Statistical Analysis Plan J1P-MC-KFAD (version 2.0)

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

NCT04081350

Approval Date: 21-Oct-2022

Statistical Analysis Plan

Sponsor:	Eli Lilly and Company
Protocol:	J1P-MC-KFAD(b)
PRA Project Id:	J1P-MC-KFAD
Version Date:	21-Oct-2022
Version No.:	2.0

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 Atopic Dermatitis
CRF Version No./Date:	3.0/16-Oct-2020

1.0 Approvals

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

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-KFAD 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 atopic dermatitis (AD).

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 atopic dermatitis.

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 atopic dermatitis (AD).
- To quantify LY3471851 plasma concentrations following multiple SC doses in patients with AD.

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 AD involving ≥10% body surface area in the affected skin and an Eczema Area and Severity Index (EASI) score of ≥16 at screening.

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

Cohort 1 stopped enrolling new subjects in March 2020 at the time of the coronavirus disease 2019 (COVID-19) pandemic and will remain on hold until interim reviews of safety, efficacy, PK, and PD data from Cohort 2 are performed.

A first interim review is planned when approximately 8 patients from Cohort 2 have had the opportunity to complete, at a minimum, the Week 6 visit. The second interim review is planned when approximately 16 patients from Cohort 2 have had the opportunity to complete, at a minimum, the Week 12 visit. Based on the first and/or the second interim reviews from Cohort 2, Cohort 1 may be restarted at the same dose or a different dose or may be terminated.

When the study restarted, enrollment began in Cohort 2 with a dose of 24 µg/kg every 2 weeks. The initiation of Cohort 2 was 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 25 patients with AD will be enrolled in each cohort for a maximum of 2 cohorts (50 patients). This will allow approximately 20 patients completing the study 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 based on 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 EASI 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 EASI 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 clinical research organization 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 • To evaluate the safety and tolerability of multiple SC doses of LY3471851 administered to adult patients with AD	Incidence of adverse events, treatment-emergent adverse events, and serious adverse events
Secondary • To quantify LY3471851 plasma concentrations following multiple SC doses in patients with AD	Cmax., Tmax, and AUC after the first dose and trough concentrations after repeated dosing
CCI	

Objectives	Endpoints
CCI	

Abbreviations: AD = atopic dermatitis; AUC = area under the plasma concentration-time curve; BSA = body surface area; Cmax = maximum observed plasma concentration; CCI

CCI

5.5 Safety Endpoints

5.5.1 Adverse Events

Treatment-emergent adverse events(TEAE) will be used for the presentation of adverse events. Treatment-emergent adverse events are those that first occur or increase in severity or relationship to the study drug after the first dose of the 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 the 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 the 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 functions (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 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 the 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. CCI

CCI

5.5.6 Physical Examination

Physical examinations included an examination of all major organ systems. Prior to the dose of the 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

5.7 Other Endpoints and Variables

CCI

5.8 Covariates and Prognostic Factors

Pre-determined covariates or prognostic factors are not planned for the analysis.

6.0 Definitions

Baseline is defined as the last measurement prior to the first injection of the 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 the baseline is not defined and is 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.

CCI

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

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

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 the first injection through the Last Study Visit (CCI

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 an End of Study CRF page is completed indicating the 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.
- 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 below. These will apply to AE and concomitant medications when applicable.

For the purpose of inclusion in TEAE and concomitant medication tables, incomplete start 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 the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow protocol.

CCI

Safety analysis population

All randomized patients who receive at least 1 dose of the 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 (PP) analysis population

The per-protocol population (PP) will be a subset of the intent-to-treat 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 the 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.

Pharmacokinetic (PK) analysis population

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

Pharmacodynamic (PD) analysis population

The PD analysis population is a subset of the ITT population and includes all subjects that have available information on one of the following assessments: Pharmacodynamics, immunogenicity, cytokine, and disease activity measures. Only the parameters of these assessments will be analyzed on this population.

Adjusted Populations

Due to performance issues at Site 200, a certain analysis will be performed excluding all subjects from this site. Hence, all populations noted above will be generated excluding patients from this site. Those populations will be named using adjusted as a prefix. For E.g. the adjusted Intent to treat population (a-ITT) will be a subset of the ITT excluding patients from site 200. For interim analyses, outputs will be generated using the adjusted populations, and all outputs of PK and PD parameters will be done on both populations. The final analysis will be conducted on the adjusted populations. Data listings will include all subjects.

CCI

9.0 Data Review

Final data for analysis should always be cleaned prior to receipt by 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 the planned outputs are adequate to summarize the data. The PRA statistician and the sponsor must approve the 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 population will be presented, together with the number and percentage of patients who were replaced and discontinued from the study prematurely and a breakdown of the corresponding reasons for discontinuation.

10.2 Important Protocol Deviations

Per PRA processes, important protocol deviation data will be entered into PRA's Clinical Trials Management System (CTMS). The study team and the sponsor will conduct ongoing 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
- Violation of key 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 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 analyzed.

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 to 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:

CCI

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. Comparisons will also be made between placebo and LY3471851 using a composite Estimand strategy where the intercurrent events of premature discontinuation and use of prohibited medication will be considered. For summary of continuous endpoints such as change from baseline and percentage change from baseline of CCI will be presented using the composite strategies with subjects either discontinued or used the prohibited medication will be excluded from that visit and later in the analyses. For binary endpoints such as CCI, a subject will be considered a non-responder if any one of the intercurrent events specified above is met.

CCI

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

Pre-specified sub-group analyses are not planned for the study but may be conducted exploratory.

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 time point 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 Log Trapezoidal method. 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.

Parameter	Description	SAS Programming Notes
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL
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.	Tmax from WNL
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	AUClast from WNL
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.	AUCINF_obs from WNL If AUC_%Extrap_obs >20% then parameter is not included
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 r2 greater than 0.80 are required to obtain a reliable λz.	Lambda_z from WNL If Rsq ≤ 0.80, then parameter is not included
t1/2	Terminal phase half-life expressed in time units. Percent extrapolation less than or equal to 20% and r2 greater than 0.80 is required to obtain a reliable t1/2.	HL_Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ 0.80, then parameter is not included
AUC%extrap	Extrapolation area portion in AUCinf, expressed as percentage of AUCinf.	AUC_%Extrap_obs from WNL
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	Rsq from WNL
Lz_Start	Lz_Start is the start time used in the regression for the determination of λz.	Lambda_z_lower from WNL
Lz_End	Lz_End is the end time used in the regression for the determination of λz.	Lambda_z_upper from WNL

Lz_N	Lz_N is the number of points used in the regression for the determination of λz.	No_points_lambda_z from WNL

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.

Additional PK analyses may be conducted as appropriate.

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 as per the schedule of activities in the KFAD Protocol Amendment C and summarized by treatment:

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 Visit 16 which is Day 134 (+/- 3 days). CCI

LS means, standard errors, confidence intervals, and p-values are from a mixed model repeated measures (MMRM) model on the response variable change from baseline and percentage change from baseline for the efficacy variable with fixed factors for treatment, time, and treatment-by-time interaction, baseline as a covariate, and subject as a random effect. An unstructured covariance matrix will be used to account for within-subject variability.

Respective estimates, confidence intervals, and p-values are derived for Placebo and Total LY3471851 from a model with two treatment arms (Pooled Placebo, Total LY3471851). Estimates for the individual doses of LY3471851will be derived using a model with four treatment arms (Pooled Placebo, 10 µg/kg LY3471851, 12 µg/kg LY3471851, and 24 µg/kg LY3471851). Differences are derived for treatment vs placebo. P-values, LS mean differences, and associated confidence intervals are presented for each treatment arm minus the placebo treatment arm.

CCI

CCI

CCI

CCI

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 antidrug antibodies (ADAs) and with treatment-emergent antidrug antibodies (TE-ADAs) to LY3471851 will be tabulated.

CCI

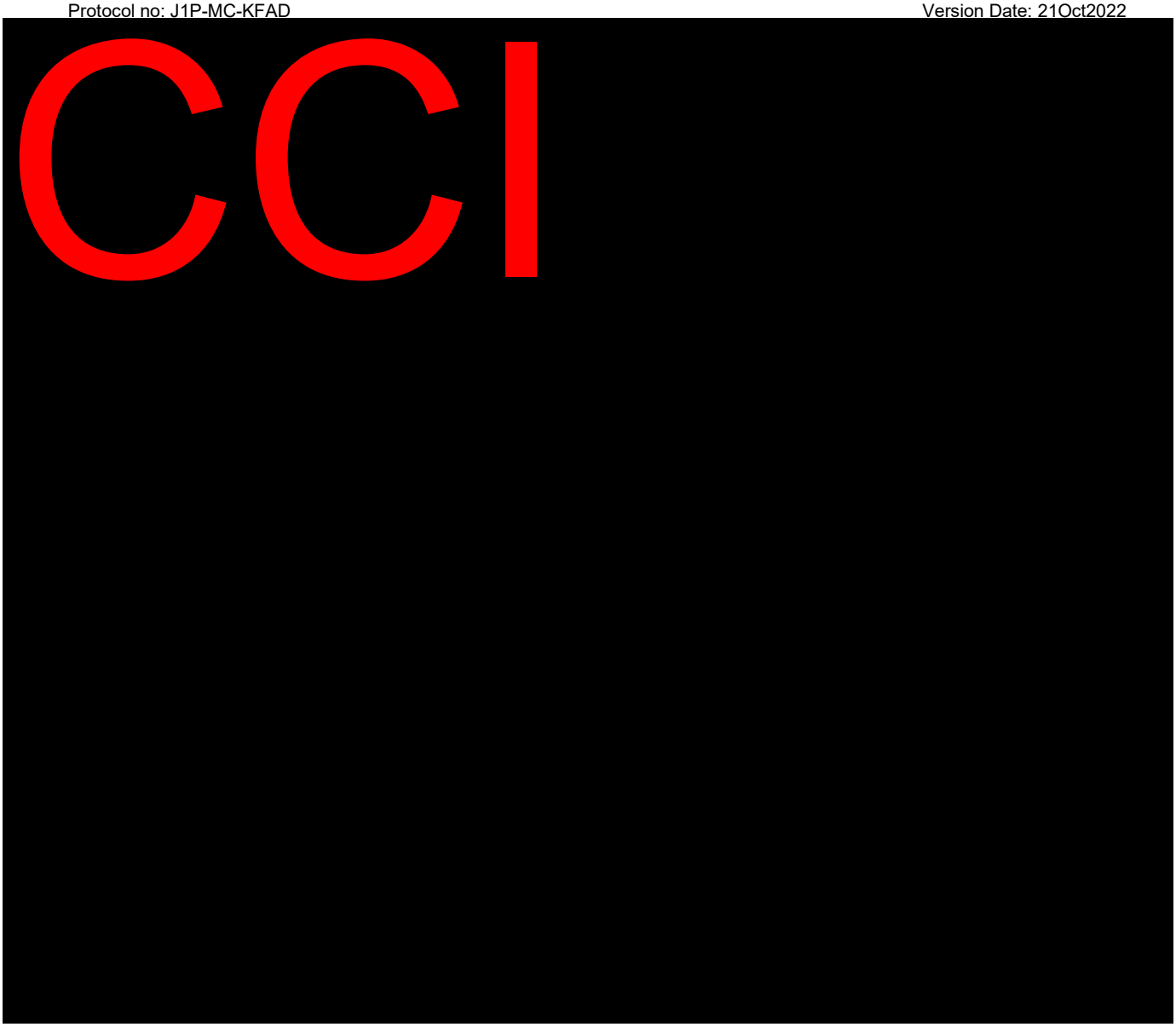
CCI

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.

CCI



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 TEAE, categorized by body system and preferred term coded according to the MedDRA dictionary, will be presented.

A further tabulation of these data, categorized by relationship to the 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 the 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.

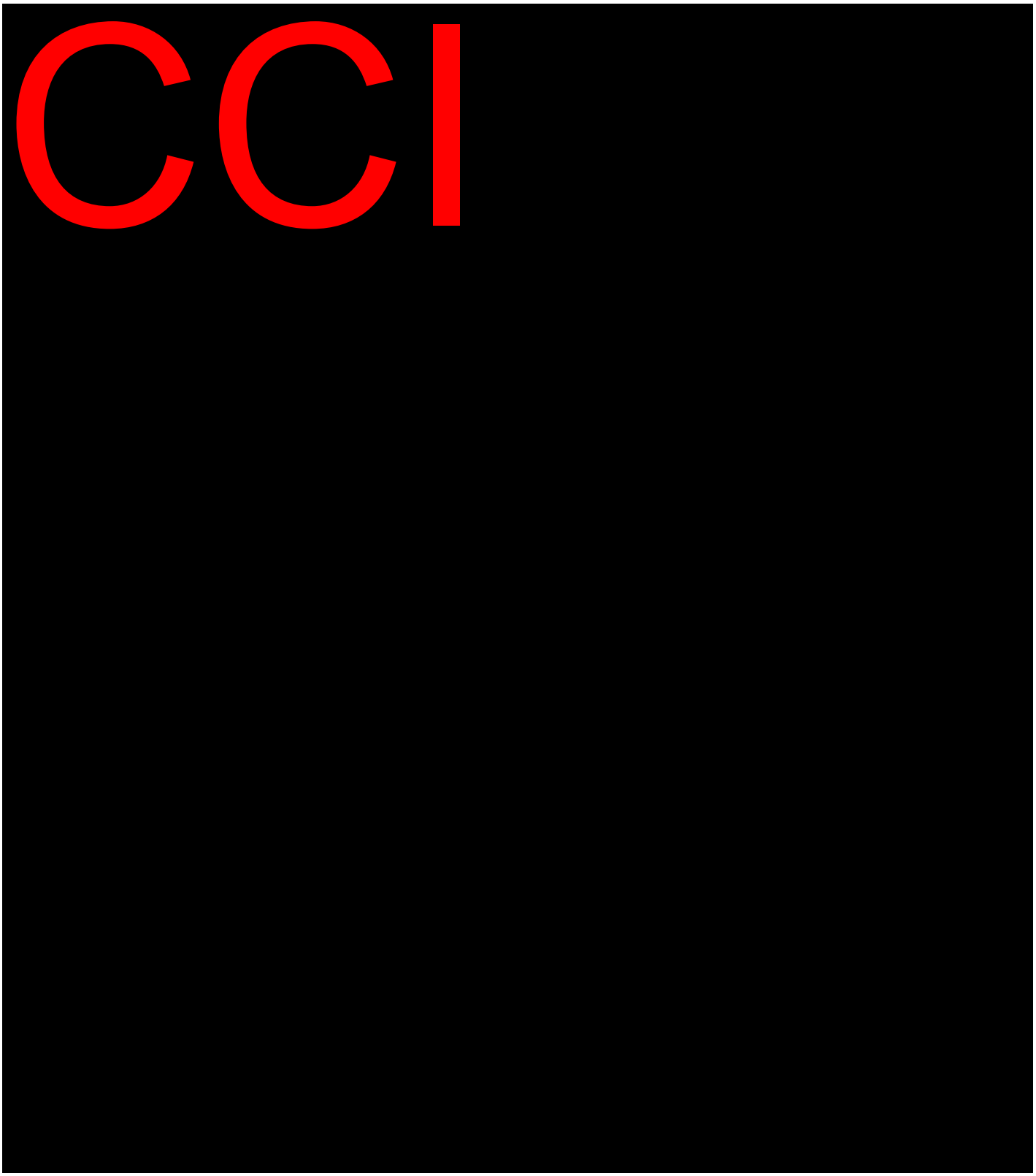
In addition, the above tables will be repeated for an adapted treatment-emergent adverse event definition, which considers a TEAE to be any AE occurring between the first dose date up to 15 days after week 12 of treatment. Tables will refer to TEAE-2 to distinguish the overall definition from the adapted definition.

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

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.



10.9.4 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 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. CCI

CCI

A summary table will also be provided for the 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 treatment due to a hepatic event or abnormality of liver tests

10.9.5 Vital Signs

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

Vital sign measurements are considered out of range if

- 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, or
- Fever: >38°C (100.4°F).

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.

10.9.6 Physical Examinations

Physical examinations will include an examination of all major organ systems including the following categories:

general appearance	hematologic/lymphatic	gastrointestinal
head	respiratory	extremities
eyes	cardiovascular	integumentary
ear/nose/mouth/throat	chest	psychiatric
neck	abdomen	

Frequencies of by timepoint will be created for physical examination by treatment and organ systems.

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 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

QTcF interval increase from baseline ≥ 30 msec during the treatment period or any value of QTcF interval ≥ 450 msec at any visit are considered to be criteria for potentially clinically important (PCI) values.

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 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

Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27-33.

Charman CR, Venn AJ, Williams, HC. The Patient-Oriented Eczema Measure. Arch Dermatol. 2004;140:1513-1519.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001;10(1):11-18.

Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. Br J Dermatol. 2002;147(suppl 62):25-54.

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.

Scarisbrick JJ, Morris S. How big is your hand and should you use it to score skin in cutaneous T-cell lymphoma? Br J Dermatol. 2013;169(2):260-265.

Appendix 1. Glossary of Abbreviations

Abbreviation	Definition
AC	assessment committee
AD	atopic dermatitis
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
CRS	cytokine release syndrome
C-SSRS	Columbia Suicide Severity Rating Scale
CCI	
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
CCI	
IL-2	interleukin-2
IV	intravenous
IWRS	interactive web-response system
MedDRA	Medical Dictionary for Regulatory Activities
CCI	

PD	pharmacodynamic(s)
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PP	per-protocol
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
CCI	
TE-ADA	treatment-emergent antidrug antibody
TEAE	treatment emergent adverse event
CCI	
TSS	Total Sign Score
ULN	upper limit of normal
CCI	
WBC	white blood cell
WNL	WinNonlin – software facilitating PK/PD analyses

Appendix 2. Clinical Laboratory Tests

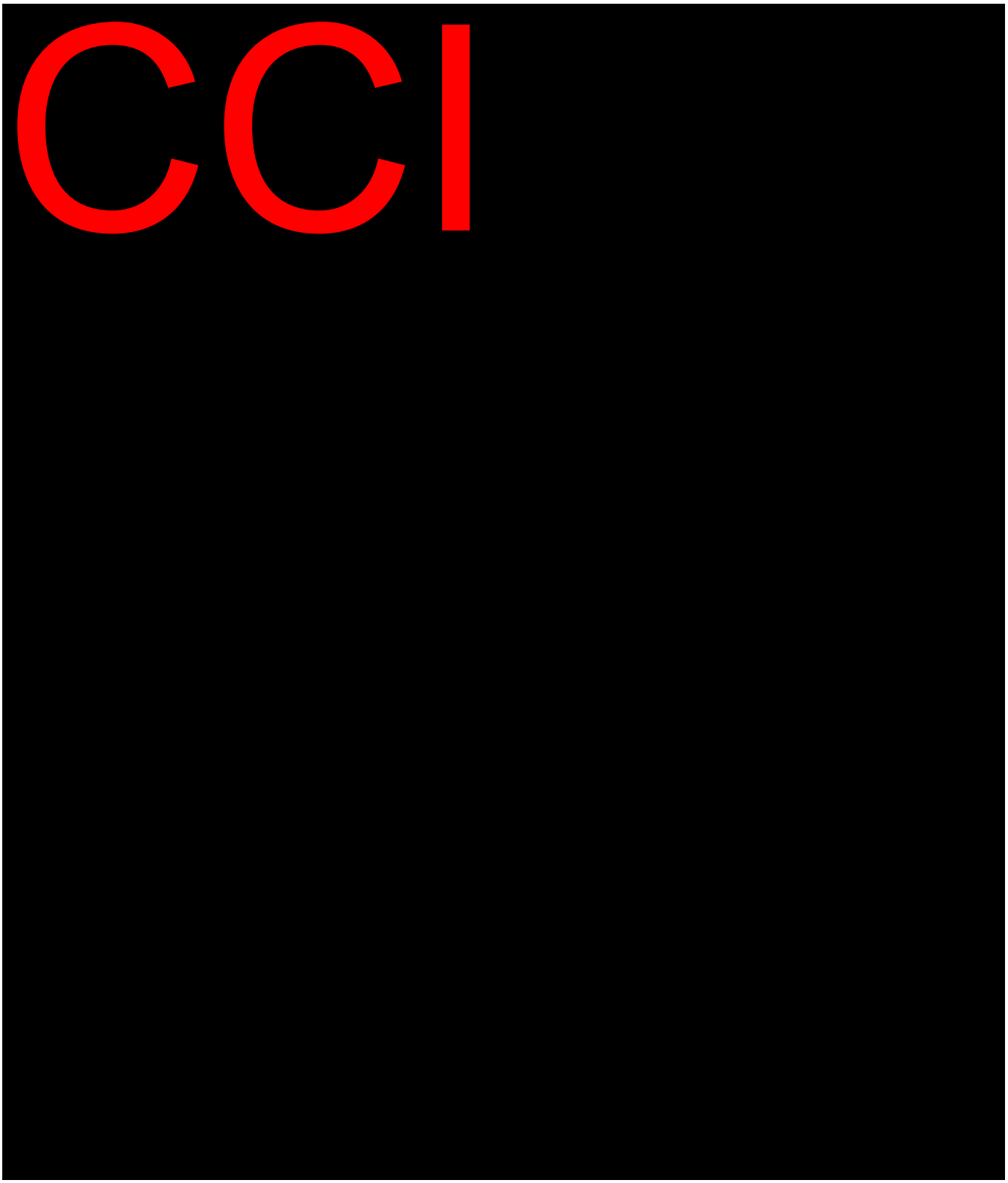
Hematology	Chemistry	Serology
• Hemoglobin[a] • Hematocrit[a] • RBC • WBC[a] • Platelet count[a] • Neutrophils (absolute)[a] • Lymphocytes (absolute) • Monocytes (absolute) • Eosinophils (absolute) • Basophils (absolute) • Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Peripheral blood mononuclear cell (PBMC) isolation	• AST (SGOT)[b] • ALT (SGPT)[b] • GGT[b] • TBL[b] • Alkaline phosphatase[b] • LDHb • Albumin • Creatinine • Glucose • Total protein • Sodium • Potassium • Chloride • CO2 content or bicarbonate • Urea nitrogen	• Hepatitis B surface antigen (HBsAg) • Hepatitis B core antibody (HBcAb+) • Hepatitis C virus antibody (anti-HCV) • Human immunodeficiency virus (HIV) antibody **Drug and Alcohol Screening** • Opioids (urine) • Cocaine (urine) • Amphetamines (urine) • Cannabinoids (urine) • Alcohol (urine) **Pregnancy (for Women of Child-bearing Potential)** • Serum human chorionic gonadotropin (hCG; mandatory for screening) • Urine

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



CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI