Statistical Analysis Plan (c): J1B-MC-FRCF

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Crossover Study to Evaluate the Efficacy and Safety of LY3454738 in Adults with Chronic Spontaneous Urticaria Inadequately Controlled with H1-Antihistamines

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Statistical Analysis Plan: J1B-MC-FRCF (c): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Crossover Study to Evaluate the Efficacy and Safety of LY3454738 in Adults with Chronic Spontaneous Urticaria Inadequately Controlled with H1-Antihistamines

LY3454738

Study J1B-MC-FRCF (c) is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 crossover study to evaluate the efficacy and safety of LY3454738 500 mg given intravenously (IV) every 2 weeks (Q2W) versus placebo IV Q2W in adults with CSU inadequately controlled with H1-antihistamines.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol J1B-MC-FRCF(c)
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

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2. Revision History

Statistical Analysis Plan (SAP) Version 2 is based on Protocol J1B-MC-FRCF (c) and was approved prior to unblinding.

SAP Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment A	*07-Jul-2020*
Original SAP	*05-Mar-2020*

Amendment A

Section # and Name	Description of Change	Brief Rationale
Section 5.2, Sample Size Determination	Updated the effect size assumption for LY3454738 and updated the power.	Clarified per ethics committee feedback.
Section 5.3.1, Analysis Populations	Added definition for Per-Protocol (PPS) population.	Added one more type of analysis populations.
Section 5.3.4.1, Demographics	Added this new subsection to clarify the patient's demographics we want to collect.	Added more details.
Section 5.3.4.2, Baseline Disease Characeteristics	Added this new subsection to clarify the patient's baseline disease activities information we want to collect.	Added more details.
Table FRCF.5.2, Description of Primary, Secondary and Exploratory Efficacy Analyses in Period 2	Added analyses of percent change from baseline for UAS7/ISS7/HSS7 at Week 12. Added analyses on PPS population for some key endpoints. Added the factors in the logistic regression model for DLQI(0,1).	Added more exploratory analyses. Added some analyses on PPS population.
Table FRCF.5.3, Description of Exploratory Efficacy Analyses in Period 3	Changed the analysis method for HSS7 change from baseline from "MMRM" to "Summary Statistics".	Typo correction.
Section 5.7.2, Adverse Events	Clarified the definition for TEAEs.	Minor clarification.

Section # and Name	Description of Change	Brief Rationale
Section 5.7.6.5, Columbia Suicide Severity Rating Scale	Deleted this whole section because this information is not available for this study.	Deleted unnecessary sections.
Section 5.8, Protocol Deviations	Changed the mITT population to PPS population.	Minor clarification.

3. Study Objectives

3.1. Primary Objective

The primary objective of this study is to test the hypothesis that treatment with LY3454738 is superior to placebo in adult participants with CSU, as assessed by the mean change from baseline at Week 12 in weekly Urticaria Activity Score (UAS7), which is the sum of weekly Itch Severity Score (ISS7) and weekly Hives Severity Score (HSS7).

3.2. Secondary Objectives

The secondary objectives of the study are the following:

Objectives	Endpoints
● To compare the efficacy of LY3454738 to placebo as measured by improvement in signs and symptoms of CSU	● Mean change from baseline to Week 12 in ○ ISS7 ○ HSS7 ● Proportion of patients achieving UAS7 ≤6 at Week 12
● To characterize the pharmacokinetics (PK) of LY3454738	● Cmax and AUC

3.3. Exploratory Objectives

Exploratory objectives and endpoints may include the following:

Objectives/Endpoints
• To evaluate signs and symptoms and measures of quality of life at various time points in Period 2 (first 12 week treatment period) and in Period 3 (second 12-week treatment period, after crossover) using the DLQI and the UPDD items. • To assess the potential development of anti-LY3454738 antibodies and their impact on the safety profile and PK of LY3454738. • To explore relationships between LY3454738 exposure and select biomarkers and clinical efficacy endpoints.

4. Study Design

4.1. Summary of Study Design

Study J1B-MC-FRCF (FRCF) is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 crossover study to evaluate the efficacy and safety of LY3454738 500 mg given intravenously (IV) every 2 weeks (Q2W) versus placebo IV Q2W in adults with CSU inadequately controlled with H_1-antihistamines.

The study duration will be up to approximately 39 weeks over 4 study periods, as shown below:

Period 1: Screening, lasting up to 35 days before Week 0 (Visit 2, baseline)

Period 2: First 12-week treatment, from Week 0 (Day 1) through Week 12:

- Participants will be randomized in a 3:1 ratio to receive either LY3454738 500 mg IV or placebo IV Q2W

Period 3: Second 12-week treatment (crossover), from Week 12 through Week 24:

- Participants who received LY3454738 500 mg IV in Period 2 will receive placebo IV Q2W in Period 3.
- Participants who received placebo IV in Period 2 will receive LY3454738 500 mg IV Q2W in Period 3.

Period 4: Post-treatment follow-up for approximately 10 weeks.

- Participants will not receive study drug in Period 4.
- The last dose of study drug is given at Week 22, which is 6 weeks before the first post-treatment follow-up visit (Visit 801). Thus, participants will have been withdrawn from study drug for a total of 12 weeks at the last post-treatment follow-up visit (Visit 802).

Approximately 85 patients will be screened to achieve approximately 60 randomized participants. A total of approximately 52 evaluable participants are expected.

Throughout the study, participants will take a second-generation H_1-antihistamine at a dose specified in approved product labeling. Certain participants may receive rescue therapy as described in Section 6.5.2 in the protocol.

Participants who permanently discontinue the study drug early will undergo early termination procedures, including an early termination visit (ETV) and the post-treatment follow-up visits specified in the Schedule of Activities (SoA) (Section 1.3 in the protocol).

Figure FRCF.4.1 illustrates the study design. The blinding procedure is described in the Protocol.

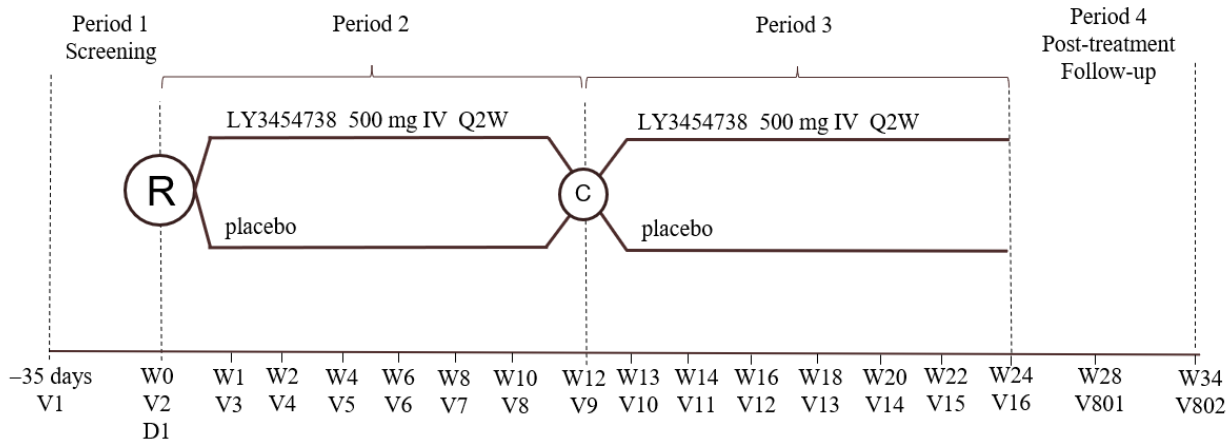

Figure FRCF.4.1. Illustration of study design for Clinical Protocol J1B-MC-FRCF.

Abbreviations: C = crossover visit; D = day; Q2W = every 2 weeks; R = randomization visit; W = study week relative to randomization visit; V = visit.

4.2. Method of Assignment to Treatment

Subjects who meet all criteria for enrollment will be randomized in a 3:1 ratio to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

5. A Priori Statistical Methods

5.1. Statistical Hypotheses

The study will compare LY3454738 with placebo in adults with CSU. The primary study objective is to demonstrate superior efficacy of LY3454738 over placebo.

The primary comparison of interest is the mean change of the UAS7 from baseline to Week 12. Secondary comparisons include the mean change of the ISS7 and the HSS7 from baseline to Week 12 as well as the proportion of participants achieving a UAS7 ≤6 at Week 12.

Efficacy comparisons will be made regardless of treatment discontinuation and without regard to changes to any background therapies. No adjustments for multiplicity will be made across the efficacy assessments.

5.2. Sample Size Determination

Assuming a 30% screen fail rate, approximately 85 participants will be screened to achieve 60 participants randomly assigned to study intervention for an estimated total of 52 evaluable participants.

The sample of 52 evaluable participants provides more than 87% power to the primary endpoint. This calculation is based on a 2-sample t-test, assuming a mean change from baseline to Week 12 in the UAS7 for LY3454738 and for placebo of 17 points and 10 points, respectively, a standard deviation of 7 points for the change from baseline, and a 0.05 two-sided significance level.

5.3. General Considerations

This plan describes *a priori* statistical analyses for efficacy, health outcomes, and safety that will be performed.

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly). The statistical analyses will be performed using SAS® Version 9.4 or higher.

Not all displays described in this SAP will necessarily be included in the clinical study report (CSR). 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 described in this SAP and not included in the CSR would be available upon request.

For continuous measures, summary statistics will include sample size, mean, standard deviation (SD), minimum, median, and maximum. The 1st quartile and 3rd quartile may also be presented. For categorical measures, summary statistics will include the sample size, frequency count, and percentage. Percentages will be presented to 1 decimal place unless otherwise stated. Percentages will not be presented for zero counts. Incidence rates and 95% confidence interval (CI) will be displayed for select safety endpoints.

Statistical tests of treatment effects and CIs will be performed at a 2-sided significance level of 0.05, unless otherwise stated.

All p-values will be rounded up to 3 decimal places. For example, any p-value strictly greater than 0.049 and less than or equal to 0.05 will be displayed as 0.050. This guarantees that on any printed statistical output, the unrounded p-value will always be less than or equal to the displayed p-value. A displayed p-value of 0.001 will always be understood to mean ≤0.001. Likewise, any p-value displayed as 1.000 will be understood to mean >0.999 and ≤1.

5.3.1. Analysis Populations

Entered: All participants who sign the informed consent form.

Modified Intent-to-Treat (mITT): All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention to which they were assigned.

Per-Protocol (PPS) population: The PPS populations is defined as all randomized patients who do not commit an Important Protocol Deviation (IPD) that could potentially compromise efficacy results. For more details, patients who missed more than one dose in Period 2 or were enrolled inadvertently will be excluded from Per-Protocol-Set.

Safety: All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received within each study period.

Pharmacokinetic (PK) Analysis: All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and have PK data available.

Efficacy analyses will be conducted on the Modified Intent-to-Treat (mITT) Population. This set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants were assigned.

Safety analyses will be conducted on the Safety Population. This set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants actually received.

5.3.2. Definition of Baseline and Postbaseline Measures

The baseline value for Period 2 is defined as the last nonmissing measurement on or before the date of first study drug administration (expected at Week 0). The baseline value for Period 3 is the last available value before the initial dose in Period 3 (expected at Week 12). Other definitions of the baseline value may be used to conduct additional supporting analyses.

A number of efficacy outcome measures are in the form of weekly scores derived from patient daily diary data. For these measures, the weekly score will be derived from the 7 days immediately prior to the study visit. The baseline score will be derived from the 7 days prior to Day 1 (Visit 2) for Period 2, and 7 days prior to Day 85 (Visit 9) for Period 3.

5.3.3. Patient Disposition

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated,

as well as number and percentage of participants completing the study (participants who receive at least 1 dose of study drug and have at least 1 postbaseline assessment), or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

5.3.4. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population. A summary of baseline participants and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported by cohort using descriptive statistics. Other participant baseline characteristics will be summarized by group as deemed appropriate.

5.3.4.1. Demographics

Patient demographics will be summarized as described above. The following demographic information will be included:

- Age
- Gender (male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)
- Region (US, Germany and Poland)
- Country
- Weight (kg)
- Height (cm)
- Body mass index (kg/m^2)

A listing of patient demographics will also be provided for the ITT population.

5.3.4.2. Baseline Disease Characteristics

The following baseline disease information (but not limited to only these) will be presented for baseline urticaria clinical characteristics, baseline health outcome measures, and other baseline demographic and disease characteristics as described above:

- Weekly Urticaria Activity Score (UAS7)
- Weekly Itch Severity Score (ISS7)
- Weekly Hives Severity Score (HSS7)
- Dermatology Life Quality Index (DLQI)

5.4. Handling of Dropouts or Missing Data

Missing continuous scores will be imputed using baseline observation carried forward (BOCF) analyses.

The UAS7 score is the sum of the daily UAS scores over 7 days each week. The daily score is the average of 2 results when both entries are made, or it is the single result when only 1 entry is made in a given day. When 1 or more of the daily UAS scores are missing, the following principles will be applied to handle the missing data:

- If a participant has at least 4 nonmissing daily UAS scores within the 7 days prior to the study visit, the UAS7 score is calculated as the sum of the available UAS scores in that week, divided by the number of days that have a nonmissing diary UAS score, multiplied by 7.
- If there are less than 4 nonmissing daily UAS scores within the prior 7 days, then the UAS7 score is missing for the week.

The same principles will be applied to handle the missing data for all of the weekly outcomes.

- Nonresponder imputation (NRI): All participants who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the analysis of categorical efficacy variables at discontinuation and subsequent visits.
- Mixed-effects model of repeated measures (MMRM): Continuous variables will be assumed to be missing after discontinuation for which an MMRM analysis will be performed. The model will include treatment, visit, and treatment-by-visit-interaction as fixed categorical effects and baseline and baseline-by-visit-interaction as fixed continuous effects. An unstructured (co)variance structure will be used to model the between- and within-patient errors. If this analysis fails to converge, the heterogeneous autoregressive [ARH(1)], followed by the heterogeneous compound symmetry (CSH), followed by the heterogeneous Toeplitz (TOEPH) will be used. The Kenward-Roger method will be used to estimate the degrees of freedom. Type III tests for the least-squares means (LSM) will be used for the statistical comparison. The LSM difference, standard error, p-value and 100(1-alpha)% CI will also be reported.
- BOCF, as previously stated.

5.5. Efficacy and Health Outcome Analyses

The general methods used to summarize efficacy data, including the definition of baseline value for assessments are described in Section 5.3.

Table FRCF.5.1 **Error! Reference source not found.**includes the descriptions and derivations of the primary, secondary, and exploratory efficacy and health outcomes.

Table FRCF.5.2 provides the detailed analyses including analysis type, method and imputation, population, time point, and comparisons for efficacy and health outcome analyses.

Table FRCF.5.1. Description and Derivation of Primary, Secondary and Exploratory Efficacy Outcomes

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Weekly Urticaria Activity Score (UAS7)	The UAS7 score is a composite measure of itch (0−3 point scale) and hives (0−3 point scale) recorded twice daily (morning and evening) that is averaged daily and summed over the course of 1 week (range 0 to 42). Scoring itch: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe. Scoring hives: 0 = None, 1 = Mild (1-6 hives/12 hour), 2 = Moderate (7-12 hives/12 hour), 3 = Intense (> 12 hives/12 hour). The UAS7 scores are categorized into five disease states: urticaria-free (UAS7 = 0), well-controlled urticaria (UAS7 = 1-6), mild-activity urticaria (UAS7 = 7-15), moderate-activity urticaria (UAS7 = 16-27) and severe-activity urticaria (UAS7 = 28-42).	▪ UAS7 score	The UAS7 score is the sum of the average daily UAS scores over 7 days each week (range 0 to 42). For each of the morning and evening entries, the UAS score is calculated as the sum of the itch and hives scores. The daily UAS score is then calculated as the average of the morning and evening UAS scores. The baseline UAS7 score is the sum of the daily UAS scores over the 7 days prior to randomization, and the UAS7 score at postbaseline visits is the sum of daily UAS scores over the 7 days prior to the visit. The same principles of calculating baseline and postbaseline weekly scores will be applied to the following weekly outcomes unless otherwise stated.	When either the morning or evening score is missing, the non-missing UAS score for that day (morning or evening) will be used as the daily score. When one or more of the daily UAS scores are missing, the following principles will be applied to handle the missing data: If a patient has at least 4 non-missing daily UAS scores within the 7 days prior to the study visit, the UAS7 score is calculated as the sum of the available UAS scores in that week, divided by the number of days that have a non-missing diary UAS score, multiplied by 7. If there are less than 4 non missing daily UAS scores within the prior 7 days, then the UAS7 score is missing for the week.
		▪ Change from baseline in UAS7 score	Change from baseline: observed UAS7 score – baseline UAS7 score	Missing if baseline or observed value is missing.
		▪ UAS7 ≤ 6	Observed UAS7 score ≤ 6	Single item, missing if missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		▪ UAS7 = 0	Observed UAS7 score = 0. UAS7 = 0 means symptom remission.	Single item, missing if missing.
		▪ Time to relapse	Relapse occurs at the first instance in Period 3 when a patient's UAS7 score is greater than 6 among the UAS7 ≤ 6 responders at Week 12.	Single item, missing if missing.
Weekly Itch Severity Score (ISS7)	The ISS7 score is the sum of daily itch score (ISS, 0−3 point scale) over 7 days (range 0 to 21), with daily itch score: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe. The daily itch score is the average of the morning and evening scores.	▪ ISS7 score	The ISS7 score is the sum of the average daily ISS scores over 7 days each week (range 0 to 21). The daily ISS score is calculated as the average of the morning and evening ISS scores.	When either the morning or evening score is missing, the non-missing ISS score for that day (morning or evening) will be used as the daily score. When one or more of the daily ISS scores are missing, the following principles will be applied to handle the missing data: If a patient has at least 4 non-missing daily ISS scores within the 7 days prior to the study visit, the ISS7 score is calculated as the sum of the available ISS scores in that week, divided by the number of days that have a non-missing diary ISS score, multiplied by 7. If there are less than 4 non missing daily ISS scores within the prior 7 days, then the ISS7 score is missing for the week.
		Change from baseline in ISS7 score	Change from baseline: observed ISS7 score – baseline ISS7 score	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		ISS7 = 0	Observed ISS7 score = 0. ISS7 = 0 means complete itch response.	Single item, missing if missing.
Weekly Hives Severity Score (HSS7)	The HSS7 score is the sum of daily number of hives score (HSS, 0−3 point scale) over 7 days (range 0 to 21), with daily number of hives score: 0 = None, 1 = Mild (1-6 hives/12 hour), 2 = Moderate (7-12 hives/12 hour), 3 = Intense (> 12 hives/12 hour). The daily number of hives score is the average of the morning and evening scores.	▪ HSS7 score	The HSS7 score is the sum of the average daily HSS scores over 7 days each week (range 0 to 21). The daily HSS score is calculated as the average of the morning and evening HSS scores.	When either the morning or evening score is missing, the non-missing HSS score for that day (morning or evening) will be used as the daily score. When one or more of the daily HSS scores are missing, the following principles will be applied to handle the missing data: If a patient has at least 4 non-missing daily HSS scores within the 7 days prior to the study visit, the HSS7 score is calculated as the sum of the available HSS scores in that week, divided by the number of days that have a non-missing diary HSS score, multiplied by 7. If there are less than 4 non missing daily HSS scores within the prior 7 days, then the HSS7 score is missing for the week.
		▪ Change from baseline in HSS7 score	Change from baseline: observed HSS7 score – baseline HSS7 score	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		▪ HSS7 = 0	Observed HSS7 score = 0. HSS7 = 0 means complete hives response.	Single item, missing if missing.
Dermatology Life Quality Index (DLQI)	The Dermatology Life Quality Index (DLQI) is a simple, patient-administered, 10-item, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include "a little," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and "not at all," or unanswered ("not relevant") responses scored as 0. Scores range from 0-30 with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related QoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).	▪ Symptoms and feelings domain	Sum of questions 1 and 2, range 0 to 6.	N/A – partial assessments cannot be saved.
		▪ Daily activities domain	Sum of questions 3 and 4, range 0 to 6.	N/A – partial assessments cannot be saved.
		▪ Leisure domain	Sum of questions 5 and 6, range 0 to 6.	N/A – partial assessments cannot be saved.
		▪ Work and school domain	Sum of questions 7 and 7B (if it is answered), range 0 to 3. Responses of "yes" and "no" on Question 7 are given scores of 3 and 0 respectively. If Question 7 is answered "no" then Question 7b is answered with "a lot", "a little", "not at all" getting scores of 2, 1, 0 respectively.	N/A – partial assessments cannot be saved.
		▪ Personal relationships domain	Sum of questions 8 and 9, range 0 to 6.	N/A – partial assessments cannot be saved.
		▪ Treatment domain	Question 10, range 0 to 3.	N/A – partial assessments cannot be saved.
		▪ DLQI total score	DLQI total score: sum of all six DLQI domain scores, range 0 to 30.	N/A – partial assessments cannot be saved.
		▪ Change from baseline in DLQI	Change from baseline: observed DLQI score – baseline DLQI score	Missing if baseline or observed value is missing.
		▪ DLQI 0/1	Observed DLQI score equals 0 or 1	N/A – partial assessments cannot be saved.

Table FRCF.5.2. Description of Primary, Secondary and Exploratory Efficacy Analyses in Period 2

Measure	Variable	Analysis Method	Population (Section 5.3.1)	Comparison/Time Point	Analysis Type
Weekly Urticaria Activity Score (UAS7)	• Change from baseline in UAS7 score at Week 12	ANCOVA using BOCF	mITT; PPS	LY3454738 500-mg vs PBO; Week 12	Primary analysis
	• Percent change from baseline in UAS7 score at Week 12	ANCOVA using BOCF	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Change from baseline in UAS7 score by visit (Week 0 through Week 12)	MMRM	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Percent change from baseline in UAS7 score by visit (Week 0 through Week 12)	MMRM	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Proportion of patients with UAS7 score ≤ 6 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline UAS7 (< median versus ≥ median) using NRI	mITT; PPS	LY3454738 500-mg vs PBO; Week 12	Secondary analysis
	• Proportion of patients with UAS7 score ≤ 6 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline UAS7 (< 28 versus ≥ 28) using NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Proportion of patients with UAS7 = 0 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline UAS7 (< median versus ≥ median) using NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Proportion of patients with UAS7 = 0 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline UAS7 (< 28 versus ≥ 28) using NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis

Measure	Variable	Analysis Method	Population (Section 5.3.1)	Comparison/Time Point	Analysis Type
Weekly Itch Severity Score (ISS7)	• Change from baseline in ISS7 score at Week 12	ANCOVA using BOCF	mITT; PPS	LY3454738 500-mg vs PBO; Week 12	Secondary analysis
	• Percent change from baseline in ISS7 score at Week 12	ANCOVA using BOCF	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Change from baseline in ISS7 score by visit (Week 0 through Week 12)	MMRM	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Percent change from baseline in ISS7 score by visit (Week 0 through Week 12)	MMRM	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Proportion of patients with ISS7 = 0 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline ISS7 (< median versus ≥ median) using NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Proportion of patients with ISS7 = 0 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline ISS7 (< 14 versus ≥ 14) using NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
Weekly Hives Severity Score (HSS7)	• Change from baseline in HSS7 score at Week 12	ANCOVA using BOCF	mITT; PPS	LY3454738 500-mg vs PBO; Week 12	Secondary analysis
	• Percent change from baseline in HSS7 score at Week 12	ANCOVA using BOCF	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Change from baseline in HSS7 score by visit (Week 0 through Week 12)	MMRM	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Percent change from baseline in HSS7 score by visit (Week 0 through Week 12)	MMRM	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Proportion of patients with HSS7 = 0 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline HSS7 (< median versus ≥ median) using NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis
	• Proportion of patients with HSS7 = 0 at Week 12	Cochran-Mantel-Haenszel test stratified by baseline HSS7 (< 14 versus ≥ 14) using NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory analysis

Measure	Variable	Analysis Method	Population (Section 5.3.1)	Comparison/Time Point	Analysis Type
Dermatology Life Quality Index (DLQI)	• DLQI total score at Week 12 • Change from baseline in DLQI at Week 12	MMRM	mITT; PPS	LY3454738 500-mg vs PBO; Week 12	Exploratory Analysis
	• Proportion of patients with DLQI 0/1 at Week 12	Logistic regression (Treatment as the only factor) with NRI	mITT	LY3454738 500-mg vs PBO; Week 12	Exploratory Analysis

Abbreviations: ANCOVA = Analysis of Covariance; BOCF = baseline observation carried forward; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; NRI = nonresponder imputation; PBO = placebo; PPS = per protocol set.

Table FRCF.5.3. Description of Exploratory Efficacy Analyses in Period 3

Measure	Variable	Analysis Method	Population (Section 5.3.1)	Analysis Type
Weekly Urticaria Activity Score (UAS7)	• Change from baseline in UAS7 score by visit (Week 12 through Week 24)	Summary Statistics	mITT	Exploratory analysis
	• Proportion of patients with UAS7 score ≤ 6 at Week 24	Summary Statistics	mITT	Exploratory analysis
	• Proportion of patients with UAS7 = 0 at Week 24	Summary Statistics	mITT	Exploratory analysis
	• Proportion of patients who maintain UAS7 score ≤ 6 at Week 24 among the responders at Week 12	Summary Statistics	mITT	Exploratory analysis
	• Median time to relapse	Summary Statistics	mITT	Exploratory analysis
Weekly Itch Severity Score (ISS7)	• Change from baseline in ISS7 score by visit (Week 12 through Week 24)	Summary Statistics	mITT	Exploratory analysis
	• Proportion of patients with ISS7 = 0 at Week 24	Summary Statistics	mITT	Exploratory analysis
Weekly Hives Severity Score (HSS7)	• Change from baseline in HSS7 score by visit (Week 12 through Week 24)	Summary Statistics	mITT	Exploratory analysis
	• Proportion of patients with HSS7 = 0 at Week 24	Summary Statistics	mITT	Exploratory analysis

Abbreviations: mITT = modified intent-to-treat

5.5.1. Primary Outcome and Methodology

The primary efficacy endpoint is the change in UAS7 score from baseline to Week 12 in Period 2, defined as the Week 12 UAS7 score minus the baseline UAS7 score. The analysis of the primary endpoint will consist of treatment comparisons made using analysis of covariance (ANCOVA) controlling for baseline UAS7 score. The ANCOVA model will be based on the mITT population. Missing Week 12 scores will be imputed by carrying forward the participants' baseline scores (BOCF) as described in Section 5.4.

The objective of the primary endpoint is to establish superiority of LY3454738 over placebo.

5.5.2. Secondary and Exploratory Efficacy and Health Outcomes Analyses

The secondary and exploratory efficacy analyses are detailed in Table FRCF.5.1**Error! Reference source not found.** and Table FRCF.5.2. There will be no adjustment for multiple comparisons forother analyses.

5.6. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic, Pharmacodynamic and Biomarker analyses to address secondary and exploratory objectives of this study will be described by Lilly in separate PK/PD and Biomarker analysis plans.

5.7. Safety Analyses

The general methods used to summarize safety data, including the definition of baseline value are described in Section 5.3.2.

Safety analyses will include data after rescue, unless otherwise stated, and patients will be analyzed according to the investigational product to which they were randomized at Week 0 (Visit 2). Additional analyses may be conducted using data after rescue to systemic therapy for some safety topics such as systemic treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs). Safety analyses will take place using the safety population defined in Section 5.3.1.

Safety topics that will be addressed include the following: AEs, clinical laboratory evaluations, vital signs and physical characteristics, Columbia Suicide Severity Rating Scale (C-SSRS), the Self-Harm Supplement Form, safety in special groups and circumstances, including adverse events of special interest (AESI) (see Section 5.7.5), and investigational product interruptions.

Unless otherwise specified, by-visit summaries will include planned on-treatment visits. For tables that summarize events (such as AEs, categorical lab abnormalities, shift to maximum value), post-last dose follow-up data will be included. Follow-up data is defined as all data occurring up to 30 days (planned maximum follow-up time) after last dose of treatment including rescue, regardless of study period except for deaths and malignancies. For deaths and malignancies, all available follow-up data up to the end of the study will be included. Listings will include all safety data.

For selected safety assessments, descriptive statistics may be presented for the last measure observed during post-treatment follow-up (up to 30 days after the last dose of treatment including rescue, regardless of study period).

5.7.1. Extent of Exposure

Duration of exposure (in days) to study drug will be summarized for the safety population in both Period 2 and 3 by treatment group using descriptive statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile, maximum).

For subjects without drug interruption, the duration of exposure for each patient is the date of last dose – date of first dose +1. If subjects have drug interruption, the duration of exposure for each patient is the (Treatment end date before drug interruption – date of first dose +1) + (date of last dose – treatment re-start date +1).

5.7.2. Adverse Events

Adverse events are recorded in the eCRFs. Each AE will be coded to system organ class (SOC) and preferred term (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.

A TEAE is defined as an event that either first occurred or worsened in severity after the first dose of study treatment and on or prior to the last visit date during the analysis period. For each event classification term, the number of participants experiencing a TEAE with that classification term will be tabulated. For this study, the TEAEs should be counted by periods: TEAEs for Period 2 for V2-V9; TEAEs for Period 3 for V10-V16; TEAEs for Period 4 after V16.

Treatment-related TEAEs are defined as events that are indicated by the investigator on the eCRF to be related to treatment. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

Adverse events are classified based upon the MedDRA PT. 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 up to first dose of the study medication will be used as baseline. If an event with missing severity is preexisting during the baseline period, and persists during the treatment period, then the baseline severity will be considered mild for determining TEAE (that is, the event is treatment-emergent if the severity is coded moderate or severe postbaseline and not treatment-emergent if the severity is coded mild postbaseline). If an event occurring postbaseline has a missing severity rating, then the event is considered treatment-emergent. The day and time for events where onset is on the day of the first dose of study treatment will both be used to distinguish between pretreatment and posttreatment in order to derive treatment-emergence. Should there be insufficient data for AE start date to make this comparison (for example, 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.

In an overview table, the number and percentage of subjects who experienced a TEAE or serious adverse event (SAE), died due to an AE, or discontinued from study due to an AE will be summarized by treatment.

The frequency and percentages of patients with TEAEs will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC. The frequency and percentages of patients with TEAEs by maximum severity will also be summarized by treatment using MedDRA PT nested within SOC.

Fisher's exact test will be performed to compare percentages for each LY3454738 dose group and Placebo at both the SOC and PT levels.

Listings will be presented for all AEs, all SAEs, all AEs leading to death, all AEs leading to study drug temporary interruption, and all AEs leading to discontinuation from the study.

In this study, the following events are being captured as study endpoints and will not be reported as AEs:

- Pruritus (itching)
- Angioedema
- Hives (wheals)

Information on these events will be captured via the UPDD (patient electronic diary).

However, if any of these events is an SAE, the event should be reported as an SAE.

5.7.2.1. Serious Adverse Event Analyses

The number and percentage of patients who experienced an SAE (including the SAEs that led to death) during the study drug period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

5.7.2.2. Other Significant Adverse Events

The number and percentage of patients who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the study drug period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency within SOC.

Fisher's exact test will be performed to compare percentages for each LY3454738 dose group and Placebo at both the SOC and PT levels.

5.7.3. Clinical Laboratory Evaluation

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol. Summaries will be provided in both Système International (SI) and United States (US) conventional (CN) units (when different). Limits from the performing lab will be used to define low and high. Analyses of laboratory values will be produced using the measurements collected at scheduled time points. All unscheduled assessments will appear only in data listings.

- **Box plots for observed values:** Values at each visit (starting at randomization) will be displayed in box plots for patients who have both a baseline and a result for the specified visit. Unplanned measurements will be excluded. Original-scale data will be used for the display. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries. The box plot will be a notched box for each treatment with outliers displayed, individual measurements outside of reference limits will also be displayed using distinct symbols overlaying the box plot, and descriptive summary statistics will be included in a table below the box plot.
- **Box plots for change values:** Change from baseline to each visit will be displayed in box plots for patients who have both a baseline and a result for the specified visit. Change from baseline to last observation will also be summarized and analyzed for patients who have both baseline and at least 1 postbaseline result. Baseline will be the last non-missing observation in the baseline period. The last non-missing observation in the Dosing Period will be used as the last observation. Unplanned measurements will be excluded. The box plot will be a notched box for each treatment with outliers displayed, change from baseline to last observation will be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot, along with a p-value using the ANCOVA model containing terms for treatment and the continuous covariate of baseline measurement. Type III sums of squares will be used. The significance of within-treatment group changes from baseline will be evaluated by testing whether the treatment group LSMean changes from baseline are different from zero using a t-statistic. In addition to the LSMeans and tests, the SD, minimum, Q1, median, Q3, and maximum will be displayed.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin will not be included in this analysis as different ranges will be used as described in Section 5.7.5.

5.7.4. Vital Signs and Other Physical Findings

Vital signs and physical characteristics include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, weight, and BMI. 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 and/or treatment-emergent abnormalities, planned and unplanned measurements will be included.

The planned analyses described for the laboratory analytes in Section 5.7.3 will be used to analyze the vital signs and physical characteristics, except for the inclusion of a threshold for change in addition to a limit for the definition of treatment-emergent.Table FRCF.5.3 defines the low and high baseline values as well as the criteria used to define treatment-emergence based on post-baseline values.

Table FRCF.5.3. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

Parameter	Low mmHg	High mmHg
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg) (Consistent clothing and timing in relationship to meals and voiding)	(Loss) decrease ≥7%	(Gain) increase ≥7%

5.7.5. Immunogenicity

Frequencies and percentages will be tabulated for the following:

- participants with pre-existing ADA, and
- participants who are treatment-emergent ADA positive (TE-ADA+) to LY3454738.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies, when available, will also be tabulated for the TE-ADA+ participants.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3454738 may be assessed.

5.7.6. Special Safety Topics, including Adverse Events of Special Interest

In addition to general safety parameters, safety information on specific topics of special interest will also be presented. Additional special safety topics may be added as warranted. The topics outlined in this section include the protocol-specified AESI.

In general, for topics regarding safety in special groups and circumstances, patient profiles and/or patient listings, where applicable, will be provided when needed to allow medical review of the time course of cases/events, related parameters, patient demographics, study drug treatment and meaningful concomitant medication use. In addition to the safety topics for which

provision or review of patient data is specified, these will be provided when summary data are insufficient to permit adequate understanding of the safety topic.

5.7.6.1. Abnormal Hepatic Tests

Analyses for abnormal hepatic tests will involve 4 laboratory analytes: ALT, AST, total bilirubin, and ALP. In addition to the analyses described in Section 5.7.3, this section describes specific analyses for this topic.

The central laboratory reference ranges (CLRM reference ranges) will be used for these laboratory assessments (ALT, AST, total bilirubin, and ALP).

Analyses for change from baseline to last observation, change from the baseline value to the minimum value during Period 2 and 3, change from the baseline value to the maximum value during Period 2 and 3, and treatment-emergent high or low laboratory results at any time are described in Section 5.7.3.

The patients with the following abnormal elevations in hepatic laboratory tests at any time will be listed for both Period 2 and 3:

- ALT measurement ≥3 times, ≥5 times and ≥10 times the central laboratory ULN.
- AST measurement ≥3 times, ≥5 times and ≥10 times the central laboratory ULN.
- Total bilirubin measurement ≥2 times the central laboratory ULN.
- ALP measurement ≥1.5 times the central laboratory ULN.

5.7.6.2. Renal Function Effects

Effects on renal function will be assessed through analysis of elevated creatinine.

The CTCAE will be applied for laboratory tests related to renal effects (Table FRCF.5.4). This CTCAE grading scheme is consistent with both Version 3.0 and Version 4.03 of the CTCAE guidelines.

Shift tables will show the number and percentage of subjects from baseline to maximum during Period 2 and 3, with baseline depicted by highest grade during the baseline period. A shift table summary displaying the number and percentage of subjects with maximum postbaseline results will be presented by treatment group within the following categories:

- Decreased; postbaseline category < baseline category
- Increased; postbaseline category > baseline category
- Same; postbaseline category = baseline category.

Treatment-emergent lab abnormalities related to elevated creatinine occurring at any time during the Dosing Period will be tabulated using the CTCAE grades shown in Table FRCF.5.4. Planned and unplanned measurements will be included.

Treatment-emergence will be characterized using 5 criteria:

- any increase in postbaseline CTCAE grade from worst baseline grade
- increase to Grade 1 or above at worst postbaseline
- increase to Grade 2 or above at worst postbaseline
- increase to Grade 3 or above at worst postbaseline
- increase to Grade 4 at worst postbaseline.

Table FRCF.5.4 Common Terminology Criteria for Adverse Events (CTCAE) Related to Renal Effects

Lab Test	CTCAE Version	Grade	Criteria in SI or CN Units
Elevated creatinine	3.0	0 (normal)	≤ ULN
		1	> ULN and ≤1.5× ULN
		2	>1.5× ULN and ≤3× ULN
		3	>3× ULN and ≤6× ULN
		4	>6× ULN

Abbreviations: CN = conventional (US); CTCAE = Common Terminology Criteria for Adverse Events; SI = Système International; ULN = upper limit of normal.

5.7.6.3. Infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC, with additional terms from the Investigations SOC being used in selected instances, as described below.

Treatment-emergent infections will be analyzed according to various groups of infectious events including:

- all infections
  - all PTs in the Infections and Infestations SOC,
- serious infections
  - all PTs in the Infections and Infestations SOC that are SAEs,
- infections that require therapeutic intervention (antibiotics, antivirals, antifungals, and so on)
  - all PTs in the Infections and Infestations SOC for which there is an antimicrobial concomitant medication associated with that event for that subject,
- herpes zoster
  - specific Lilly-defined PTs from the Herpes Viral Infections high-level term (HLT) in the Infections and Infestations SOC, shown in Appendix 1,
- tuberculosis
  - specific Lilly-defined PTs from the Tuberculous Infections HLT and the Investigations SOC, shown in Appendix 2
- viral hepatitis
  - all PTs from the Hepatitis Viral Infections HLT (HLT code 10057212) in the Infections and Infestations SOC.

For each infection event, the frequency for each PT will be provided, ordered by decreasing frequency in the LY3454738 highest dose group by infection group: all infections, serious infections (overall and on each approach to identifying SAEs), infections that require therapeutic intervention, herpes zoster infections, tuberculosis, and viral hepatitis.

In addition to the incidence of infectious AEs by MedDRA PT as described above, the number and percentage of subjects with treatment-emergent infectious AEs by treatment group will be summarized and listed.

Potential Opportunistic Infections:

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

POIs are identified from TEAEs based on a Lilly-defined list of MedDRA PTs, shown in the Appendix 3. These PTs are a subset of terms from the Infections and Infestations SOC.

For the POIs identified from MedDRA PTs, the number and percentage of subjects overall and for each specific PT will be summarized by treatment group, with specific event terms ordered by decreasing frequency in the LY3454738 highest dose.

Association of Infections with Lymphopenia or Neutropenia:

The relationship between the occurrence of lymphopenia and neutropenia with the occurrence of infections will be evaluated based on case reviews. Inferential analyses and/or graphical displays may be conducted if warranted. Infection outcomes considered for this analysis are any infection, any serious infection, infections that require therapeutic intervention (antibiotics, antivirals, antifungals, and so on), tuberculosis, herpes zoster, and viral hepatitis.

5.7.6.4. Allergic Reactions/Hypersensitivities

A search will be performed using the current MedDRA version 20.0 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.

5.8. Protocol Deviations

Protocol deviations will be tracked by the clinical team, and their importance will be assessed by key team members during protocol deviation review meetings. Out of all important protocol deviations (IPDs) identified, a subset occurring during Period 2 prior to the primary endpoint (Week 12) with the potential to affect efficacy analyses will result in exclusion from the PP population.

Potential examples of deviations include patients who receive excluded concomitant therapy, significant non-compliance with study medication (<80% of assigned doses taken, failure to take study medication and taking incorrect study medication), patients incorrectly enrolled in the study, and patients whose data are questionable due to significant site quality or compliance issues. Refer to a separate document for the important protocol deviations.

The number and percentage of patients having IPD(s) will be summarized within category and subcategory of deviation by treatment group for Period 2 using the mITT population. Individual patient listings of IPDs will be provided. A summary of reasons patients were excluded from the PPS will be provided by treatment group.

5.9. Interim Analyses and Data Monitoring

The assessment committee is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are given in a separated unblinding plan.

Analysis for the primary database lock will be conducted when all participants have completed the Period 2 (or discontinued Period 2 treatment). An interim analysis prior to the primary database lock may be conducted when approximately 50% of the participants have had the opportunity to complete Period 2 (including those who discontinued Period 2 treatment). Other interim analyses may be conducted as needed. All interim analyses will be used to support planning activities associated with the development program. No adjustment of type I error will be performed.

The assessment will be conducted by an internal assessment committee with a limited number of prespecified team members who do not have direct site contact or data entry/validation responsibilities. A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses may be conducted to review unblinded safety data. The analyses will be conducted and reviewed by an internal assessment committee composed of personnel who do not have direct site contact or data entry/validation responsibilities.

Details of the planned interim data analyses and the assessment committee data review process are included in an assessment committee charter.

5.10. Annual Report Analyses

Annual report analyses, such as the Development Update Safety Report (DSUR), will be documented in a separate document.

5.11. 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 a summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AE are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE 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/patients 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.

Similar methods will be used to satisfy the European Clinical Trials Database (EudraCT) requirements.

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7. Appendices

Appendix 1. Lilly-Defined MedDRA Preferred Terms for Herpes Zoster

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Herpes zoster	10019974
Ophthalmic herpes zoster	10030865
Herpes zoster infection neurological	10061208
Herpes zoster oticus	10063491
Herpes zoster disseminated	10065038
Genital herpes zoster	10072210
Herpes zoster pharyngitis	10074245
Herpes zoster meningoencephalitis	10074248
Herpes zoster meningomyelitis	10074251
Herpes zoster meningitis	10074259
Herpes zoster cutaneous disseminated	10074297
Varicella zoster virus infection	10075611

Appendix 2. Lilly-Defined MedDRA Preferred Terms for Tuberculosis

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Adrenal gland tuberculosis	10001358
Bone tuberculosis	10056377
Bovine tuberculosis	10006049
Choroid tubercles	10008779
Congenital tuberculosis	10010657
Conjunctivitis tuberculous	10010754
Cutaneous tuberculosis	10011684
Disseminated tuberculosis	10013453
Ear tuberculosis	10014027
Epididymitis tuberculous	10015004
Erythema induratum	10015213
Extrapulmonary tuberculosis	10064445
Female genital tract tuberculosis	10061150
Immune reconstitution inflammatory syndrome associated tuberculosis	10072797
Interferon gamma release assay positive	10072866
Intestinal tuberculosis	10075268
Joint tuberculosis	10056367
Latent tuberculosis	10065048
Lupus vulgaris	10025143
Lymph node tuberculosis	10025183
Male genital tract tuberculosis	10061234
Meningitis tuberculosis	10027259
Mycobacterium tuberculosis complex test positive	10070325
Oesophogeal tuberculosis	10030200
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
Tuberculin test positive	10044728
Tuberculoma of central nervous system	10052883
Tuberculosis	10044755
Tuberculous abscess central nervous system	10052884
Tuberculosis bladder	10044758
Tuberculosis gastrointestinal	10061390

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Tuberculosis liver	10058120
Tuberculosis of central nervous system	10061391
Tuberculosis of eye	10044819
Tuberculosis of genitourinary system	10044828
Tuberculosis of intrathoracic lymph nodes	10044846
Tuberculosis of peripheral lymph nodes	10044965
Tuberculosis ureter	10045026
Tuberculous endometritis	10071559
Tuberculous laryngitis	10045072
Tuberculous pleurisy	10045104
Tuberculous tenosynovitis	10059161

Appendix 3. Lilly-Defined MedDRA Preferred Terms for Potential Opportunistic Infections

Preferred Term (MedDRA Version 18.0)	Preferred Term Code
Candida pneumonia	10053158
Respiratory moniliasis	10038705
Gastrointestinal candidiasis	10017938
Oesophageal candidiasis	10030154
Coccidioides encephalitis	10054214
Coccidioidomycosis	10009825
Cutaneous coccidioidomycosis	10068747
Meningitis coccidioides	10027207
Cryptococcal cutaneous infection	10054216
Cryptococcal fungaemia	10067112
Disseminated cryptococcosis	10013439
Gastroenteritis cryptococcal	10011485
Meningitis cryptococcal	10027209
Neurocryptococcosis	10068368
Biliary tract infection cryptosporidial	10067319
Gastroenteritis cryptosporidial	10017899
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
Cytomegalovirus hepatitis	10011830
Cytomegalovirus mucocutaneous ulcer	10065036
Cytomegalovirus myelomeningoradiculitis	10065621
Cytomegalovirus myocarditis	10056261
Cytomegalovirus oesophagitis	10049018
Cytomegalovirus pancreatitis	10049566
Cytomegalovirus pericarditis	10056721
Cytomegalovirus proctocolitis	10049019
Cytomegalovirus urinary tract infection	10051350
Disseminated cytomegaloviral infection	10049075
Encephalitis cytomegalovirus	10014586

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