J1P-MC-KFAH Statistical Analysis Plan Version 1

An Adaptive Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3471851 (NKTR-358) in Patients with Moderately to Severely Active Ulcerative Colitis

NCT04677179

Approval Date: 18 Mar 2022

Protocol Title: An Adaptive Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3471851 (NKTR-358) in Patients with Moderately to Severely Active Ulcerative Colitis

Protocol Number: J1P-MC-KFAH

Compound Number: LY3471851

Short Title: INSTRUCT-UC

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

Registry	ID
IND	151216
EudraCT	2020-003017-35

Approved on 18 Mar 2022 GMT

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Version history

This Statistical Analysis Plan (SAP) for study J1P-MC-KFAH (KFAH) is based on the protocol dated 18Nov2020 and approved prior to unblinding.

Table KFAH.1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version

1. Introduction

Study J1P-MC-KFAH is an adaptive Phase 2, randomized, double-blind, placebo-controlled trial of LY3471851 (NKTR-358) in patients with moderately to severely active ulcerative colitis.

There are no changes to the analyses described in the protocol.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To determine whether LY3471851 is superior to placebo in inducing clinical remission at Week 12 in patients with moderately to severely active ulcerative colitis (UC)	• The difference in the proportion of participants who achieve clinical remission based on MMS at Week 12 without permanently discontinuing treatment
Secondary	
• To evaluate the efficacy of induction treatment with LY3471851 compared to placebo with respect to clinical, endoscopic, and histologic improvement	• The difference between LY3471851 and placebo in the proportion of participants who have not permanently discontinued at Week 12 and have achieved at Week 12: o clinical response o endoscopic remission o endoscopic response o symptomatic remission o symptomatic response o histologic remission o histologic-endoscopic mucosal healing
• To evaluate the efficacy of maintenance treatment with LY3471851 compared to placebo with respect to clinical,	• The difference between LY3471851 and placebo in the proportion of participants who were responders at

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endoscopic, and histologic improvement	Week 12 (Week 12 Responders) and have not permanently discontinued at Week 52, who at Week 52 still have: ○ clinical remission ○ clinical response ○ endoscopic remission ○ endoscopic response ○ symptomatic remission ○ symptomatic response ○ histologic remission ○ histologic-endoscopic mucosal healing
• To evaluate the efficacy of treatment with LY3471851 compared to placebo with respect to patient-reported outcomes and quality of life measures	• Comparison of mean changes from baseline to Week 12 and to Week 52 in scores for ○ IBDQ ○ Urgency NRS ○ Abdominal Pain NRS ○ Nocturnal Stools ○ Bristol Stool Scale ○ PGR-S ○ Fatigue NRS
• To evaluate the PK of LY3471851	• Week 12 LY3471851 trough concentrations
Tertiary/Exploratory	
CCI [redacted]	

Abbreviations: CCI ; IBDQ = Inflammatory Bowel Disease Questionnaire; MMS = modified Mayo score, NRS = numeric rating scale; PGR-S = Patient's Global Rating of Severity; PK = pharmacokinetics; UC = ulcerative colitis; CCI .

Primary estimand

The primary clinical question of interest is: What is the intervention difference in successful response rate of clinical remission based on MMS at Week 12 of intervention in patients with moderately to severely active UC, where successful response is defined as patient who achieves clinical remission without discontinuing treatment, without increasing mandatory stable medications, and without taking prohibited medications prior to the time point of interest? The primary comparison will be assessed using a composite estimand strategy to address the intercurrent events.

The estimand is described by the following attributes:

Population: patients with moderately to severely active UC. Further details can be found in Section 3.

Endpoint: clinical remission based on MMS at Week 12 in MMS.

Treatment condition: the randomized treatment without rescue medication or change in background medication (treatment policy strategy). Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.

The 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention” are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

Population-level summary: difference in proportion of participants achieving clinical remission at Week 12 between intervention conditions.

Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will be categorized as nonresponder.

Secondary estimands

1) Clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 12

The secondary clinical question of interest is: What is the intervention difference in successful response rate of clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 12 of intervention in patients with moderately to severely active UC, where successful response is defined as patient who achieves clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing without discontinuing treatment, without increasing mandatory stable medications, and without taking prohibited medications prior to the time point of interest? The secondary comparisons will be assessed using a composite estimand strategy to address the intercurrent events.

The estimand is described by the following attributes:

Population: patients with moderately to severely active UC who have not permanently discontinued at Week 12 and have achieved at Week 12. Further details can be found in Section 3.

Endpoint: clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 12.

Treatment condition: the randomized treatment without rescue medication or change in background medication (treatment policy strategy). Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.

The 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention “ are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

Population-level summary: difference in proportion of participants achieving clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 12 between intervention conditions.

Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will be categorized as nonresponder.

2) Clinical remission / clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 52

The secondary clinical question of interest is: What is the intervention difference in successful response rate of clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 52 of intervention in patients with moderately to severely active UC, where successful response is defined as patient who achieves clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing without discontinuing treatment, without increasing mandatory stable medications, and without taking prohibited medications prior to the time point of interest?

The estimand is described by the following attributes:

Population: patients with moderately to severely active UC who were responders at Week 12, have not permanently discontinued at Week 52, have achieved at Week 52. Further details can be found in Section 3.

Endpoint: clinical remission / clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 52.

Treatment condition: the randomized treatment without rescue medication or change in background medication (treatment policy strategy). Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.

The 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention “ are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

Population-level summary: difference in percentage of participants achieving clinical remission / clinical response / endoscopic remission / endoscopic response / symptomatic remission / symptomatic response / histologic remission / histologic-endoscopic mucosal healing at Week 52 between intervention conditions.

Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will be categorized as nonresponder.

3) IBDQ / Urgency NRS / Abdominal Pain NRS / Nocturnal Stools / Bristol Stool Scale / PGR-S / Fatigue NRS

The secondary clinical question of interest is: What is the intervention difference in IBDQ / Urgency NRS / Abdominal Pain NRS / Nocturnal Stools / Bristol Stool Scale / PGR-S / Fatigue NRS at Week 12 and Week 52 of intervention in patients with moderately to severely active UC regardless of intervention discontinuation for any reason and regardless of initiation of rescue intervention or change in background intervention?

The estimand is described by the following attributes:

Population: patients with moderately to severely active UC. Further details can be found in Section 3.

Endpoint: IBDQ / Urgency NRS / Abdominal Pain NRS / Nocturnal Stools / Bristol Stool Scale / PGR-S / Fatigue NRS at Week 12 and Week 52.

Treatment condition: the randomized treatment without rescue medication or change in background medication (treatment policy strategy). Further details on study interventions and concomitant, including rescue, interventions can be found in Section 6.

The 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention “ are both addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

Population-level summary: difference in mean change in IBDQ / Urgency NRS / Abdominal Pain NRS / Nocturnal Stools / Bristol Stool Scale / PGR-S / Fatigue NRS at Week 12 and Week 52 between intervention conditions.

Rationale for estimand: The data collected after the treatment discontinuation or post-rescue medication will not represent the true efficacy effects.

1.2. Study Design

Study KFAH is an adaptive Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of multiple dose levels of LY3471851 in adult patients with moderately to severely active UC. Enrolled study participants will have either

- an inadequate response to, loss of response to, or be intolerant to corticosteroid or immunomodulator therapy for UC (termed "conventional-failed"), or
- an inadequate response to, loss of response to, or are intolerant to biologic or JAK inhibitor therapy for UC (termed "advanced therapy-failed").

Study Stages

This adaptive study has two stages.

Stage 1: Approximately 100 participants will be randomly assigned to one of three treatment groups, including placebo. Interim analyses will be conducted for safety, dosing tolerability, and efficacy. These interim analyses will determine the doses to be used in Stage 2.

Note: Participants enrolled during Stage 1 of the study will remain on their randomly assigned Stage 1 doses. Their doses will be changed only if necessary due to safety reasons or due to their clinical response status at the end of Stage 1.

Stage 2: Approximately 100 additional study participants will be enrolled and randomly assigned to study treatment groups as well as placebo. The treatment doses used in Stage 2 may include any of the doses used in Stage1, as well as one or more additional LY3471851 doses, not exceeding1800 µg. The Stage 2 LY3471851 treatment doses will be determined by the sponsor based on results of the Stage 1 interim analyses and recommendations of the sponsor's IAC. A small group of sponsor personnel having pre-identified roles and no contact with investigative sites may review the IAC recommendation and may also review unblinded data in order to further assess the recommendation. The IAC charter that describes the process for internal decision-making and action plan will be provided.

Thus, whereas Stage 1 will have three treatment groups (including placebo), Stage 2 could have more treatment groups or fewer (including placebo).

The sponsor intends for the transition from Stage 1 to Stage 2 to be seamless, with participant screening and enrollment activities occurring continuously in the transition period. The study IWRS will allocate newly enrolling participants to groups according to the Stage 1 randomization ratio until the Stage 2 groups have been decided upon and implemented. The randomization ratios are described in Section 1.2.1.

Study Periods

This study has multiple periods.

Screening period

This period begins with Visit 1, which occurs 5 weeks (or less) before the planned randomization visit. A participant's screening evaluations must be completed and reviewed to confirm the participant's eligibility before randomization and dosing occurs at Visit 2.

Blinded induction and blinded maintenance periods

The double-blind, placebo-controlled, 12-week induction treatment period begins at Visit 2. Dosing, sample collection, and assessments continue Q2W, as shown in the SOA in the protocol. Between Week 12 and Week 14, based on samples and assessments collected at Week 12, participants will be classified as either "Week 12 Responders" or "Week 12 Nonresponders" based on the "clinical response" criteria defined in the protocol.

- "Week 12 Responders" will continue to receive their same randomly assigned treatment throughout the blinded 40-week Maintenance Period, with the final dose occurring at Week 50 and the last maintenance assessments and sample collections at Week 52.
- "Week 12 Nonresponders" will enter the Extension Induction and Extension Maintenance Periods.

Extension induction and maintenance periods

Beginning at Week 14, participants who were classified as Week 12 Nonresponders will receive the high dose (CCI µg) of LY3471851 Q2W, unless a lower dose is selected for Stage 2 based on interim analyses.

Between Week 26 and Week 28, based on samples and assessments collected at Week 26, these participants will again be classified according to their clinical response status based on MMS (responder or nonresponder).

- Participants who are classified as responders based on the samples and assessments at Week 26 will continue to receive LY3471851 Q2W as maintenance through the remainder of the study. These participants have their final dose at Week 50 and their last maintenance assessments and sample collections at Week 52.
- Participants who are classified as nonresponders based on the Week 26 samples and assessments will be permanently discontinued from study drug when his/her status as a nonresponder has been determined; such participants will enter the post-treatment follow-up period.

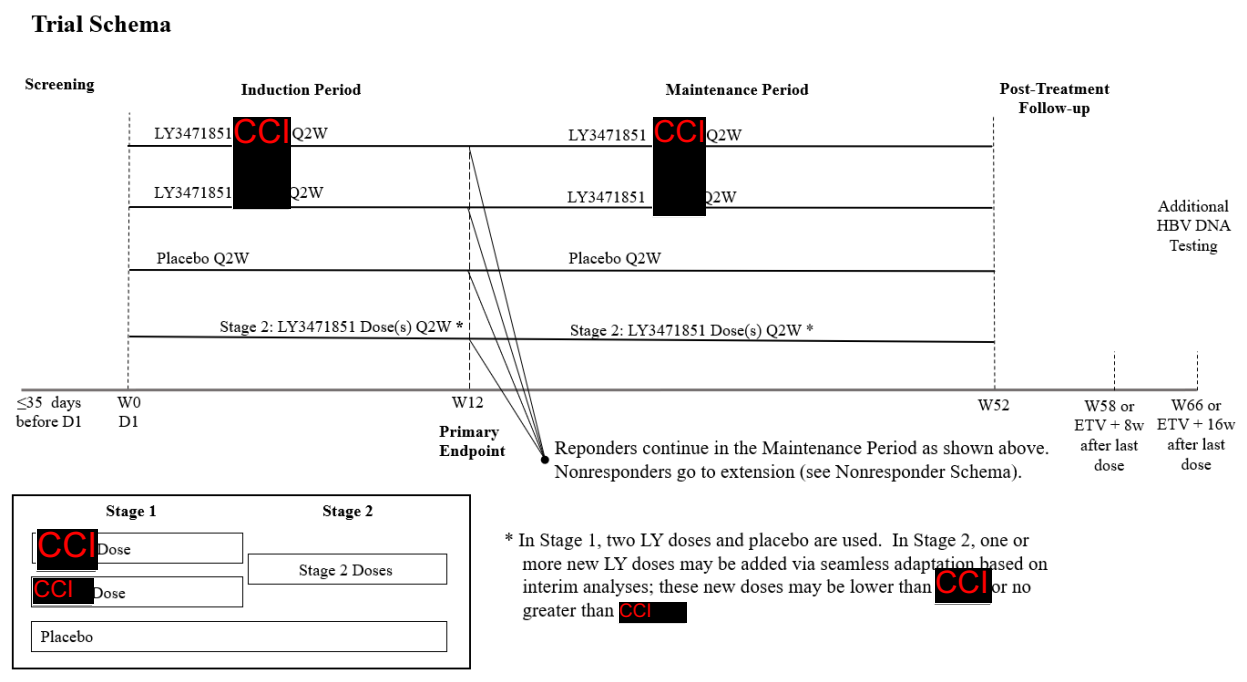
Post-treatment follow-up period

All participants will have a post-treatment follow-up visit (Visit 801) for safety assessments. Visit 801 occurs approximately 6 weeks after the Week 52 visit. The last dose of study drug is given at Week 50. Thus, participants will have been withdrawn from study drug for approximately 8 weeks at Visit 801. Participants who were positive for anti-HBc at screening will have one additional post-treatment follow-up visit (Visit 802).

Early discontinuation

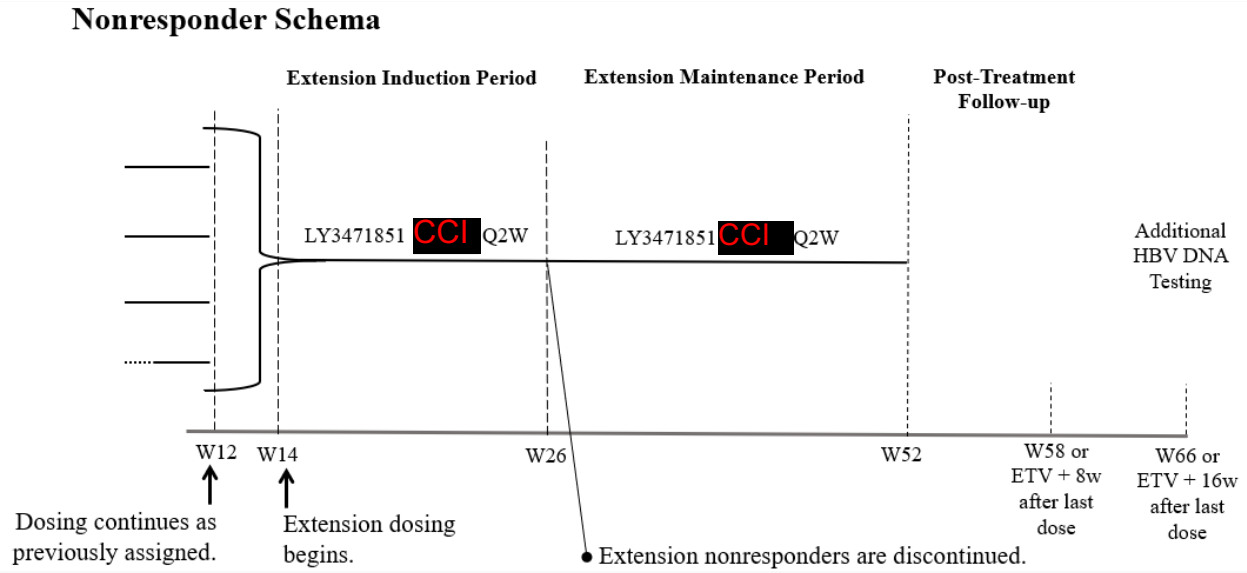
Participants who permanently discontinue the study drug early or withdraw from the study will undergo early termination procedures, including an ETV and the post-treatment follow-up visits specified in the SoA.

Figure KFAH.1 and Figure KFAH.2 show the study design.



Abbreviations: D = day; DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; LY= LY3471851; Q2W = every 2 weeks; W = Week; w = weeks.

Figure KFAH.1. Study Schematic (Induction and Maintenance Periods)



Abbreviations: DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; Q2W = every 2 weeks; W = Week; w = weeks.

Note: The extension dose could be lower than CCI µg LY3471851, based on interim analyses.

Figure KFAH.2. Study Schematic (Nonresponder Extension Periods)

1.2.1. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to treatment at the baseline visit. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS), and then the site will be responsible for administering the treatment to the patients.

During Induction Period in Stage 1, approximately 100 participants will be randomized to 1 of 3 treatment groups in a 2:2:1 ratio:

- CCI µg LY3471851 Q2W SC,
- CCI µg LY3471851 Q2W SC, or
- placebo.

During Induction Period in Stage 2, up to approximately 100 additional participants will be randomized. The number of treatment groups and randomization ratio for Stage 2 will be determined and documented based on the last interim analysis of Stage 1. This decision making will occur following Stage 1, and the choice in allocation ratio including placebo may be adjusted to achieve the planned allocation across treatment arms.

The randomization will be stratified based on the following factors:

- previous advanced therapy failure status (yes/no)
- baseline corticosteroid use (yes/no), and
- baseline disease activity (MMS: [4 to 6] or [7 to 9]).

After the Induction Period, participants enter either Maintenance Period or Extension Induction and Extension Maintenance Periods, based on samples and assessments collected at Week 12, as described in Section 1.2.

2. Statistical Hypotheses

The primary objective is to demonstrate that LY3471851 is superior to placebo in achieving clinical remission at Week 12. Thus, the null hypothesis to be tested in relation to the primary estimand is that LY3471851 is not different from placebo with respect to the achievement of clinical remission at Week 12.

2.1. Multiplicity Adjustment

Multiplicity adjustment will not be employed in the analysis for this study.

3. Analysis Sets

Table KFAH.2 describes the populations planned for use in the analyses. The mITT population, as defined below, will be used in analyses of efficacy and PRO, unless otherwise noted in the SAP.

Table KFAH.2. Analysis Populations

Population	Description
ITT Population	All randomized participants. Participants will be analyzed according to the treatment to which they were assigned.
mITT Population	All randomized participants who receive at least 1 dose of study treatment (regardless of whether the participant fails to receive the correct treatment, or otherwise fails to follow the protocol). Participants will be analyzed according to the treatment to which they were assigned.
Safety Population	Same as mITT population
Pharmacokinetic Evaluable	All participants who receive at least 1 dose of investigational product and have sufficient blood sampling to allow for pharmacokinetic evaluation.

Abbreviations: GCP = Good Clinical Practice; ITT = intent-to-treat; mITT = modified intent-to-treat; SAP = statistical analysis plan.

Analyses of the maintenance dosing period and the extension periods will be based on the corresponding enrolled population as described in the table above.

4. Statistical Analyses

4.1. General Considerations

This SAP is intended to describe the analyses of all objectives, as well as safety assessments, for study KFAH.

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter Lilly) or its designee. For primary and key secondary objectives, statistical analyses will be performed using SAS® Enterprise 7.1 or higher, SAS® Version 9.4 or higher, or RStudio Server Pro Version R.3.6.3. or higher.

Efficacy analyses will be conducted on the mITT population. Safety analyses will be conducted on the Safety population (same as mITT population, as described in Section 3). The efficacy analysis of the primary endpoint and secondary endpoints will be repeated for ITT population. Additional safety analyses may be performed as deemed appropriate.

The baseline modified Mayo Score (MMS) is calculated from valid daily diary entries obtained prior to endoscopy during the screening period and the endoscopic appearance of the mucosa at this screening endoscopy. For other efficacy, health outcome and safety assessments, baseline is defined as the last non-missing assessment recorded on or prior to the date of the randomization visit (Visit 2).

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Not all displays and analyses described in this SAP will necessarily be included in the CSR. Not all displays will necessarily be created as a "static" display. Some displays may be incorporated as interactive display tools instead of or in addition to a static display. Any display described in this SAP and not provided in CSR would be available upon request.

4.1.1. Analysis Methods

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (*n*), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will be calculated using *n* (the number of observations with non-missing values) as the denominator.

Unless otherwise specified, analysis of hypotheses will be tested without multiplicity control at a significance level of 0.05. A 2-sided 95% CI will be provided along with the p-value. P-values

which are greater than or equal to 0.001, and less than or equal to 0.999, will be presented to three decimal places. All other p-values which are less than 0.001 will be presented as '<0.001', while p-values greater than 0.999 will be presented as '>0.999'. CIs will be presented to one more decimal place than the raw data.

Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. However, if it is deemed more statistically appropriate, a transformation, such as to the logarithmic scale, may be applied before analysis. The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, is considered to be more fitting.

For assessments of the primary endpoint, other categorical (binary) efficacy, the Cochran-Mantel-Haenszel (CMH) chi-square test will be used to compare the treatment groups with the following factors:

- previous advanced therapy failure status (yes/no)
- baseline corticosteroid use (yes/no)
- baseline disease activity (MMS: [4 to 6] or [7 to 9]), and
- region (North America/Europe/Other).

The CMH chi-square p-value and the relative risk along with its 2-sided CI will be provided. In addition, the absolute treatment difference in proportions will be provided along with the 2-sided CI estimate. The differences between each treatment group and placebo will also be tested separately using a logistic regression model that controls for at least previous advanced therapy failure status (yes/no) and corticosteroid use (yes/no). If deemed necessary, additional analyses of categorical efficacy variables may be conducted to address sparse data and/or small sample sizes.

Treatment comparisons of continuous efficacy and health outcome variables with multiple postbaseline time points will be made using MMRM analysis. The MMRM will include the following effects and covariates:

- treatment group
- previous advanced therapy failure status (yes/no)
- corticosteroid use (yes/no)
- disease activity (MMS: [4 to 6] or [7 to 9]) at baseline)
- region (North America/Europe/Other)
- baseline value in the model
- visit, and
- the interactions of treatment-by-visit and baseline-by-visit as fixed factors.

The covariance structure to model the within-participant errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The first structure to yield convergence will be used for inference. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The Kenward-Roger

method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons with placebo at Week 12 and all other appropriate time points will be tested.

Treatment comparisons of continuous efficacy and health outcome variables with a single postbaseline time point will be made using ANCOVA with the following in the model:

- treatment group
- previous advanced therapy failure status (yes/no)
- corticosteroid use (yes/no)
- disease activity (MMS: [4 to 6] or [7 to 9]) at baseline)
- region (North America/Europe/Other), and
- baseline value.

Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% CI, unless otherwise specified, will also be reported.

4.1.2. Handling of Dropouts or Missing Data

Intercurrent events (FDA 2017) are events which occur after the study intervention initiation and make it impossible to measure a variable or influence how it should be interpreted. Examples of such events include treatment discontinuation due to death or adverse events (AEs), rescue treatment, and loss to follow-up. The missing data handling methods described below describe how intercurrent events will be used for the different estimands.

4.1.2.1. Non-Responder Imputation (NRI)

The primary outcome is the proportion of patients with clinical remission at Week 12. For this and other categorical efficacy endpoints (for example, clinical remission (week 52), clinical response (week 12, 52), and endoscopic remission (week 12, 52)), non-responder imputation (NRI) will be used for missing clinical assessment values. Specifically, all patients who discontinue from the study at any time prior to week 12 for any reason or fail to have an adequate week 12 efficacy assessment will be considered a non-responder at week 12. Patients who discontinue from the study for any reason at any time prior to week 52 after having enrolled into the Maintenance Period or fail to have an adequate week 52 efficacy assessment, will be considered a non-responder at week 52.

The NRI may be applied at any time point specified for analysis.

4.1.2.2. Mixed-Effects Model for Repeated Measures

For the continuous secondary and exploratory efficacy and health outcome variables, MMRM analyses will be the main method to mitigate the impact of missing data. This approach assumes that missing observations are missing-at-random (missingness is related to observed data) during the study and takes into account both the missingness of data and the correlation of the repeated measurements.

All continuous endpoints will utilize MMRM to patients who permanently discontinued study drug or who were rescued.

4.1.2.3. Modified Baseline Observations Carried Forward (mBOCF)

For patients discontinuing investigational product due to an AE, the baseline observation for the endpoint will be carried forward to the corresponding visit for all missing observations after the patient discontinued study treatment. For patients discontinuing investigational product for any other reason, the last non-missing postbaseline observation before discontinuation will be carried forward to the corresponding visit for all missing observations after the patient discontinued. For all patients with sporadically missing observations prior to discontinuation, the last non-missing observation before the sporadically missing observation will be carried forward to the corresponding visit. Randomized patients without at least 1 postbaseline observation will not be included for evaluation with the exception of patients discontinuing study treatment due to an AE.

The mBOCF method is based on an estimand that handles the intercurrent event of discontinuing study drug due to an AE by defining the patient as not receiving any benefit from study drug after the event. That is the patient is defined as reverting back to baseline regardless of any continuing efficacy benefits they may still have received after the event. For other intercurrent events (e.g., rescue treatment and discontinuation due to reasons other than an AE) or sporadic missingness the "while on treatment" strategy is applied. That is, the endpoint is defined as the last observed value at or before the visit of interest before the patient discontinued study treatment.

4.2. Participant Dispositions

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized, the number and percentage of participants who complete the study or discontinue, both overall and by reason for discontinuation, and the frequency and percentage of patients who discontinue study treatment. A summary of important protocol deviations will be provided.

4.3. Primary Endpoint Analysis

4.3.1. Definition of endpoint

Rate of clinical remission at Week 12 is the primary efficacy outcome for this study and will be analyzed using the mITT population.

Clinical remission is defined as achieving a rectal bleeding (RB) subscore of 0, and stool frequency subscore (SF) of 0, or 1 with a decrease of $\geq$1 point from baseline, and endoscopic (ES) subscore of 0 or 1, excluding friability. SF and RB subscores are calculated by averaging and rounding the 4-point daily scores over 3 days as described in 6.6.

4.3.2. Main analytical approach

The primary objective of this study is to test the hypothesis that treatment with LY3471851 is superior to placebo in inducing clinical remission at Week 12 in patients with moderate to severe ulcerative colitis (UC).

The rates of clinical remission and non-remission will be summarized by treatment group and by the stratification factors, previous advanced therapy failure status (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (MMS: [4 to 6] or [7 to 9]), and region (North America/Europe/Other).

The primary analysis will use the CMH chi-square test to compare LY3471851 to placebo at Week 12. The stratification factors used for CMH test are (a) previous advanced therapy failure status (yes/no), (b) baseline corticosteroid use (yes/no), (c) baseline disease activity (MMS: [4 to 6] or [7 to 9]), and (d) region (North America/Europe/Other). See Section 4.1.1 for details on the methods to be used to test the differences between each active treatment arm and placebo.

Ninety five percent confidence interval along with the p-value for the difference in proportions (LY arm – placebo) for each pairwise comparison will be obtained. For a pairwise comparison, if p-value is less than 0.05, then that LY arm will be considered to be superior to placebo.

A composite strategy is proposed for other intercurrent events including discontinuing study intervention, taking prohibited medications or increase the dose of mandatory stable medications. The NRI methodology described in Section 4.1.2.1 will be applied when any of these events occur.

4.3.3. Bayesian Model Averaging

A Bayesian model averaging will be performed for additional analysis of the clinical remission at Week 12. A Bayesian model averaging (BMA) approach will be used to estimate the dose response relationship. This Bayesian model averaging approach is the Bayesian analog of the MCP-MOD methodology (Bretz et al., 2005), and "the Qualification of the MCP-Mod procedure" (FDA, 2015) is supportive in the use of MCP-MOD or Bayesian model averaging to assist in dose selection decisions.

Bayesian model averaging is a general mixture distribution, where each mixture component is a different parametric model. Prior weights are placed on each model and the posterior model weights are updated based on how well each model fits the data. Let $\mu(d)$ represent the mean of the dose response curve at dose d, $y = \{y_1, \ldots, y_n\}$ be the observed data, and $m \in \{1, \ldots, M\}$ be an index on the M parametric models described below. Then the posterior of the dose response curve, $\mu(d)$, of the Bayesian model averaging model is

$$p(\mu(d) \mid y) = \sum_{m=1}^{M} p(\mu(d) \mid y, m)\, p(m \mid y)$$

$$p(m \mid y) = \frac{p(y \mid m)p(m)}{\sum_{m^*} p(y \mid m^*)p(m^*)}$$

where $p(\mu(d) \mid y, m)$ is the posterior mean dose response curve from model m, $p(m \mid y)$ is the posterior weight of model m, $p(y \mid m)$ is the marginal likelihood of the data under model m, and $p(m)$ is the prior weight assigned to model m. In cases where $p(y \mid m)$ is difficult to compute, Gould (2019) propose using the observed data's fit to the posterior predictive distribution as a surrogate in calculating the posterior weights; this is the approach used in this analysis.

4.3.3.1. BMA Analysis and Reporting

BMA will be executed for the proportion of participants who achieve clinical remission at Week 12.

BMA analysis will be summarized by dose and provide

- Observed response
- BMA estimated
  - Mean response
  - Standard error and standard deviation of the mean response
  - 2.5% and 97.5% quantiles
  - Summaries of posterior probability of LY - PBO treatment effect, i.e., Pr(LY – PBO > EOI) where EOI is effect of interest
- Plot that includes observed response, BMA estimated response, 2.5% and 97.5% posterior quantiles

BMA analysis will be summarized by component and model parameter and provide

- Posterior mean
- Standard error and standard deviation of the posterior mean
- 2.5% and 97.5% posterior quantiles of the posterior distribution
- Convergence diagnostics
- Effective sample size
- Prior distributions
- Plot of the fitted BMA
- Plot of the BMA components

4.4. Secondary Endpoints Analyses

4.4.1. Secondary Efficacy Endpoints

4.4.1.1. Definition of Endpoints

In the analyses of secondary efficacy outcomes, no adjustments for multiple testing will be performed unless otherwise specified.

The efficacy assessments of secondary endpoints are shown in the following table:

Table KFAH.3. Efficacy Assessments

Clinical Remission	SF subscore = 0, or SF = 1, and RB subscore = 0, and ES = 0 or 1, excluding friability.
Clinical Response	A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and a decrease of ≥1 point in the RB subscore from baseline or a RB score 0 or 1.
Endoscopic Remission	Mayo ES = 0 or 1, excluding friability.

Endoscopic Response	A decrease in the Mayo ES of ≥1 point compared to baseline.
Symptomatic Remission	SF = 0, or SF = 1 with a decrease of ≥1 point from baseline, and RB = 0.
Symptomatic Response	≥30% decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores.
Histologic Remission	Geboes score <2 or Geboes subscores = 0 for Grade 2a, 2b, 3, 4, and 5.
Histologic-Endoscopic Mucosal Healing	Geboes scroe <2 and endoscopic remission.

Abbreviations: ES = endoscopic subscore; MMS = modified Mayo score; RB = rectal bleeding; SF = stool frequency.

4.4.1.2. Secondary Efficacy Endpoints for the Induction Period

Secondary efficacy endpoints for the induction dosing period for participants who have not permanently discontinued at Week 12 and have achieved at Week 12 include clinical response, endoscopic remission, endoscopic response, symptomatic remission, symptomatic response, histologic remission, and histologic-endoscopic mucosal healing at Week 12.

Analyses will be performed as per the methodology described in Section 4.1.1.

The mITT population will be used for the secondary efficacy outcome analyses.

4.4.1.3. Secondary Efficacy Endpoints for the Maintenance Period

Secondary efficacy endpoints for the maintenance period for participants who were responder per IWRS at Week 12, have not permanently discontinued at Week 52, and have achieved at Week 52 include clinical remission, clinical response, endoscopic remission, endoscopic response, symptomatic remission, symptomatic response, histologic remission, and histologic-endoscopic mucosal healing at Week 52.

Analyses will be performed as per the methodology described in Section 4.1.1.

The mITT population will be used for the secondary efficacy outcome analyses.

4.4.2. Secondary Health Outcome Endpoints

The following are patient-reported outcome instruments collected using a participant eDiary:

- Rectal Bleeding
- Stool Frequency
- Nocturnal Stool
- Bristol Stool Scale

- Urgency NRS
- Abdominal Pain NRS
- Fatigue NRS, and
- PGR-S

The following are patient-reported outcome instruments collected electronically:

- PGI-C and
- IBDQ

Where appropriate, the total scores and sub-totals for individual dimensions collected will be summarized with means and 95% CIs by time point and by treatment group. The summary table will also include the change from baseline scores wherever applicable. The mean raw scores and mean change from baseline scores with corresponding 95% CIs will be presented graphically by treatment group and in a longitudinal fashion.

The ITT population will be used for all health outcome analyses

Mean change from baseline will be summarized by treatment group.

4.4.3. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

PK/PD analyses to address secondary and exploratory objectives of this study will be described by Lilly in separate PK/PD analysis plans. Conduct of the PK/PD analyses will be the responsibility of Eli Lilly and Company.

The PK/PD analyses will be initiated up to approximately three weeks before the planned database lock dates. All analyses will be performed by unblinded Lilly PK personnel, who are unblinded to subject treatment assignments to support dose adjustments. Results from the PK/PD analyses will not be shared with site or blinded study team personnel prior to the respective database lock.

4.5. Tertiary/Exploratory Endpoints Analyses

4.6. Safety Analyses

All safety data will be descriptively summarized by treatment groups and analyzed based on the safety population as defined in Section 3. The safety analyses include AEs, safety in special groups and circumstances, including Adverse Events of Special Interest (AESI), laboratory analytes, QIDS-SR16, C-SSRS, ECGs, and vital signs. The duration of exposure will also be summarized. The categorical safety measures will be summarized using incidence rates and analyzed by Fisher's exact test. The mean change in the continuous safety measures including vital signs, QIDS-SR16, physical characteristics, and laboratory values will be summarized by visits and analyzed by ANCOVA, with treatment and baseline values in the model. More details are provided in subsequent sections.

For specific events of special interest (see Section 4.6.3 for more details), an incidence rate, IR per 100 patient-years of observation (PYO), will be provided. Patient-years of observation will be calculated as the sum of all patient observation time in the treatment group. For a patient with an event, the observation time will be censored at the event date; for a patient without the event, the observation time will be counted until the patient's last treatment dose date plus 30 days or the patient's last visit, whichever occurs first. Only events that occur within 30 days after the patient's treatment discontinuation date will be considered.

See formula as follows:

$$PYO = \sum_{pt\ w\ event} \frac{event\ start\ date - first\ trt\ dose\ date + 1}{365.25} + \sum_{pt\ w/o\ event} \frac{last\ observation\ date - first\ trt\ dose\ date + 1}{365.25}$$

Incidence rate will be calculated as follows:

$$IR = \frac{unique\ number\ of\ patients\ with\ event}{PYO} \text{x}100$$

For each IR provided, a 95% CI will be calculated based on the Poisson distribution. Treatment group comparisons based on IR will be provided based on the incidence rate difference (IRD) together with its 95% CI.

Not all displays described in this section will necessarily be included in the CSRs. Any display described and not provided in the CSR would be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display created interactively will be included in the CSR if deemed relevant to the discussion.

4.6.1. Extent of Exposure

Duration of exposure to study treatment (defined as time since first injection of study treatment in days) will be summarized by treatment group during the Induction Period, the Maintenance Period, and the Extension Period.

Duration of exposure during the Induction Period for the Safety Population will be calculated as:

(Disposition date (for those who have discontinued the Induction Period), OR Maintenance/Extension Start date -1 (for those who have completed the Induction Period), OR Date of last study visit in the Induction Period (for those who are still being treated in the Induction Period) – Date of first injection of study treatment + 1)

Duration of exposure during the Maintenance Period will be calculated as:

(Disposition date (for those who have discontinued the Maintenance Period), OR Date of last study visit in the Maintenance Period (for those who are still being treated in the Maintenance Period) – Date of the Visit 10 injection of study treatment + 1)

Duration of exposure to LY3471851 during the Extension Period will be calculated as:

(Disposition date (for those who have discontinued the Extension Period), OR Date of last study visit in the Extension Period (for those who are still being treated in the Extension Period) – Date of the Visit 10 injection of study treatment + 1)

Duration of exposure to LY3471851 for the combined Induction Period and Maintenance Period will be calculated as:

(Disposition date (for those who have discontinued the Maintenance Period), OR Date of last study visit in the Maintenance Period (for those who are still being treated in the Maintenance Period)– Date of first injection of LY3471851 + 1)

Duration of exposure to LY3471851 for the combined Induction Period and Extension Period will be calculated as:

(Disposition date (for those who have discontinued the Extension Period), OR Date of last study visit in the Extension Period (for those who are still being treated in the Extension Period)– Date of first injection of LY3471851 + 1)

The date of first injection of LY3471851 is defined in Table KFAH.4**Error! Reference source not found.**.

Table KFAH.4. First Injection of LY3471851 by Treatment Group

	Visit of first LY3471851
All patients randomized to LY3471851 (regardless of Week 12 response status)	Week 0 (Visit 2)
Week 12 Inadequate Responders originally randomized to placebo and assigned to LY3471851 at Visit 10	Week 14 (Visit 10)

Descriptive statistics (n, mean, SD, minimum, first quartile, median, third quartile, and maximum) will be provided for patient-days of exposure and the frequency of patients falling into different exposure ranges will be summarized. Exposure ranges are as follows:

- >0, ≥4 weeks, ≥12 weeks, and ≥52 weeks.
- >0 to <4 weeks, ≥4 weeks to <12 weeks, ≥12 weeks to <52 weeks, and ≥52 weeks.

Additional exposure ranges may be considered if necessary.

A by-patient listing of exposure duration will be provided.

Patients who had dose modification will be grouped under the randomized treatment arm and will not be grouped by the modified dose amount.

No inferential analysis for comparison between treatment arms will be performed.

4.6.2. Adverse Events

4.6.2.1. Adverse Events

Adverse events are recorded in the eCRF. Each AE will be coded to SOC and PT, using the *Medical Dictionary for Regulatory Activities* (MedDRA) version that is current at the time of database lock. Severity of AEs is recorded as mild, moderate, or severe.

Treatment-emergent adverse events (TEAEs) are defined as events that either first occurred or worsened in severity after the first dose of study drug and the earliest of the visit study drug disposition date or the last visit date during the treatment period, whichever occurred first, and up to 30 days after study treatment discontinuation. The MedDRA Lowest Level Term (LLT) will be used in defining which events are treatment-emergent. The maximum severity for each LLT during the baseline period until the first dose of the study medication will be used as baseline. If an event is preexisting during the baseline period, but it has missing severity, and the event persists during the treatment period or up to 30 days after treatment discontinuation, then the baseline severity will be considered mild for determining any postbaseline treatment-emergence (i.e., the event is treatment-emergent unless the severity is coded mild at postbaseline). If an event occurring postbaseline has a missing severity rating, then the event is considered treatment-emergent. Should there be insufficient data for an AE start date to make this comparison (e.g., the AE start year is the same as the treatment start year, but the AE start month and day are missing), the AE will be considered treatment-emergent. For events occurring on the day of the first dose of study treatment, the day of the onset of the event will

both be used to distinguish between pretreatment and posttreatment in order to derive treatment-emergence.

In general, summaries will include the number of patients in the safety population (*N*), frequency of patients experiencing the event (*n*), and relative frequency (i.e., percentage; n/N*100).

In an AE overview table, the number and percentage of patients in the safety analysis set who experienced death, a serious adverse event (SAE), any TEAE, permanent discontinuation from study drug due to an AE, or a severe TEAE will be summarized by treatment group.

The number and percentage of patients with TEAEs will be summarized by treatment group in 2 formats listed below. For events that are gender specific, the denominator and computation of the percentage will only include patients from the given gender.

- by MedDRA PT nested within SOC with SOCs ordered alphabetically, and events ordered within each SOC by decreasing frequency in the LY3471851 1800µg treatment group.
- by MedDRA PT with events ordered by decreasing frequency in the LY3471851 1800µg treatment group.

Adverse events leading to permanent discontinuation of study drug and AEs leading to temporary interruption of study drug will also be summarized by treatment group using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC in the LY3471851 1800µg treatment group.

A summary of temporary interruptions of study drug will also be provided, showing the number of patients who experienced at least 1 temporary interruption and the number of temporary interruptions per patient with an interruption. Further, the duration of each temporary interruption (in days) and the cumulative duration of dose interruption (in days) using basic descriptive statistics (n, mean, SD, minimum, first quartile, median, third quartile, and maximum) will be displayed.

Common TEAEs are defined as TEAEs that occurred in ≥1% (before rounding) of patients in any treatment group including placebo. The number and percentage of patients with common TEAEs will be summarized by treatment using MedDRA PT ordered by decreasing frequency in the LY3471851 1800µg treatment group.

The number and percentage of patients with TEAEs will be summarized by maximum severity by treatment using MedDRA PT ordered by decreasing frequency for the common TEAEs. For each patient and TEAE, the maximum severity for the MedDRA level being displayed is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA PT.

4.6.2.2. Serious Adverse Events

An individual listing of all AEs including preexisting conditions will be provided. A separate listing will include AEs that led to permanent discontinuation from the study drug. In addition, a listing of AEs that occur more than 30 days after study treatment discontinuation will be provided.

With the International Conference on Harmonisation (ICH) E2A guideline, a SAE is any AE that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threating experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

The number and percentage of patients who experienced any ICH-defined SAE will be summarized by treatment group during the treatment and follow-up periods using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC in the LY3471851 1800µg treatment group. In addition, the SAEs will be summarized by treatment group using MedDRA PT without SOC. An individual listing of all SAEs will be provided.

4.6.3. Adverse Events of Special Interest

4.6.3.1. Infections

Infections will be defined using all PTs from the MedDRA Infections and Infestations SOC. Serious infection will be defined as all the infections that meet the SAE criteria.

The number and percentage of patients with TEAEs of infections, serious infections, and infections resulting in study drug discontinuation will be summarized by treatment group using MedDRA PTs.

The number and percentage of patients with TEAEs of infections by maximum severity will be summarized by treatment group using MedDRA PTs.

For infections of special interest (serious infections, potential opportunistic infections [POIs], herpes zoster, and herpes simplex), the IR (for detail, see Section 4.6) and 95% CI will be calculated.

Treatment-emergent infectious events will be reviewed in context of other clinical and laboratory parameters. A listing of patients experiencing treatment-emergent infectious AEs will be provided. The listing will include patient demographics, treatment group, treatment start and stop dates, infectious event, event start and stop dates, total leukocytes, total lymphocytes, absolute neutrophils, event seriousness, and event outcome.

The infectious TEAE will be further analyzed in terms of potential opportunistic infection, herpes zoster, and herpes simplex. A summary of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) monitoring results and association between infection and neutropenia/lymphopenia will also be provided in the context of infections.

Potential Opportunistic Infections

Potential opportunistic infections will be identified according to 2 different approaches.

First, POIs will be identified from TEAEs based on a Lilly-defined list of MedDRA PTs shown in 6.8. These PTs are a subset of terms from the Infections and Infestations SOC.

Second, a list of all the infection details captured from the infection-specific eCRF (including primary/secondary infecting organism and infection site) will be provided. Of note, the infecting organism that was entered as free text by the investigator (instead of as a selection from the pull-down list) will also be provided.

The summary analysis of POIs identified using the 2 approaches above will be provided. Each case meeting the case definition for an opportunistic infection will be summarized by PT nested under infection pathogen. Events will be ordered by decreasing frequency of pathogen nested under pathogen species (mycobacteria, bacteria, fungal, viral, parasites). The order of frequency will be determined using the LY3471851 1800µg group.

Potential opportunistic infections identified through these approaches will be combined in 1 list for medical assessment for final classification of whether the case definition was met according to the consensus paper after database lock (i.e., Winthrop 2015). An additional summary may be conducted based on medical assessment.

Herpes Zoster

A summary table of herpes zoster will be provided. Herpes zoster will be defined based on the MedDRA PTs as listed under Herpes zoster (any form) (II) in 6.8, excluding Varicella virus text (10070444). The summary table will also include event maximum severity, seriousness, whether resulting in temporary study drug interruption, whether resulting in study drug discontinuation, whether treated with antiviral medication, and event outcome.
If a patient has more than 1 event of herpes zoster, the event with the maximum severity will be used in these summary tables. If more than 1 event of herpes zoster occurs with the same severity, the event with the longest duration will be used in the summary table.

Herpes Simplex

A summary analysis of herpes simplex will be provided. Herpes simplex will be defined based on the MedDRA PTs as listed under Herpes simplex (invasive disease only) (IV) in 6.8. The summary table will include event maximum severity, seriousness, whether resulting in temporary study drug interruption, whether resulting in study drug discontinuation, and whether treated with antiviral medication. Antiviral medication will be selected based on ATC code level 2 "antiviral for systemic use."
If a patient has more than 1 event of herpes simplex, the event with the maximum severity will be used in these summary tables. If more than 1 event of herpes simplex occurs with the same severity, the event with the longest duration will be used in the summary table.

HBV DNA

A listing of patients with detectable HBV DNA will be provided.

HBV DNA status (not detectable, detectable but not quantifiable [ie, <29 IU/mL], quantifiable [ie, ≥29 IU/mL]) will be summarized by treatment group stratified by baseline HBV serology status, specifically:

- HBsAb- / HBcAb-
- HBsAb+ / HBcAb-

- HBsAb+ / HBcAb+
- HBsAb- / HBcAb+

Association between Infection and Neutropenia/Lymphopenia

To evaluate the association between infection and neutropenia and also between infection and lymphopenia, the frequency of infections will be provided by the worst Common Terminology Criteria for Adverse Events (CTCAE) grades of neutropenia and lymphopenia, respectively. Infection outcomes considered for this analysis are any treatment-emergent infection, serious infection, and herpes zoster. For this analysis, no statistical comparison will be provided.

In addition, a summary table will be provided for treatment-emergent infections that were preceded or accompanied by neutropenia/lymphopenia. For this analysis, neutropenia is defined as CTCAE Grade 2 or greater. Infection events with onset date ≤14 days before or after the Grade 2 neutrophil/lymphocyte count collection date will be considered as infections preceded or accompanied by neutropenia.

4.6.3.2. Systemic Hypersensitivity Reactions (including cytokine release syndrome)

A search will be performed using the current MedDRA version Standardised MedDRA Queries (SMQs) to search for relevant events, using the following queries:

- Anaphylactic reaction SMQ (20000021)
- Hypersensitivity SMQ (20000214)
- Angioedema SMQ (20000024)

Events that satisfy the queries will be listed, by temporal order within patient ID, and will include SOC, PT, SMQ event categorization including detail on the scope (narrow or broad), reported AE term, AE onset and end dates, severity, seriousness, outcome, etc.

4.6.3.3. Malignancies

Malignancies will be identified using terms from the malignant tumors SMQ (SMQ 20000194). Malignancies excluding nonmelanoma skin cancers (NMSC) and NMSC will be reported separately.

A listing including all malignancy cases will be provided. An NMSC flag will be provided using the following MedDRA PTs (the list will be updated depending on the MedDRA version used for analysis):

- Squamous cell carcinoma of skin (10041834)
- Bowen's disease (10006059)
- Basal cell carcinoma (10004146)
- Basosquamous carcinoma (10004178)
- Basosquamous carcinoma of skin (10004179)
- Squamous cell carcinoma (10041823)
- Skin squamous cell carcinoma metastatic (10077314)
- Skin cancer (10040808)
- Carcinoma in situ of skin (10007390)

The number and percentage of patients with TEAE-associated malignancies excluding NMSC and NMSC will be summarized by treatment group. In addition, the IR (for detail, see Section 4.6) and 95% CI will be calculated for the overall observation time. All cases identified by malignant tumors SMQ will be assessed after database lock by the medical team to determine (1) confirmed NMSC cases and (2) symptom and date that triggered the malignancy investigation or diagnosis. An additional listing based on medical review may also be provided if deemed necessary. All cases reported in the study database or by Lilly Safety System (LSS) report, disregarding the length of gap between the last treatment dose date and the event date will be included.

4.6.3.4. Gastrointestinal Perforations

Treatment-emergent adverse events potentially related to gastrointestinal (GI) perforations will be analyzed using reported AEs. Identification of these events will be based on the PTs of the MedDRA Gastrointestinal Perforations SMQ (SMQ 20000107); note that this SMQ holds only narrow terms and has no broad terms. Potential GI perforations identified by the above SMQ search will be provided as a listing for internal review by the medical safety team. Each case will be assessed to determine whether it is a GI perforation. Frequency and relative frequency for each PT will be provided, ordered by decreasing frequency in the LY3471851 1800µg treatment group. Comparisons between each LY3471851 treatment group and placebo will be made using Fisher's exact test.

4.6.4. Injection Site Reaction

If a participant spontaneously reports symptoms of an injection site reaction, an authorized member of the site staff who, in the opinion of the investigator, is qualified to assess reports of potential ISRs and who is not involved with any other study procedure will evaluate the participant's report.

The number and percentage of patients who experienced ISR will be summarized by treatment group and by visit. The number and percentage of patients with the following ISR records will be summarized by treatment group and by visit. Details about ISR records are referred to the Case Report Form (CRF).

- Anatomical location of the injection site reaction
- Abdomen Side
- Directionality of the anatomical location of the administration
- Arm side
- Whether the subject has any injection site erythema (reddening) or not
- Severity of the injection site erythema
- Whether the subject has any injection site induration (hardening or thickening of tissue) or not
- Severity of the injection site induration
- Whether the subject has any injection site pain (including burning) or not
- Severity of the injection site pain
- Whether the subject has any injection site pruritus
- Severity of the injection site pruritus

- Whether the subject has any injection site edema (swelling or accumulation of fluid in tissues at height above normal skin) or not
- Severity of the injection site edema
- When the Injection related event occurred in relationship to the study treatment

Ordinal logistic regression will be used for the ordinal ISR reported. The frequency of the maximum severity of ISRs will be summarized by treatment group.

4.6.5. Clinical Laboratory Evaluation

Laboratory evaluations will be summarized and analyzed for the following periods:

- Induction Period,
- Maintenance Period,
- Extension Period (including Extension Induction and Extension Maintenance)

All laboratory tests will be presented using the Système International of units (SI) and conventional (CN) units. For topics of safety in special groups and circumstances, laboratory test units will be specified for each analysis.

Lilly Large Clinical Trial Population Based (LCTPB) reference limits will be used to define the low and high limits because it is generally desirable for limits used for analyses to have greater specificity (identify fewer false positive cases) than reference limits used for individual patient management. When Lilly LCTPB reference ranges are unavailable, then central laboratory (Labcorp) reference ranges will be used. For the 4 key hepatic laboratory assessments (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and alkaline phosphatase [ALP]), central laboratory reference ranges (Labcorp) will be used and all results pertaining to these assessments will be included as a separate analysis to address the risk of liver injury as a special safety topic (see Section 4.6.3.1). Central laboratory reference ranges (Labcorp) will also be used to evaluate immunoglobulins and lymphocyte cell subsets (see Sections 4.6.5.2 and 4.6.5.6). See 6.10 for details of the reference range by laboratory analytes.

The low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio will be derived as the ratio of LDL cholesterol to HDL cholesterol. There are no Lilly LCTPB reference ranges or central lab reference ranges for the LDL/HDL ratio.

The following will be conducted for laboratory analyte measurements collected quantitatively:

- Box plots for observed values: Values at each visit (starting at randomization) and change from baseline to each visit and to last postbaseline measure will be displayed in box plots for patients who have a baseline and at least 1 postbaseline visit. For visits included in the treatment period, patients will be included only if the visit occurs on or before the date of treatment discontinuation/completion. Follow-up visit will be the first visit that occurred during the Follow-up period. Individual measurements outside of reference limits will also be displayed using distinct symbols overlaying the box plot. Original-scale data will be used for the display but for some analytes (e.g., immunoglobulins) a logarithmic scale will be used to aid in viewing the measures of central tendency and dispersion. Unplanned measurements will be excluded. Descriptive summary statistics will be included in a table below the box plot. These box plots will be

used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries. A p-value for change from baseline to endpoint will be provided using an ANCOVA model with explanatory term for treatment and the baseline value as a covariate. Endpoint will be the last observation where patient is on treatment.

- Treatment-emergent high/low analyses: The number and percentage of patients with treatment-emergent high and low laboratory results at any time will be summarized by treatment group. Planned and unplanned measurements will be included. A treatment-emergent **high** result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time during the treatment period and up to 60 days after treatment discontinuation. A treatment-emergent **low** result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time during the treatment period and up to 60 days after treatment discontinuation. The Fisher's exact test will be used for the treatment comparisons.

For laboratory analyte measurements collected qualitatively, a listing of abnormal findings will be created. The listing will include patient ID, treatment group, laboratory collection date, analyte name, and analyte finding.

4.6.5.1. Abnormal Hepatic Tests

Analyses for abnormal hepatic tests involve 4 laboratory analytes: ALT, AST, total bilirubin, and ALP. Analyses for the change from baseline to last visit that occurred on or before the date of treatment discontinuation and shift tables are described in Section 4.6.5. This section describes additional analyses for the topic. The central laboratory reference ranges (Labcorp) will be used for ALT, AST, total bilirubin, and ALP hepatic laboratory assessments.

The number and percentage of patients with the following abnormal elevations in hepatic laboratory tests at any time up to 60 days after treatment discontinuation will be summarized by treatment group. LY3471851 groups will be compared to placebo using Fisher's exact text:

- The percentages of patients with an ALT measurement ≥3×, 5×, and 10× the central laboratory upper limit of normal (ULN) during the treatment and follow-up periods will be summarized for all patients with a postbaseline value.
- The percentages of patients with an AST measurement ≥3×, 5×, and 10× the central laboratory ULN during the treatment and follow-up periods will be summarized for all patients with a postbaseline value.
- The percentages of patients with a total bilirubin measurement ≥2 × the central laboratory ULN during the treatment period will be summarized for all patients with a postbaseline value.
- The percentages of patients with an ALP measurement ≥3× the central laboratory ULN during the treatment and follow-up periods will be summarized for all patients with a postbaseline value.

Second, to further evaluate potential hepatotoxicity, an Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will be created for all patients whether treated with LY3471851 and/or other treatment using the whole study and follow-up periods. Each patient with at least 1 postbaseline ALT and total bilirubin will be included in the eDISH. The points correspond to maximum total bilirubin and maximum ALT, even if not obtained from the same blood draw. A listing of patients potentially meeting Hy's rule will be provided (defined as greater than or equal to 3× ULN for ALT or AST, and greater than or equal to 2× ULN for total bilirubin, not necessarily at the same time).

Third, a listing will be provided to the medical safety team for internal review according to the following SMQs:

- Broad and narrow terms in the Liver-related investigations, signs and symptoms SMQ (SMQ 20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (SMQ 20000009)
- Broad and narrow terms in the Hepatitis non-infectious SMQ (SMQ 20000010)
- Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (SMQ 20000013)
- Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (SMQ 20000015).

4.6.5.2. Lymphocyte Subset Cell Counts

The following lymphocyte subsets will be analyzed:

CD3+ T Cells – %

CD3+ T Cells – Absolute

CD3+CD8+ T cells (CD8) – %

CD3+CD8+ T cells (CD8) – Absolute

CD3+CD4+ T cells (CD4) – %

CD3+CD4+ T cells (CD4) – Absolute

CD56+/CD16+ NK cells – %

CD56+/CD16+ NK cells – Absolute

CD19+ B cells – %

CD19+ B cells – Absolute

CD4/CD8 Ratio – Calculated

CD3+4+8+ %

CD3+4+8+ Abs

CD3/CD19 Ratio - Calculated

For each type of cells, both the absolute count and the relative count (i.e., as a percentage of the total lymphocyte population) will be analyzed. In addition, the ratio of CD4 cell counts to CD8 cell counts will be analyzed.

The analyses for these parameters will be performed using the same approaches as described for analysis of clinical laboratory measurements in Section 4.6.5. For determining treatment-emergent abnormal, high, or low lymphocyte subset cell counts, central laboratory reference ranges (Labcorp) will be used when available; note that reference ranges are available only for some of the lymphocyte subset cell count analytes.

4.6.5.3. Lipids Effects

Analyses for the change from baseline to last observation, and shift tables in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides are described in Section 4.6.5.

Treatment-emergent adverse events potentially related to hyperlipidemia will also be analyzed, based on reported AEs. The target surveillance term "Hyperlipidemia" is a Lilly-defined MedDRA search criteria list that is a subset of the PTs in the MedDRA SMQ "Dyslipidemia" that are related to elevated or increased lipids. MedDRA PTs, each with a narrow scope from the SMQ, for the target surveillance term are shown in 6.9. Frequency and relative frequency for each PT will be provided, ordered by decreasing frequency in the LY3471851 1800µg treatment group.

4.6.5.4. Renal Function Effects

Effects on renal function will be assessed through analyses of creatinine, which are described in Section 4.6.5.

4.6.5.5. Elevations in Creatine Phosphokinase

Analyses of creatine phosphokinase are described in Section 4.6.5.

4.6.5.6. Serum Immunoglobulin Concentrations

Each serum Ig concentration (IgA, IgG, and IgM) will be analyzed. The analyses for these parameters will be performed using the same approaches as described for analysis of clinical laboratory measurements in Section 4.6.5. For determining treatment-emergent abnormal, high, or low serum Ig concentrations for IgA, IgG, and IgM, central laboratory reference ranges (Labcorp) will be used.

4.6.6. Vital Signs and Other Physical Characteristics

Vital signs and physical characteristics include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, weight, BMI, and body temperature. Original-scale data will be analyzed. When these parameters are analyzed as continuous numerical variables, unplanned measurements will be excluded. When these parameters are analyzed as categorical outcomes, planned and unplanned measurements will be included.

Vital signs and physical characteristics will be summarized and analyzed for the following periods:

- Induction Period

- Maintenance Period
- Extension Period

The planned analyses described for the laboratory analytes in Section 4.6.5 will be used to analyze the vital signs and physical characteristics.

Table KFAH.5 defines the low and high baseline values as well as the criteria used to define treatment-emergence based on postbaseline values. Postbaseline values include all values after baseline in the treatment and follow-up periods. The blood pressure and pulse rate criteria are consistent with the document *Selected Reference Limits for Blood Pressure, Orthostasis, and ECG Numerical Parameters (Including Heart Rate) for Use in Phase II-IV Clinical Trials Version 1.1* approved on 8 March 2013 as recommended by the Lilly Cardiovascular Safety Advisory Committee (CVSAC).

Table KFAH.5. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

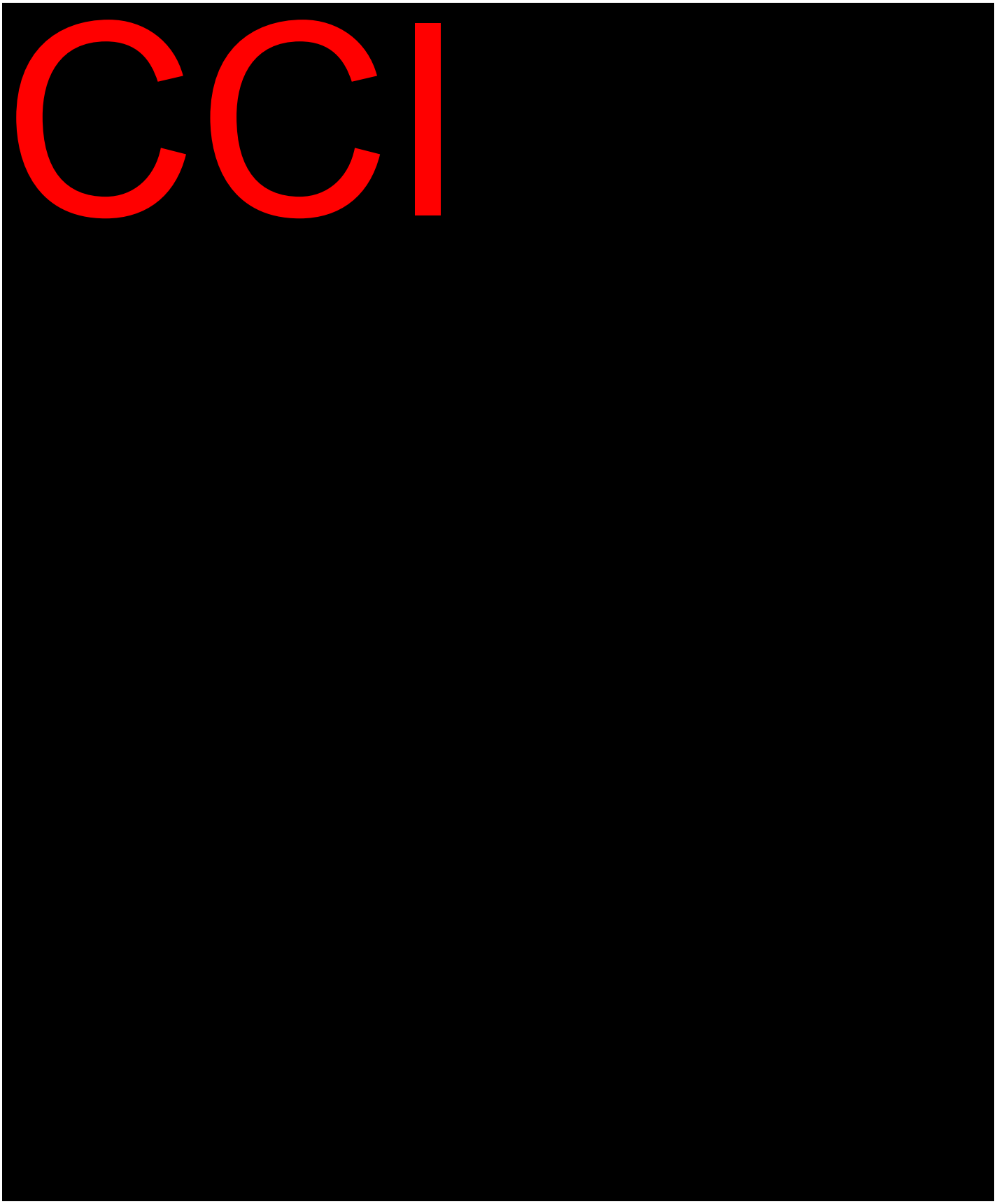
	Low	High
Systolic Blood Pressure (mm Hg)	≤90 (low limit) and decrease from lowest value during baseline ≥20 if >90 at each baseline visit	≥140 (high limit) and increase from highest value during baseline ≥20 if <140 at each baseline visit
Diastolic Blood Pressure (mm Hg)	≤50 (low limit) and decrease from lowest value during baseline ≥10 if >50 at each baseline visit	≥90 (high limit) and increase from highest value during baseline ≥10 if <90 at each baseline visit
Pulse (beats per minute)	<50 (low limit) and decrease from lowest value during baseline ≥15 if ≥50 at each baseline visit	>100 (high limit) and increase from highest value during baseline ≥15 if ≤100 at each baseline visit
Weight (kilograms)	(Loss) decrease ≥7% from lowest value during baseline	(Gain) increase ≥7% from highest value during baseline

Abbreviation: mm Hg = millimeters of mercury.

4.6.7. Electrocardiograms

Detailed Electrocardiogram results are part of the clinical database for this study. Should an ECG be performed in association with an AE or medical history event, the occurrence of the ECG ("Yes/No") will be provided in a by-patient listing.

If any clinically significant ECG measurement occurs, this will be recorded as an AE. ECG data will not be analyzed.


CCI

4.6.9. Suicidal Ideation/Behavior and Depression

During the study, suicidal ideation and behavior, and depression will be assessed prospectively by the investigator via signs and symptoms and through the use of the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16).

Analyses will include:

- C-SSRS: Only a listing of the C-SSRS data will be provided.
- QIDS-SR16: Shift table will be provided showing the number and percentage of patients within each baseline category (maximum value) versus each post-baseline category (maximum value) by treatment. Additionally, outcomes such as any increase in depression will be compared between treatments.

4.7. Other Analyses

4.7.1. Efficacy Subgroup Analysis

Subgroup analyses will be conducted on the mITT population for the following:

- Clinical remission
- Clinical response
- Endoscopic remission
- Endoscopic response
- Symptomatic remission
- Symptomatic response
- Histologic remission
- Histologic-endoscopic mucosal healing

The following subgroups (but not limited to only these) will be evaluated:

- Gender
- Age category
- Body weight
- Race
- Geographic region
- Baseline disease severity and activity
- Duration and location of disease

- Previous systemic therapy
- Previous advanced therapy, and
- Concomitant therapy for UC.

Descriptive statistics will be provided for each treatment and stratum of a subgroup as outlined, regardless sample size.

Each categorical variable will be analyzed individually with a logistic regression model that contains the treatment, the subgroup variable, and subgroup by treatment interaction. The treatment-by-subgroup interaction will be tested at the 10% significant level. Within each subgroup category, the proportion of responders by treatment, treatment differences, and 95% CIs will be displayed.

For continuous variables, MMRM analysis will be performed with subgroup-by-treatment interaction. Within each subgroup, LS means by treatment, LS mean differences, and 95% CIs will be displayed.

If the number of patients in any subgroup category is less than 10% of the total population, only summaries of the efficacy data will be provided. Additional subgroup analyses may be performed as deemed necessary.

4.7.2. Safety Subgroup Analyses

Safety subgroup analysis for safety related endpoints will be performed within the context of the integrated safety analysis. No safety subgroup analysis will be performed specifically for this study unless there is a potentially relevant finding during the periodic study safety reviews.

4.8. Interim Analyses

Analyses for the primary database lock will be conducted when all participants have completed the Induction Period (that is, have completed the Week 12 visit) or else have discontinued study treatment.

The following interim analyses may be conducted to assess the primary efficacy results:

- for early termination assessment and decision when approximately 50 patients have either completed the dosing induction period or discontinued study treatment,
- for early termination or Stage 2 dose decisions when approximately 100 patients have either completed the dosing induction period or discontinued study treatment,
- for early trigger to Phase 3 assessment when approximately 150 patients have either completed the dosing induction period or discontinued study treatment, and
- for Phase 3 study trigger when approximately 200 patients have either completed the dosing induction period or discontinued study treatment.

Bayesian pairwise comparisons (LY3471851 dose to placebo) will be employed for potential decisions at each interim analysis using Bayesian posterior probability. Note that Stage 2 treatment doses will be determined based on results of the second interim analysis and recommendations of the sponsor's IAC.

The interim efficacy results will be used for internal decision making to terminate or trigger planning activities associated with the investigational product and to aid development of PK/PD modeling. Hence, there will be no alpha adjustment at the interim analyses. For each pairwise comparison at each interim analysis, a alpha of 0.05 will be used. The study may not be stopped for positive efficacy. The assessment will be conducted by a sponsor assessment committee with a limited number of pre-identified team members who do not have direct site contact or data entry/validation responsibilities. To minimize any bias being introduced into the analysis of the study results, the SAP and PK/PD analysis plan will be finalized and approved before the first efficacy interim analysis is initiated.

Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until a decision is made to unblind the entire study team.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will be continued throughout the study using blinded data. Reviewing details are specified in the trial level safety review (TLSR) plan or a separate document.

4.8.1. Data Monitoring Committee (DMC)

Not applicable. An assessment of unblinded interim data will be conducted by an internal assessment committee (IAC) with a limited number of prespecified team members who do not have direct site contact or data entry or validation responsibilities. An AC charter will provide details on AC membership and the governing processes.

4.9. Changes to Protocol-Planned Analyses

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) are defined as those deviations from the protocol that would potentially compromise patients' safety, data integrity, or study outcome.

A separate document known as the "The KFAH Trial Issues Management Plan" describes the categories and subcategories of important protocol deviations, whether or not these deviations are IPDPPs, and how the IPDs would be identified.

The number and percentage of patients having IPDs will be summarized within category and subcategory of deviations by dosing regimen for the mITT population.

5. Sample Size Determination

Approximately 200 participants, in total, may be randomized across all study stages.

During Stage 1, approximately 100 participants will be randomized to a high dose (CCI µg) of LY3471851, a lower (CCI µg) dose of LY3471851, or placebo groups in a 2:2:1 ratio.

During Stage 2, up to approximately 100 additional participants will be randomized. Stage 2 will have a placebo group and may have more LY3471851 treatment groups than Stage 1, or fewer, based on decisions taken after the last interim analysis of Stage 1.

The power calculations for this study assume the following:

- At end of study, three non-placebo treatment groups will have sample size of approximately either 40, 60, or 80 patients.
- At end of study, the placebo group will have a sample size of approximately 40 patients.
- For the sake of simplicity in the power calculation, it is assumed that there is no difference in treatment effect between advanced therapy-failed and conventional-failed patients. To simplify, it is also assumed that all treatment groups have the same treatment effect.
- It is assumed that the true placebo response rate is approximately 5% and the true treatment response is approximately 35%.
- Power is calculated for 3 hypothesis tests, 1 for each treatment group against placebo, and adjust for multiple comparisons using the conservative Bonferroni adjustment. Power is calculated using a family-wise error rate of α=.05.

Given these assumptions, the power to reject the null hypotheses for the treatment groups with sample sizes equal to 40, 60, and 80 are 89.5%, 94.5%, and 96.5%, respectively. As an example, in a fixed design, with the placebo and LY3471851 treatment groups each having 80 participants, a 17% or larger difference between the groups can be detected with 90% power and assuming a 5% placebo effect.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

The patient's year of birth, sex, weight, height, smoking habits, previous biologic treatment, and other demographic characteristics are collected at the screening visit. Age and body mass index will be calculated.

Only the year of birth is collected at screening. For the purpose of age calculation, the month and day of birth will be imputed as July 01, of the year of birth. Age is computed as follows;

Age= (Informed Consent Date –Date of Birth +1)/365.25.

Demographic and baseline characteristics (including age, gender, race, and ethnicity) will be summarized for each treatment group.

Certain characteristics, that are collected at baseline or after baseline but not summarized in the demographic summary, will be reported as a listing.

No inferential analysis for the comparability of baseline covariates across treatment groups will be performed.

6.2. Appendix 2: Preexisting Conditions

Preexisting condition is defined the condition/event recorded on the Preexisting Conditions and Medical History electronic case report form (eCRF) page with a start date prior to the date of informed consent, and no end date (that is, the event is ongoing) or an end date on or after the date of informed consent. In addition, the AEs occurring prior to first dose are also included. Notice if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on the AE eCRF page with the date of worsening as the start date. The number and percentage of patients with preexisting conditions will be summarized by treatment group using the MedDRA Preferred Term (PT) nested within System Organ Class (SOC). Summaries will be performed for the ITT population.

6.3. Appendix 3: Treatment Compliance

Study treatment administration and compliance will be listed for all entered patients. The number and percentage of patients who are treatment compliant by week (that is, at each injection time point) will be summarized by treatment group for each treatment period.

No patient will be excluded from the ITT population as a consequence of significant noncompliance.

Participants who are noncompliant with treatment will be listed by treatment group.

No analyses are planned to assess treatment compliance.

6.4. Appendix 4: Prior and Concomitant Therapy

Prior and concomitant medications will be summarized by treatment group and will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to

the date of first dose of treatment in each treatment period to allow medications to be classified as Concomitant for each treatment period.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment. Concomitant medications are those medications that start before, on or after the first day of study treatment of the defined treatment period and continue into the treatment period.

6.5. Appendix 5: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

6.6. Appendix 6: Daily Diary Calculations

Weekly summary measures of daily diary data will be created for each patient. The 7-day period associated with each week will be defined using a visit centric approach. The table below displays the interval for each week:

Week (Visit)	Start Day[a]	End Day[a]
Baseline	Week 0 Visit Date – 7	Week 0 Visit Date – 1
Week 1 (V3)	Max(Week 0 Visit Date, Week 1 Visit Date – 7)	Week 1 Visit Date – 1
Week 2 (V4)	Max(Week 1 Visit Date , Week 2 Visit Date – 7)	Week 2 Visit Date – 1

Week 3	Max (Week 2 Visit Date, Week 4 Visit Date – 14)	Week 4 Visit Date – 8
Week 4 (V5)	Max (Week 2 Visit Date, Week 4 Visit Date – 7)	Week 4 Visit Date – 1
Week 5	Max (Week 4 Visit Date, Week 6 Visit Date – 14)	Week 6 Visit Date – 8
Week 6 (V6)	Max (Week 4 Visit Date, Week 6 Visit Date – 7)	Week 6 Visit Date – 1
Week 7	Max (Week 6 Visit Date, Week 8 Visit Date – 14)	Week 8 Visit Date – 8
Week 8 (V7)	Max (Week 6 Visit Date, Week 8 Visit Date – 7)	Week 8 Visit Date – 1
Week 9	Max (Week 8 Visit Date, Week 10 Visit Date – 14)	Week 10 Visit Date – 8
Week 10 (V8)	Max (Week 8 Visit Date, Week 10 Visit Date – 7)	Week 10 Visit Date – 1
Week 11	Max (Week 10 Visit Date, Week 12 Visit Date – 14)	Week 12 Visit Date – 8
Week 12 (V9)	Max (Week 10 Visit Date, Week 12 Visit Date – 7)	Week 12 Visit Date – 1
Week 13	Max (Week 12 Visit Date, Week 14 Visit Date – 14)	Week 14 Visit Date – 8
Week 14 (V10)	Max (Week 12 Visit Date, Week 14 Visit Date – 7)	Week 14 Visit Date – 1
Week 15	Max (Week 14 Visit Date, Week 16 Visit Date – 14)	Week 16 Visit Date – 8
Week 16 (V11)	Max (Week 14 Visit Date, Week 16 Visit Date – 7)	Week 16 Visit Date – 1
Week 17	Max (Week 16 Visit Date, Week 18 Visit Date – 14)	Week 18 Visit Date – 8
Week 18 (V12)	Max (Week 16 Visit Date, Week 18 Visit Date – 7)	Week 18 Visit Date – 1
Week 19	Max (Week 18 Visit Date, Week 20 Visit Date – 14)	Week 20 Visit Date – 8
Week 20 (V13)	Max (Week 18 Visit Date, Week 20 Visit Date – 7)	Week 20 Visit Date – 1
Week 21	Max (Week 20 Visit Date, Week 22 Visit Date – 14)	Week 22 Visit Date – 8
Week 22 (V14)	Max (Week 20 Visit Date, Week 22 Visit Date – 7)	Week 22 Visit Date – 1
Week 23	Max (Week 22 Visit Date, Week 24 Visit Date – 14)	Week 24 Visit Date – 8
Week 24 (V15)	Max (Week 22 Visit Date, Week 24 Visit Date – 7)	Week 24 Visit Date – 1
Week 25	Max (Week 24 Visit Date, Week 26 Visit Date – 14)	Week 26 Visit Date – 8
Week 26 (V16)	Max (Week 24 Visit Date, Week 26 Visit Date – 7)	Week 26 Visit Date – 1
Week 27	Max(Week 26 Visit Date, Week 28 Visit Date – 14)	Week 28 Visit Date – 1
Week 28 (V17)	Max(Week 26 Visit Date , Week 28 Visit Date – 7)	Week 28 Visit Date – 1

Week 29	Max (Week 28 Visit Date, Week 30 Visit Date – 14)	Week 30 Visit Date – 8
Week 30 (V18)	Max (Week 28 Visit Date, Week 30 Visit Date – 7)	Week 30 Visit Date – 1
Week 31	Max (Week 30 Visit Date, Week 32 Visit Date – 14)	Week 32 Visit Date – 8
Week 32 (V19)	Max (Week 30 Visit Date, Week 32 Visit Date – 7)	Week 32 Visit Date – 1
Week 33	Max (Week 32 Visit Date, Week 34 Visit Date – 14)	Week 34 Visit Date – 8
Week 34 (V20)	Max (Week 32 Visit Date, Week 34 Visit Date – 7)	Week 34 Visit Date – 1
Week 35	Max (Week 34 Visit Date, Week 36 Visit Date – 14)	Week 36 Visit Date – 8
Week 36 (V21)	Max (Week 34 Visit Date, Week 36 Visit Date – 7)	Week 36 Visit Date – 1
Week 37	Max (Week 36 Visit Date, Week 38 Visit Date – 14)	Week 38 Visit Date – 8
Week 38 (V22)	Max (Week 36 Visit Date, Week 38 Visit Date – 7)	Week 38 Visit Date – 1
Week 39	Max (Week 38 Visit Date, Week 40 Visit Date – 14)	Week 40 Visit Date – 8
Week 40 (V23)	Max (Week 38 Visit Date, Week 40 Visit Date – 7)	Week 40 Visit Date – 1
Week 41	Max (Week 40 Visit Date, Week 42 Visit Date – 14)	Week 42 Visit Date – 8
Week 42 (V24)	Max (Week 40 Visit Date, Week 42 Visit Date – 7)	Week 42 Visit Date – 1
Week 43	Max (Week 42 Visit Date, Week 44 Visit Date – 14)	Week 44 Visit Date – 8
Week 44 (V25)	Max (Week 42 Visit Date, Week 44 Visit Date – 7)	Week 44 Visit Date – 1
Week 45	Max (Week 44 Visit Date, Week 46 Visit Date – 14)	Week 46 Visit Date – 8
Week 46 (V26)	Max (Week 44 Visit Date, Week 46 Visit Date – 7)	Week 46 Visit Date – 1
Week 47	Max (Week 46 Visit Date, Week 48 Visit Date – 14)	Week 48 Visit Date – 8
Week 48 (V27)	Max (Week 46 Visit Date, Week 48 Visit Date – 7)	Week 48 Visit Date – 1
Week 49	Max (Week 48 Visit Date, Week 50 Visit Date – 14)	Week 50 Visit Date – 8
Week 50 (V28)	Max (Week 48 Visit Date, Week 50 Visit Date – 7)	Week 50 Visit Date – 1
Week 51	Max (Week 50 Visit Date, Week 52 Visit Date – 14)	Week 52 Visit Date – 8
Week 52 (V29)	Max (Week 50 Visit Date, Week 52 Visit Date – 7)	Week 52 Visit Date – 1

Abbreviations: V = Visit.

[a] If End Day < Start Day, do not assign specified visit week. Visit date will be calculated by selecting the first date from the following list (i.e., first in list order): (1) date of earliest bowel preparation if bowel preparation date is available, (2) date of endoscopy if endoscopy was performed, (3) date of treatment if treatment was given, (4) office visit date if available, or (5) imputed date of visit center of the protocol-defined window for that visit. The screening endoscopy is assumed to be associated with the Week 0 visit.

For the Mayo SF and RB subscores, the most recent 3 nonmissing days of the 7-day period in the table above will be averaged and rounded to the nearest integer to calculate the weekly score for each patient. Patients with less than 3 measurements in the 7 day period will be considered missing.

For the Bristol Stool Scale the worst (i.e. maximum) of the available measures during the 7 period in the table above will be used to calculate a weekly score for each patient. If fewer than 4 days are available (i.e., not missing), the patient will be considered to be missing data for that week.

For all other daily diary measures, all available days of the 7 days will be averaged and rounded to the nearest integer to calculate the weekly score for each patient. If fewer than 4 days are available (i.e., not missing), the patient will be considered to be missing data for that week.

If multiple diary assessments on a single day are present, use the earliest nonmissing assessment. Data from the following days will be considered missing: (i) days when patients receive bowel preparation, (ii) the day of an endoscopy, and (iii) two days after an endoscopy.

If the baseline assessment is missing per the above rules, the first available postbaseline assessment starting with Week 1 will be used to impute the baseline so that the patient can be included in the analysis.

6.7. Appendix 7: Execution for Bayesian Model Averaging

6.7.1. R DREAMER Package to Execute BMA

BMA will be executed using the R package *DREAMER*: **D**ose **RE**sponse b**A**yesian **M**odel averaging. *DREAMER* package and supporting documentation may be found at GitHub - rich-payne/dreamer and on CRAN.

6.7.2. BMA Components, Priors, and Weights

E-max, quadratic, log-quadratic, linear, and log-linear dose response models are the prespecified component to the BMA model that will be used to analyze the KFAH dose response and are described in the DREAMER supporting documentation. BMA components and weights are summarized in **Error! Reference source not found.** The priors for each parameter are normal distributions, except b_4 in the Sigmoidal EMAX model, which is truncated normal (to be positive). A logistic link function will be used for each model.

Table KFAH.6. Prespecified Dose Response Models with Prior

Component	Weight	Model	Parameter	mu	sigma
Sigmoidal EMAX	1/6	$f(d) = b_1 + \frac{(b_2 - b_1)d^{b_4}}{\exp(b_3 b_4) + d^{b_4}}$	b_1	-2	2
			b_2	0	4

			b_3	log([CCI])	log(600)
			b_4	1	2
Hyperbolic EMAX	1/6	$f(d) = b_1 + \frac{(b_2 - b_1)d}{\exp(b_3) + d}$	b_1	-2	2
			b_2	0	4
			b_3	log([CCI])	log(600)
Quadratic	1/6	$f(d) = b_1 + b_2 d + b_3 d^2$	b_1	-2	2
			b_2	0	2
			b_3	0	2
Log-Quadratic	1/6	$f(d) = b_1 + b_2 \log(d+1) + b_3 \log(d+1)^2$	b_1	-2	2
			b_2	0	1
			b_3	0	1
Linear	1/6	$f(d) = b_1 + b_2 d$	b_1	-2	2
			b_2	0	2
Log-Linear	1/6	$f(d) = b_1 + b_2 \log(d+1)$	b_1	-2	2
			b_2	0	1

6.8. Appendix 8: List of MedDRA Preferred Terms for Potential Opportunistic Infections (POI)

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
Mycobacterial/ Actino	Nocardiosis (II)	Nocardia sepsis	10064952	Narrow
		Nocardiosis	10029444	
		Nocardia test positive	10070131	Broad
Mycobacterial/ Actino	Nontuberculous mycobacterium disease (II)	Atypical mycobacterial infection	10061663	Narrow
		Atypical mycobacterial lower respiratory tract infection	10075026	
		Atypical mycobacterial lymphadenitis	10003755	
		Atypical mycobacterium pericarditis	10055036	
		Atypical mycobacterial pneumonia	10071075	
		Borderline leprosy	10006029	
		Bovine tuberculosis	10006049	
		Indeterminate leprosy	10021700	
		Leprosy	10024229	
		Lepromatous leprosy	10024227	
		Mycobacterial infection	10062207	
		Mycobacterial peritonitis	10073514	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Mycobacterium abscessus infection	10064789	
		Mycobacterium avium complex immune restoration disease	10058449	
		Mycobacterium avium complex infection	10058806	
		Mycobacterium chelonae infection	10071401	
		Mycobacterium fortuitum infection	10049659	
		Mycobacterium kansasii infection	10028447	
		Mycobacterium marinum infection	10028452	
		Mycobacterium ulcerans infection	10066289	
		Superinfection mycobacterial	10075381	
		Tuberculoid leprosy	10044729	
		Type 1 lepra reaction	10070516	
		Type 2 lepra reaction	10070517	
		Atypical mycobacterium test positive	10070326	Broad
		Mycobacterial disease carrier	10075025	
		Mycobacterium leprae test positive	10070324	
		Mycobacterium test	10070407	
		Mycobacterium test positive	10070323	
		Ureaplasmal ulvovaginitis	10081280	
Mycobacterial/ Actino	Tuberculosis (I)	Adrenal gland tuberculosis	10001358	Narrow
		Bone tuberculosis	10056377	
		Choroid tubercles	10008779	
		Congenital tuberculosis	10010657	
		Conjunctivitis tuberculous	10010754	
		Cutaneous tuberculosis	10011684	
		Disseminated Bacillus Calmette-Guerin infection	10076666	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Disseminated tuberculosis	10013453	
		Ear tuberculosis	10014027	
		Epididymitis tuberculous	10015004	
		Extrapulmonary tuberculosis	10064445	
		Female genital tract tuberculosis	10061150	
		Immune reconstitution inflammatory syndrome associated tuberculosis	10072797	
		Intestinal tuberculosis	10075268	
		Joint tuberculosis	10056367	
		Lupus vulgaris	10025143	
		Lymph node tuberculosis	10025183	
		Male genital tract tuberculosis	10061234	
		Meningitis tuberculous	10027259	
		Oesophageal tuberculosis	10030200	
		Oral tuberculosis	10076879	
		Pericarditis tuberculous	10055069	
		Peritoneal tuberculosis	10053583	
		Prostatitis tuberculous	10064743	
		Pulmonary tuberculoma	10066927	
		Pulmonary tuberculosis	10037440	
		Renal tuberculosis	10038534	
		Salpingitis tuberculous	10039463	
		Silicotuberculosis	10068876	
		Spleen tuberculosis	10041640	
		Thyroid tuberculosis	10043774	
		Tuberculoma of central nervous system	10052883	
		Tuberculosis	10044755	
		Tuberculosis bladder	10044758	
		Tuberculosis gastrointestinal	10061390	
		Tuberculosis liver	10058120	
		Tuberculosis of central nervous system	10061391	
		Tuberculosis of eye	10044819	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Tuberculosis of genitourinary system	10044828	
		Tuberculosis of intrathoracic lymph nodes	10044846	
		Tuberculosis of peripheral lymph nodes	10044965	
		Tuberculosis ureter	10045026	
		Tuberculous abscess central nervous system	10052884	
		Tuberculous endometritis	10071559	
		Tuberculous laryngitis	10045072	
		Tuberculous pleurisy	10045104	
		Tuberculous tenosynovitis	10059161	
		Interferon gamma release assay	10073542	Broad
		Interferon gamma release assay positive	10072866	
		Mycobacterium tuberculosis complex test	10070472	
		Mycobacterium tuberculosis complex test positive	10070325	
		Tuberculid	10044725	
		Tuberculin test	10044726	
		Tuberculin test false negative	10074840	
		Tuberculin test positive	10044728	
Bacteria	Bartonellosis (disseminated disease only) (V)	Bacillary angiomatosis	10003971	Narrow
		Trench fever	10044582	
		Bartonella test	10075209	Broad
		Bartonella test positive	10070157	
		Bartonellosis	10004145	
		Cat scratch disease	10007729	
		Peliosis hepatis	10034229	
		Splenic peliosis	10068851	
	Campylobacteriosis (invasive disease only) (V)	Campylobacter sepsis	10070681	Narrow
		Campylobacter colitis	10076769	Broad
		Campylobacter gastroenteritis	10007048	
		Campylobacter infection	10051226	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Campylobacter test positive	10070025	
	Legionellosis (II)	Legionella infection	10061266	Narrow
		Pneumonia legionella	10035718	
		Pontiac fever	10054161	
		Legionella test	10070410	Broad
		Legionella test positive	10070092	
Bacteria	Listeria monocytogenes (invasive disease only) (II)	Listeria encephalitis	10054116	Narrow
		Listeria sepsis	10063085	
		Meningitis listeria	10027248	
		Listeria test	10075707	Broad
		Listeria test positive	10070094	
		Listeriosis	10024641	
	Salmonellosis (invasive disease only) (II)	Aortitis salmonella	10074937	Narrow
		Arthritis salmonella	10003271	
		Meningitis salmonella	10027254	
		Osteomyelitis salmonella	10031262	
		Paratyphoid fever	10033971	
		Pneumonia salmonella	10035733	
		Salmonella bacteraemia	10058924	
		Salmonella sepsis	10058878	
		Typhoid fever	10045275	
		Salmonella test positive	10070127	Broad
		Salmonellosis	10039447	
		Salmonella test	10079854	
Bacteria	Shigellosis (invasive disease only) (V)	Shigella sepsis	10074481	Narrow
		Shigella infection	10054178	Broad
		Shigella test positive	10070129	
	Vibriosis (invasive disease due to *V. vulnificus*) (V)	Gastroenteritis vibrio	10017917	Broad
		Vibrio test positive	10070161	
		None		Narrow
	Infective Pneumonia SMQ	Pneumonia acinetobacter	10079866	Narrow
		Pneumonia proteus	10079867	
		Pneumonia serratia	10079868	
Fungal	Aspergillosis (invasive disease only) (II)	Aspergillosis oral	10003489	
		Cerebral aspergillosis	10051597	
		Meningitis aspergillus	10073245	
		Oro-pharyngeal aspergillosis	10053029	
		Aspergillus infection	10074171	
		Aspergillus test	10070450	
		Aspergillus test positive	10070448	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Bronchopulmonary aspergillosis	10006473	
		Sinusitis aspergillus	10051016	
	Blastomycosis (IV)	Blastomycosis	10005098	Narrow
		Epididymitis blastomyces	10015001	
		Osteomyelitis blastomyces	10031255	
		Pneumonia blastomyces	10035671	
		None		Broad
	Candidiasis (invasive disease, or oral not limited to the tongue) (II)	Candida endophthalmitis	10059449	Narrow
		Candida osteomyelitis	10064699	
		Candida pneumonia	10053158	
		Candida retinitis	10068612	
		Candida sepsis	10053166	
		Candida urethritis	10081262	
		Candidiasis of trachea	10064459	
		Cerebral candidiasis	10078126	
		Endocarditis candida	10014669	
		Gastrointestinal candidiasis	10017938	
		Hepatic candidiasis	10049653	
		Hepatosplenic candidiasis	10051590	
		Meningitis candida	10027205	
		Oesophageal candidiasis	10030154	
		Oral candidiasis	10030963	
		Oropharyngeal candidiasis	10050346	
		Peritoneal candidiasis	10056562	
		Splenic candidiasis	10051725	
		Systemic candida	10042938	
		Bladder candidiasis	10058523	Broad
		Candida infection	10074170	
		Candida test	10070453	
		Candida test positive	10070451	
		Mucocutaneous candidiasis[1]	10028080	
		Respiratory moniliasis	10038705	
	Coccidioidomycosis (II)	Coccidioides encephalitis	10054214	Narrow
		Coccidioidomycosis	10009825	
		Cutaneous coccidioidomycosis	10068747	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Meningitis coccidioides	10027207	
		None		Broad
	Cryptococcosis (II)	Cryptococcal cutaneous infection	10054216	Narrow
		Cryptococcal fungaemia	10067112	
		Cryptococcosis	10011490	
		Disseminated cryptococcosis	10013439	
		Gastroenteritis cryptococcal	10011485	
		Meningitis cryptococcal	10027209	
		Neurocryptococcosis	10068368	
		Pneumonia cryptococcal	10067565	
		Cryptococcus test	10070456	Broad
		Cryptococcus test positive	10070455	
	Histoplasmosis (II)	Acute pulmonary histoplasmosis	10001027	Narrow
		Chronic pulmonary histoplasmosis	10009115	
		Endocarditis histoplasma	10014676	
		Histoplasmosis	10020141	
		Histoplasmosis cutaneous	10049142	
		Histoplasmosis disseminated	10020144	
		Meningitis histoplasma	10027243	
		Pericarditis histoplasma	10034489	
		Retinitis histoplasma	10038912	
		Presumed ocular histoplasmosis syndrome	10063664	Broad
	Microsporidiosis (IV)	Microsporidia infection	10053982	Narrow
		None		Broad
	Other invasive fungi: Mucormycosis (=zygomycosis) [Rhizopus, Mucor, and Lichtheimia], *Scedosporum/ Pseudallescheria boydii*, *Fusarium* (II)	Allescheriosis	10001754	Narrow
		Fusarium infection	10051919	
		Mucormycosis	10028098	
		Scedosporium infection	10059045	
		Pseudallescheria infection	10061919	
		Pseudallescheria sepsis	10058973	
		See “Non-specific terms” below		Broad

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
	Paracoccidioides infections (V)	Paracoccidioides infection	10061906	Narrow
		None		Broad
	Penicillium marneffei (V)	Penicillium infection	10078580	Narrow
		None		Broad
	Pneumocystis jirovecii (II)	Pneumocystis jirovecii infection	10073756	Narrow
		Pneumocystis jirovecii pneumonia	10073755	
		Blood beta-D-glucan	10068725	Broad
		Blood beta-D-glucan abnormal	10051795	
		Blood beta-D-glucan increased	10051793	
		Gomori methenamine silver stain	10075549	
		Carbon monoxide diffusing capacity decreased	10065906	
		Carbon monoxide diffusing capacity	10071738	
		Pneumocystis test positive	10070454	
	Sporothrix schenckii (V)	Cutaneous sporotrichosis	10011676	Narrow
		Sporotrichosis	10041736	
		None		Broad
Viral	Cytomegalovirus disease (V)	Cytomegalovirus chorioretinitis	10048843	Narrow
		Cytomegalovirus colitis	10048983	
		Cytomegalovirus duodenitis	10049014	
		Cytomegalovirus enteritis	10049074	
		Cytomegalovirus enterocolitis	10049015	
		Cytomegalovirus gastritis	10049016	
		Cytomegalovirus gastroenteritis	10051349	
		Cytomegalovirus gastrointestinal infection	10052817	
		Cytomegalovirus gastrointestinal ulcer	10075619	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Cytomegalovirus hepatitis	10011830	
		Cytomegalovirus infection	10011831	
		Cytomegalovirus mononucleosis	10011834	
		Cytomegalovirus mucocutaneous ulcer	10065036	
		Cytomegalovirus myelomeningoradiculitis	10065621	
		Cytomegalovirus myocarditis	10056261	
		Cytomegalovirus nephritis	10079095	
		Cytomegalovirus oesophagitis	10049018	
		Cytomegalovirus pancreatitis	10049566	
		Cytomegalovirus pericarditis	10056721	
		Cytomegalovirus syndrome	10056262	
		Cytomegalovirus urinary tract infection	10051350	
		Cytomegalovirus viraemia	10058854	
		Disseminated cytomegaloviral infection	10049075	
		Encephalitis cytomegalovirus	10014586	
		Pneumonia cytomegaloviral	10035676	
		Cytomegalovirus test	10061806	Broad
		Cytomegalovirus test positive	10051620	
	HBV reactivation (IV)	None		Narrow
		Asymptomatic viral hepatitis	10063838	Broad
		Chronic hepatitis B	10008910	
		HBV-DNA polymerase increased	10058937	
		Hepatitis B	10019731	
		Hepatitis B antigen	10063414	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Hepatitis B antigen positive	10063411	
		Hepatitis B core antigen	10051160	
		Hepatitis B core antigen positive	10052328	
		Hepatitis B DNA assay	10060027	
		Hepatitis B DNA assay positive	10060047	
		Hepatitis B DNA increased	10068379	
		Hepatitis B e antigen	10050914	
		Hepatitis B e antigen positive	10052329	
		Hepatitis B reactivation	10058827	
		Hepatitis B surface antigen	10050529	
		Hepatitis B surface antigen positive	10019742	
		Hepatitis B virus test	10068415	
		Hepatitis B virus test positive	10070217	
		Hepatitis A	10019780	
		Hepatitis post transfusion	10019791	
		Hepatitis viral	10019799	
		Withdrawal hepatitis	10071220	
Viral	HCV progression (V)	None		Narrow
		Chronic hepatitis C	10008912	Broad
		Hepatitis C	10019744	
		Hepatitis C RNA	10019748	
		Hepatitis C RNA fluctuation	10068727	
		Hepatitis C RNA increased	10068377	
		Hepatitis C RNA positive	10019750	
		Hepatitis C virus test	10068416	
		Hepatitis C virus test positive	10070218	
	Herpes simplex (IV)	Colitis herpes	10051782	Narrow
		Eczema herpeticum	10014197	
		Gastritis herpes	10051784	
		Herpes oesophagitis	10052330	
		Herpes sepsis	10058876	
		Herpes simplex colitis	10074239	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Herpes simplex encephalitis	10019953	
		Herpes simplex gastritis	10074240	
		Herpes simplex hepatitis	10067389	
		Herpes simplex meningitis	10019956	
		Herpes simplex meningoencephalitis	10074247	
		Herpes simplex meningomyelitis	10074250	
		Herpes simplex necrotising retinopathy	10074252	
		Herpes simplex oesophagitis	10074242	
		Herpes simplex pneumonia	10065046	
		Herpes simplex sepsis	10074246	
		Herpes simplex visceral	10019963	
		Meningitis herpes	10027242	
		Meningoencephalitis herpetic	10027285	
		Meningomyelitis herpes	10074249	
		Pneumonia herpes viral	10035703	
		Genital herpes simplex	10073931	
		Herpes dermatitis	10062639	
		Herpes pharyngitis	10066888	
		Herpes simplex otitis externa	10019959	
		Herpes simplex pharyngitis	10074244	
		Ophthalmic herpes simplex	10073938	
		Proctitis herpes	10036780	
		Kaposi's varicelliform eruption	10051891	
		Herpes simplex test positive	10077969	Broad
		Herpes simplex	10019948	
		Herpes virus infection	10019973	
		Nasal herpes	10074936	
		Oral herpes	10067152	
		Genital herpes	10018150	
	Herpes zoster (any form) (II)	Disseminated varicella zoster vaccine virus infection	10076667	Narrow

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Encephalitis post varicella	10014603	
		Genital herpes zoster	10072210	
		Herpes zoster	10019974	
		Herpes zoster cutaneous disseminated	10074297	
		Herpes zoster disseminated	10065038	
		Herpes zoster infection neurological	10061208	
		Herpes zoster meningitis	10074259	
		Herpes zoster meningoencephalitis	10074248	
		Herpes zoster meningomyelitis	10074251	
		Herpes zoster meningoradiculitis	10079327	
		Herpes zosternecrotising retinopathy	10074253	
		Herpes zoster oticus	10063491	
		Herpes zoster pharyngitis	10074245	
		Necrotising herpetic retinopathy	10065119	
		Ophthalmic herpes zoster	10030865	
		Varicella	10046980	
		Varicella keratitis	10077496	
		Varicella post vaccine	10063522	
		Varicella zoster gastritis	10074241	
		Varicella zoster oesophagitis	10074243	
		Varicella zoster pneumonia	10074254	
		Varicella zoster virus infection	10075611	
		Herpes ophthalmic	10062004	
		Varicella virus test	10070444	Broad
		Varicella virus test positive	10070214	
		BK virus infection	10055181	Narrow
		Human polyomavirus infection	10057366	
		JC virus granule cell neuronopathy	10074361	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
	Human Polyomavirus infection including BK virus disease and PVAN (V), and Progressive Multifocal Leukoencephalopathy (IV)	JC virus infection	10023163	
		Polyomavirus-associated nephropathy	10065381	
		Progressive multifocal leukoencephalopathy	10036807	
		JC virus test	10068794	Broad
		Polyomavirus test	10075038	
		Polyomavirus test positive	10070342	
	Post-transplant lymphoproliferative disorder (EBV) (V)	Epstein-Barr virus associated lymphoproliferative disorder	10068349	Narrow
		Post transplant lymphoproliferative disorder	10051358	
		Epstein-Barr viraemia	10065110	Broad
		Epstein-Barr virus associated lymphoma	10071441	
		Epstein-Barr virus infection	10015108	
		Lymphoproliferative disorder	10061232	
		Lymphoproliferative disorder in remission	10061233	
		Oral hairy leukoplakia	10030979	
Parasites	Trypanosoma cruzi infection (Chagas' Disease) (disseminated disease only) (V)	None		Narrow
		American trypanosomiasis	10001935	Broad
		Trypanosomiasis	10044707	
		Meningitis trypanosomal	10027258	
	Cryptosporidium species (chronic disease only) (IV)	Biliary tract infection cryptosporidial	10067319	Narrow
		Cryptosporidiosis infection	10011502	Broad
		Gastroenteritis cryptosporidial	10017899	
	Leishmaniasis (Visceral only) (IV)	Visceral leishmaniasis	10047505	Narrow
		Leishmaniasis	10024198	Broad
	Stronglyoides (hyperinfection syndrome and disseminated forms only) (IV)	None		Narrow
		Strongyloidiasis	10042254	Broad

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
	Toxoplasmosis (IV)	Cerebral toxoplasmosis	10057854	Narrow
		Eye infection toxoplasmal	10015939	
		Hepatitis toxoplasmal	10019798	
		Meningitis toxoplasmal	10048848	
		Myocarditis toxoplasmal	10028617	
		Pneumonia toxoplasmal	10067566	
		Toxoplasma serology	10050941	Broad
		Toxoplasmosis	10044272	
Non-specific terms	Non-specific terms	None		Narrow
		Delftia acidovorans infection	10081339	
		Sphingomonas paucimobilis bacteraemia	10081563	
		Central nervous system immune reconstitution inflammatory response	10080100	Broad
		Abscess fungal	10000269	
		Alternaria infection	10054207	
		Arthritis fungal	10060966	
		Biliary tract infection fungal	10065203	
		Central nervous system fungal infection	10072805	
		Cerebral fungal infection	10049657	
		Encephalitis fungal	10065170	
		Erythema induratum	10015213	
		Eye infection fungal	10015933	
		Fungaemia	10017523	
		Fungal abscess central nervous system	10017524	
		Fungal endocarditis	10017529	
		Fungal labyrinthitis	10065174	
		Fungal oesophagitis	10049656	
		Fungal peritonitis	10061138	
		Fungal pharyngitis	10076516	
		Fungal retinitis	10068613	
		Fungal sepsis	10058872	
		Fungal urethritis	10081163	
		Hepatic infection fungal	10065217	
		Meningitis fungal	10027236	
		Mycotic endophthalmitis	10063202	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		Myocarditis mycotic	10059026	
		Oral fungal infection	10061324	
		Oropharyngitis fungal	10061891	
		Osteomyelitis fungal	10065239	
		Otitis media fungal	10065175	
		Pancreatitis fungal	10065190	
		Pericarditis fungal	10065220	
		Phaehyphomycosis	10034799	
		Pneumonia fungal	10061354	
		Pulmonary mycosis	10037422	
		Pulmonary trichosporonosis	10068184	
		Sinusitis fungal	10058678	
		Splenic infection fungal	10065194	
		Systemic mycosis	10052366	
Pneumonia	Infective Pneumonia SMQ	All PTs	20000231	Narrow

Abbreviations: DNA = deoxyribonucleic acid; EBV= Epstein-Barr virus; HBV = hepatitis B virus; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PVAN = Polyomavirus-associated nephropathy; SMQ = standardized MedDRA query.

6.9. Appendix 9: List of MedDRA Preferred Terms for Elevated or Increased Lipids from the Dyslipidemia SMQ (SMQ20000026)

Preferred Term (MedDRA Version 20.0)	Preferred Term Code
Apolipoprotein B/Apolipoprotein A-1 ratio increased	10065516
Autoimmune hyperlipidaemia	10071577
Blood cholesterol abnormal	10005423
Blood cholesterol increased	10005425
Blood triglycerides abnormal	10005837
Blood triglycerides increased	10005839
Diabetic dyslipidaemia	10070901
Dyslipidaemia	10058108
Familial hypertriglyceridaemia	10059183
Fat overload syndrome	10074028
High density lipoprotein abnormal	10020051
High density lipoprotein decreased	10020060
High density lipoprotein increased	10020061
Hypercholesterolaemia	10020603
Hyperlipidaemia	10062060
Hypertriglyceridaemia	10020869
Hypo HDL cholesterolaemia	10068961

Intermediate density lipoprotein increased	10064236
LDL/HDL ratio increased	10049030
Lipid metabolism disorder	10061227
Lipids abnormal	10024588
Lipids increased	10024592
Lipoprotein (a) abnormal	10054023
Lipoprotein (a) increased	10054009
Low density lipoprotein abnormal	10024901
Low density lipoprotein increased	10024910
Non-high-density lipoprotein cholesterol increased	10063967
Remnant hyperlipidaemia	10038316
Total cholesterol/HDL ratio abnormal	10058633
Total cholesterol/HDL ratio increased	10058630
Type I hyperlipidaemia	10060749
Type II hyperlipidaemia	10045254
Type IIa hyperlipidaemia	10045261
Type IIb hyperlipidaemia	10045263
Type III hyperlipidaemia	10060751
Type IV hyperlipidaemia	10060753
Type V hyperlipidaemia	10060755
Very low density lipoprotein abnormal	10047352
Very low density lipoprotein increased	10047361

6.10. Appendix 10: List of Planned Laboratory Analytes with Reference Range Sources

Laboratory Group/Order	Laboratory Analyte	Reference Range Name	Analysis Type	
			Central Tendency	Outlier/Shift Analysis
Hematology				
1	Hemoglobin	LCTPB	Yes	Yes
2	Hematocrit	LCTPB	Yes	Yes
3	Erythrocyte Count	LCTPB	Yes	Yes
4	Mean Cell Volume	LCTPB	Yes	Yes
5	Mean Cell Hemoglobin	LCTPB	Yes	Yes
6	MCHC	LCTPB	Yes	Yes
7	Platelets	LCTPB	Yes	Yes
8	Leukocyte Count	LCTPB	Yes	Yes
9	Bands	LCTPB	Yes	Yes
10	Neutrophils	LCTPB	Yes	Yes
11	Lymphocytes	LCTPB	Yes	Yes
12	Monocytes	LCTPB	Yes	Yes
13	Eosinophils	LCTPB	Yes	Yes
14	Basophils	LCTPB	Yes	Yes
Chemistry				

Laboratory Group/Order	Laboratory Analyte	Reference Range Name	Analysis Type	
			Central Tendency	Outlier/Shift Analysis
1	ALT/SGPT	Labcorp	Yes	Yes
2	AST/SGOT	Labcorp	Yes	Yes
3	Alkaline Phosphatase	Labcorp	Yes	Yes
4	Total Bilirubin	Labcorp	Yes	Yes
5	Direct Bilirubin	Labcorp	Yes	Yes
6	Albumin	LCTPB	Yes	Yes
7	Creatine Phosphokinase	LCTPB	Yes	Yes
8	Creatinine	Labcorp	Yes	Yes
9	Urea Nitrogen	LCTPB	Yes	Yes
11	estimated GFR	Labcorp	Yes	Yes
12	Creatinine Clearance	Labcorp	Yes	Yes
13	Sodium	LCTPB	Yes	Yes
14	Potassium	LCTPB	Yes	Yes
15	Calcium	LCTPB	Yes	Yes
16	Total Protein	LCTPB	Yes	Yes
17	Fasting Glucose	LCTPB	Yes	Yes
18	Glucose, Non-Fasting or Random	LCTPB	Yes	Yes
19	Uric Acid	LCTPB	Yes	Yes
20	Cholesterol	LCTPB	Yes	Yes
21	Triglycerides	LCTPB	Yes	Yes
22	LDL Cholesterol – Direct	Labcorp	Yes	Yes
23	HDL Cholesterol – Direct	Labcorp	Yes	Yes
24	LDL/HDL Ratio – Calculated	None	Yes	No
Immunoglobulins				
1	Immunoglobulin A	Labcorp	Yes	Yes
2	Immunoglobulin G	Labcorp	Yes	Yes
3	Immunoglobulin M	Labcorp	Yes	Yes
Urinalysis				
1	Specific Gravity	LCTPB	Yes	Yes
2	pH	LCTPB	Yes	Yes
3	UA-color	None	No	Yes
4	UA-glucose	None	No	Yes
5	UA-protein	None	No	Yes
6	UA-bilirubin	None	No	Yes
7	UA-urobilinogen	None	No	Yes
8	UA-nitrites	None	No	Yes
9	UA-leukoesterase	None	No	Yes
10	UA-ketones	None	No	Yes
11	UA-occult blood	None	No	Yes
Flow Cytometry				
1	CD3+ T Cells – %	Labcorp	Yes	Yes
2	CD3+ T Cells – Absolute	Labcorp	Yes	Yes
3	CD3+CD4+ T cells (CD4) – %	Labcorp	Yes	Yes
4	CD3+CD4+ T cells (CD4) – Absolute	Labcorp	Yes	Yes
5	CD3+CD8+ T cells (CD8) – %	Labcorp	Yes	Yes

Laboratory Group/Order	Laboratory Analyte	Reference Range Name	Analysis Type	
			Central Tendency	Outlier/Shift Analysis
6	CD3+CD8+ T cells (CD8) – Absolute	Labcorp	Yes	Yes
7	CD56+/CD16+ NK cells – %	Labcorp	Yes	Yes
8	CD56+/CD16+ NK cells – Absolute	Labcorp	Yes	Yes
9	CD19+ B cells – %	Labcorp	Yes	Yes
10	CD19+ B cells – Absolute	Labcorp	Yes	Yes
11	CD4+CXCR3+CCR6- Th1 cells - %	None	Yes	No
12	CD4+CXCR3+CCR6- Th1 cells - Absolute	None	Yes	No
13	CD4+CXCR3-CCR6+ Th17 cells - %	None	Yes	No
14	CD4+CXCR3-CCR6+ Th17 cells - Absolute	None	Yes	No
15	CD3+CD4+CD127-/loCD25+FoxP3+ (CD4+) T regulatory cells - %	None	Yes	No
16	CD3+CD4+CD127-/loCD25+FoxP3+ (CD4+) T regulatory cells - Absolute	None	Yes	No
17	CD3+CD4+CD127-/loCD25+ (CD4+) IL2-producing naïve and central memory Helper T cells - %	None	Yes	No
18	CD3+CD4+CD127-/loCD25+ (CD4+) IL2-producing naïve and central memory Helper T cells - Absolute	None	Yes	No
19	CD20+ B cells – %	None	Yes	No
20	CD20+ B cells – Absolute	None	Yes	No
21	CD19+CD27-IgD+ mature naïve B cells – %	None	Yes	No
22	CD19+CD27-IgD+ mature naïve B cells – Absolute	None	Yes	No
23	CD19+CD27+IgD- switched memory B cells – %	None	Yes	No
24	CD19+CD27+IgD- switched memory B – Absolute	None	Yes	No
25	CD19+CD27+IgD+ non-switched memory B cells – %	None	Yes	No
26	CD19+CD27+IgD+ non-switched memory B – Absolute	None	Yes	No
27	CD19+CD27-IgD- Immature/transitional B cells – %	None	Yes	No
28	CD19+CD27-IgD- Immature/transitional B – Absolute	None	Yes	No
29	CD4/CD8 Ratio – Calculated	None	Yes	No
--	CD4+CD45RA-CCR7- effector memory T cells	None	No	No

Laboratory Group/Order	Laboratory Analyte	Reference Range Name	Analysis Type	
			Central Tendency	Outlier/Shift Analysis
--	CD4+CD45RA+CCR7- effector memory T cells	None	No	No
--	CD4+CD45RA+CCR7- naïve T cells	None	No	No
--	CD4+CD45RA-CCR7+ central memory T cells	None	No	No
--	CD8+CD45RA+CCR7+ naïve T cells	None	No	No
--	CD8+CD45RA-CCR7+ central memory T cells	None	No	No
--	CD8+CD45RA-CCR7- effector memory T cells	None	No	No
	CD8+CD45RA+CCR7- effector memory T cells	None	No	No

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; CD = cluster of differentiation; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LCTPB = Lilly Large Clinical Trial Population Based; LDL = low-density lipoprotein; MCHC = mean corpuscular hemoglobin concentration; NK = natural killer; UA = urinalysis.

7. References

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Approval	PPD Statistician 18-Mar-2022 02:51:35 GMT+0000

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