>• Platelet count[a]<br>• Neutrophils (absolute)[a]<br>• Lymphocytes (absolute)<br>• Monocytes (absolute)<br>• Eosinophils (absolute)<br>• Basophils (absolute)<br>• Mean corpuscular volume (MCV)<br>• Mean corpuscular hemoglobin (MCH)<br>• Mean corpuscular hemoglobin concentration (MCHC)<br>• Peripheral blood mononuclear cell (PBMC) isolation | • AST (SGOT)[b]<br>• ALT (SGPT)[b]<br>• GGT[b]<br>• TBL[b]<br>• Alkaline phosphatase[b]<br>• LDH[b]<br>• Albumin<br>• Creatinine<br>• Glucose<br>• Total protein<br>• Sodium<br>• Potassium<br>• Chloride<br>• $CO_2$ content or bicarbonate<br>• Urea nitrogen | • Hepatitis B surface antigen (HBsAg)<br>• Hepatitis B core antibody (HBcAb+)<br>• Hepatitis C virus antibody (anti-HCV)<br>• Human immunodeficiency virus (HIV) antibody<br>**Drug and Alcohol Screening**<br>• Opioids (urine)<br>• Cocaine (urine)<br>• Amphetamines (urine)<br>• Cannabinoids (urine)<br>• Alcohol (urine)<br>**Pregnancy (for Women of Child-bearing Potential)**<br>• Serum human chorionic gonadotropin (hCG; mandatory for screening)<br>• Urine |

| **Urinalysis (by dipstick)** | |
|---|---|
| • Specific gravity<br>• pH<br>• Glucose<br>• Protein<br>• Bilirubin<br>• Ketones<br>• Leukocytes<br>• Blood | For positive protein, WBC or blood, a microscopic examination including:<br>• RBC<br>• WBC<br>• Epithelial cells<br>• Bacteria<br>• Crystals<br>• Casts |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase, LDH = lactate dehydrogenase; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TBL = total bilirubin level; WBC = white blood cell.

[a] Values for these parameters need to be in the normal range to be considered as normal hematologic function for the purpose of inclusion.

[b] These tests will constitute the additional testing of hepatic function.