Statistical Analysis Plan Version 3 J1P-MC-KFAJ

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of LY3471851 (NKTR-358) in Adults with Systemic Lupus Erythematosus

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1. Statistical Analysis Plan: J1P-MC-KFAJ: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of LY3471851 (NKTR-358) in Adults with Systemic Lupus Erythematosus

Confidential Information

LY3471851

Study J1P-MC-KFAJ is a randomized, double-blind, placebo-controlled, Phase 2 study of LY3471851 (NKTR-358), designed to investigate the efficacy and safety of LY3471851 CCI in adult patients with Systemic Lupus Erythemotosus.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol J1P-MC-KFAJ
Phase 2

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List of Abbreviations and Definitions of Terms

Term	Definition
CCI	
AE	adverse events
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group – 2004
CCI	
CD	cluster of differentiation
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Registry
ECG	electrocardiogram
eCRF	electronic case report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
ETV	early termination visit
HbsAb	hepatitis B surface antigen
HbcAb	hepatitis B core antibody
HBV	hepatitis B virus

Term	Definition
HDL	high-density lipoprotein
IAC	internal assessment committee
ICE	intercurrent event
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IL	interleukin
IR	incidence rate
ISR	injection site reaction
IWRS	interactive web-response system
LCTPB	Large Clinical Trial Population Based
LDL	low-density lipoprotein
LLDAS	Lupus Low Disease Activity State
LS	least squares
LTT	Lowest Level Term
CCI [redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed models for repeated measures
NRI	nonresponder imputation
CCI [redacted]	
NK	natural killer
NMSC	nonmelanoma skin cancers
CCI [redacted]	
PEG	polyethylene glycolated
PK	pharmacokinetic
POI	potential opportunistic infections

Term	Definition
PRO	patient-reported outcomes
PT	Preferred Term
PY	patient-year
Q2W	every 2 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology Self-Rated
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLEDAI-4	a ≥4-point reduction in SLEDAI-2K score from baseline
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SRI-4	Systemic Lupus Erythematosus Responder Index-4
CCI	[redacted]
TEAE	treatment-emergent adverse events
ULN	upper limit of normal


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4. Study Objectives

4.1. Primary Objective

Objectives	Endpoints/Estimands
• To determine whether treatment with LY3471851 Q2W is superior to placebo in reducing the signs and symptoms of SLE as measured by SLEDAI-4	• The study will compare LY3471851 with placebo in participants with SLE. • The primary comparison of interest is the difference in proportion of participants who achieve SLEDAI-4 response at Week 24. • The primary comparison will be assessed using a composite estimand where the intercurrent events of premature discontinuation and use of prohibited medication are part of the response definition.

Abbreviations: Q2W = every 2 weeks; SLE = systemic lupus erythematosus; SLEDAI-4 = a ≥4-point reduction in SLEDAI-2K score from baseline; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

4.2. Secondary Objectives

The secondary objectives of the study are the following:

Objectives	Endpoints/Estimands
• To determine whether treatment with LY3471851 Q2W is superior to placebo in reducing other measures of signs and symptoms of SLE	• The study will compare LY3471851 with placebo in participants with SLE. • Secondary comparisons of interest are the difference in proportion of participants who at Week 24 (V15) achieve: o BILAG-based Composite Lupus Assessment (BICLA) response o SRI-4 response o Lupus Low Disease Activity State (LLDAS) • Secondary objectives will be assessed using a composite estimand.
• To characterize the pharmacokinetics of LY3471851 in participants with SLE	• LY3471851 plasma trough concentrations at Week 24 (V15)

Abbreviations: BILAG = British Isles Lupus Assessment Group – 2004; Q2W = every 2 weeks; SLE = systemic lupus erythematosus; SRI-4 = Systemic Lupus Erythematosus Responder Index-4; V = Visit.


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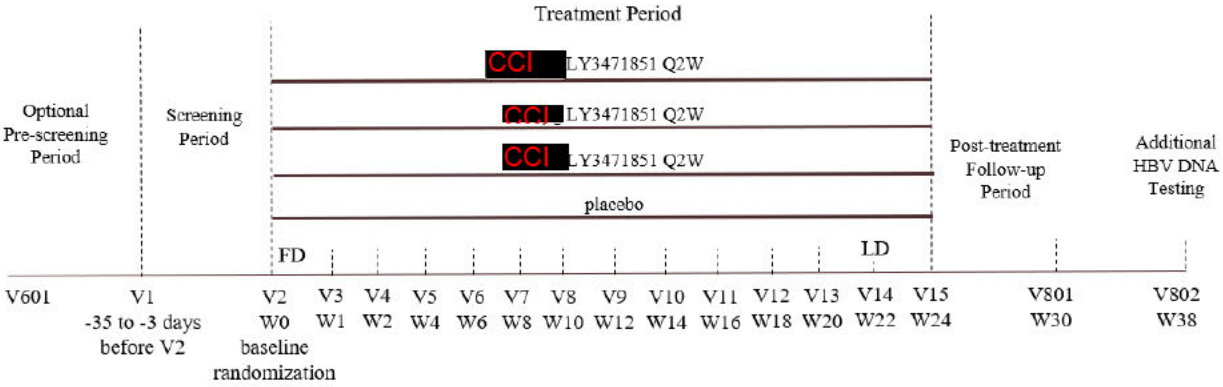
5. Study Design

5.1. Summary of Study Design

Study KFAJ is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study to evaluate the efficacy and safety of LY3471851 in adult study participants with at least moderately active SLE. The study has 3 required study periods and an optional prescreening period. A schematic of the study design is presented in Figure 5.1.



Note: Visit 802 is for HBV DNA testing of randomized participants who were positive for antibody to hepatitis B core antigen (anti-HBc) at screening.

Abbreviations: anti-HBc = hepatitis B core antibody; FD = first dose administered; HBV = hepatitis B virus; LD = last dose administered; Q2W = every 2 weeks; V = eCRF visit; W = study week relative to baseline visit.

Figure 5.1. Schema of Study J1P-MC-KFAJ, a Phase 2 study to evaluate the efficacy and safety of LY3471851 in adults with systemic lupus erythematosus.

Optional prescreening period: The optional prescreening period is prior to Visit 1. The optional prescreening visit (Visit 601) is intended for those investigators who opt for central laboratory assessment of the prospective participant's antinuclear antibodies, anti-double stranded DNA, and anti-Smith antibody status before full screening activities are initiated. The prescreening visit can be repeated 2 times (no more) per participant, with a minimum of 4 weeks between visits.

Screening period: The required screening period begins with Visit 1, which occurs within 5 weeks before the planned randomization visit (Week 0, Visit 2). Participants found to be eligible according to all of the study entry criteria will be randomly assigned in a 1:1:1:1 ratio to receive one of the following study interventions:

- CCI LY3471851 Q2W
- CCI LY3471851 Q2W
- CCI LY3471851 Q2W, and
- placebo Q2W.

Participants will be stratified at randomization according to disease activity at baseline, corticosteroid dose at baseline, and geographic region (Section 5.2). Study interventions will be administered via subcutaneous injection.

Double-blind treatment period: Randomized participants will begin the double-blind, placebo-controlled, 24-week treatment period at Visit 2. Participants will receive the first dose of the assigned study intervention at that visit and will continue to receive doses through the last scheduled dosing visit specified in protocol. Participants will maintain their usual standard-of-care medication regimen for SLE and for other diseases throughout the study, unless these medication regimens are specifically excluded by the study entry criteria. Safety and efficacy assessments and laboratory sample collections will be performed as specified in the protocol.

Follow-up period: All participants will have a posttreatment follow-up visit (Visit 801) for safety assessments. Randomized participants who were positive for anti-HBc at screening will have one additional posttreatment 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 protocol.

5.2. Method of Assignment to Treatment

Subjects who meet all criteria for enrollment will be randomized 1:1:1:1 to double-blind treatment at Visit 2. Participants will be stratified at randomization according to disease activity at baseline (SLEDAI-2K <10; SLEDAI-2K ≥10), corticosteroid dose at baseline (<10 mg/day or ≥10 mg/day), and geographic region. Table KFAJ.5.1 describes how each region will be defined for the stratification at randomization as well as the statistical analyses and summaries.

Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign vials containing double-blind investigational product to each patient. Site personnel will confirm that they have located the correct vials by entering a confirmation number found on the vials into the IWRS. The IWRS will be used to assign investigational product to each patient. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on packages into the IWRS.

Table KFAJ.5.1. Countries and Their Geographical Regions

Geographical Region	Country or Countries
North America	Canada, United States, Puerto Rico
Latin America	Argentina, Mexico
Europe	Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Romania, Spain, United Kingdom
Asia	South Korea, Taiwan
Japan	Japan
Rest of World	Australia, India, Israel, Russia, Ukraine

6. A Priori Statistical Methods

6.1. Determination of Sample Size

CCI [redacted] will be randomly assigned to study intervention. All randomized participants in the mITT population as defined in Section 6.6 will be considered evaluable.

Pairwise 2-sided tests of proportions with alpha = 0.05 will be performed on each LY3471851 dose versus placebo CCI [redacted], a placebo response of 0.40, and a LY3471851 response of 0.64 for the maximally efficacious LY3471851 dose, there is at least 80% power to detect a statistically-significant difference in SLEDAI-4 response between LY3471851 and placebo at Week 24 (Visit 15).

6.2. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee. For primary and key secondary objectives, statistical analyses will be performed CCI [redacted]

Not all displays described in this SAP will necessarily be included in the CSR. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools such as Spotfire 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.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. The p-values will be rounded up to 3 decimal places. For example, any p-value strictly >0.049 and ≤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.

The primary analysis method for treatment comparisons of categorical efficacy and health outcome variables will be made using a logistic regression analysis with treatment group, baseline disease activity (SLEDAI-2K <10; SLEDAI-2K ≥10), corticosteroid dose at baseline (<10 mg/day or ≥10 mg/day), and geographic region (North America, Latin America, Europe, Asia, Japan, Rest of World) in the model. For each treatment comparison, an estimate of the treatment difference with corresponding Wald 95% CI, the odds ratio with corresponding Wald 95% CI and p-value will be presented. Each treatment group will be compared to the placebo group. The p-value for all other explanatory variables will also be presented. When logistic regression sample size requirements are not met (<5 subjects in any category for any factor), treatment comparison will be performed using the Fisher's exact test.

The primary analyses for continuous efficacy and health outcome variables will be made using MMRM. When MMRM is used, the model will include treatment, baseline score, baseline disease activity (SLEDAI-2K <10; SLEDAI-2K ≥10), corticosteroid dose at baseline (<10 mg/day or ≥10 mg/day), geographic region (North America, Latin America, Europe, Asia, Japan, Rest of World), visit (as categorical variable), the interaction of treatment-by-visit, and

the interaction of baseline value-by-visit as fixed factors. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If this analysis fails to converge, the following structures will be tested in this pre-specified order: 1) heterogeneous Toeplitz, 2) heterogeneous autoregressive, 3) heterogeneous compound symmetry, 4) Toeplitz, 5) autoregressive), and 6) compound symmetry. The first covariance structure that converges using this prespecified order will be used. The Kenward-Roger method will be used to estimate the degrees of freedom. Type III sums of squares for the LS means will be used for the statistical comparison. The LS mean for each treatment group along with the estimate of the difference between treatments (difference between each LY3471851 dose group and placebo), standard error, p-value, and the 95% CIs will be reported at each visit along with p-values. For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected, due to early discontinuation visits. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM analyses (Andersen and Millen 2013). However, the data will still be used in other analyses.

When ANCOVA is used for efficacy/Health Outcomes measures, the model will include treatment, baseline score, baseline disease activity (SLEDAI-2K <10; SLEDAI-2K ≥10), corticosteroid dose at baseline (<10 mg/day or ≥10 mg/day), and geographic region as fixed factors. Type III sums of squares will be used. Differences in LS means between treatment groups will be displayed, with the p-value associated with the LS mean comparison to placebo (for each LY3471851 dose group) along with the 95% CI of the LS mean difference also provided. In addition to the LS means and tests, mean, SD, minimum, first quartile, median, third quartile, and maximum will be displayed.

When Cox regression is used for time-to-event variables, the model will include treatment, baseline score, baseline disease activity (SLEDAI-2K <10; SLEDAI-2K ≥10), corticosteroid dose at baseline (<10 mg/day or ≥10 mg/day) and geographic region (North America, Latin America, Europe, Asia, Japan, Rest of World). Treatment comparisons will use the hazard ratios and corresponding p-values from the Cox regression. The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-event variables. Patients completing the treatment period without event will be censored at the date of completion. Patient without an event, a date of completion, or discontinuation for the treatment period will be censored at the latest nonmissing date out of the following dates: date of last dose and date of last attended visit in the treatment period. Under the hypothetical estimand strategy, patients without an event prior to the first violation of concomitant medication rules will be censored at the time of the first violation of concomitant medication rules.

Efficacy and PRO analysis models may contain the independent variables such as treatment group, baseline disease activity, and geographic region.

Any change to the data analysis methods described in the SAP will require an amendment only if the change affects a principal feature of the SAP. Any other change to the data analysis methods described in the SAP, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

6.4. Definition of Baseline and Postbaseline Measures

Baseline will be defined as the last available value before the first dose of study drug for both efficacy and safety analyses, unless otherwise specified. In most cases, this will be the measure recorded at Week 0 (Visit 2). The treatment period starts after the first study drug administration and ends on one of the following:

- date of Visit 15 (Week 24) for patients who completed the treatment period
- for patients who discontinued treatment early
    - date of ETV, if ETV occurs less than 42 days after treatment discontinuation
    - date of the last visit that occurs less than 42 days after treatment discontinuation, if ETV occurs after 42 days since treatment discontinuation.

Change from baseline will be calculated as the visit value of interest minus the baseline value. Percent change from baseline will be calculated as 100 times change from baseline divided by baseline.

Postbaseline measurements are collected after study drug administration through Visit 15 (Week 24) or an early discontinuation visit. For electronic PROs related to efficacy assessments, unscheduled postbaseline visits that fall within the protocol-defined visit windows will be summarized in the by-visit analyses if there is no scheduled visit available. If more than 1 value is reported for the same scheduled visit, then the first value will be summarized in the by-visit analyses.

The Follow-up Period includes all visits that are 42 days or more after treatment discontinuation for patients who discontinue the treatment period early. For patients who complete the treatment period, the Follow-up Period includes Visit 801 for safety assessment. Randomized participants who were positive for anti-HBc at screening will have one additional posttreatment follow-up visit (Visit 802). The baseline value for the safety analysis of the posttreatment follow-up period is defined as the last nonmissing assessment prior to entering the posttreatment Follow-up Period, that is Week 24 (Visit 15) for treatment completers or last visit that occurred less than 42 days after treatment discontinuation for patients that discontinued treatment early. When the

Follow-up Period includes more than 1 visit, any safety analyses that are done for this period will only include the first visit of this period.

6.5. Primary, Secondary, and Supportive Estimands

Unless otherwise specified, a composite strategy will be used for categorical efficacy endpoints, as described in Section 6.5.1. A hypothetical strategy will be used for continuous efficacy endpoints, as described in Section 6.5.4.

6.5.1. Primary Estimand

The primary clinical question of interest is: What is the difference between LY3471851 and placebo in the target patient population, in achieving a successful response at Week 24 without violating concomitant medication rules?

The violation of concomitant medication rules for this study includes (i) initiating or increasing in dose of corticosteroids, antimalarial, or immunosuppressant, or (ii) using prednisone >10 mg per day (or equivalent) after Week 12.

The estimand for the primary objective is described by the following attributes:

- population: modified intent-to-treat population
- endpoint: SLEDAI-4 at Week 24
- how to account for ICEs: A **composite estimand strategy** will be used. Participants with violation of concomitant medication rules will be considered as treatment failure, that is, a nonresponder, after the first occurrence of violation of concomitant medication rules.
- population-level summary: difference in response rate of SLEDAI-4 at Week 24 between LY3471851 and placebo, and
- rationale for estimand: the primary estimand strategy assumes that a participant, who violates concomitant medications, was not receiving sufficient benefits from study intervention. This estimand is free of confounding effects of increase in concomitant medication use. Under the primary estimand strategy, a participant is considered a SLEDAI-4 responder at Week 24 if both of the following are met:
  - ≥ 4 points reduction from baseline in SLEDAI-2K score at Week 24
  - no violation of concomitant medication rules prior to Week 24.

If either or both of these criteria are not met, a participant is considered as a SLEDAI-4 nonresponder at Week 24. Apart from the primary estimand strategy, missing data imputation is described separately in Section 6.11.

6.5.2. Secondary Estimands

The secondary estimands for the secondary objectives are described by the following attributes:

- population: mITT population
- endpoints: SRI-4 at Week 24, BICLA at Week 24 (in the subset of participants with ≥1 A or ≥2 B at baseline), LLDAS at Week 24

- ICE will be accounted using the same estimand strategy as for the primary estimand (Section 6.5.1).
- population-level summary: difference in response rate of a secondary endpoint between LY3471851 and placebo
- rationale for estimand is provided in Section 6.5.1.

6.5.3. Supportive Estimand for Primary and Secondary Objectives

A supportive estimand for the primary and secondary objectives will be considered to address a clinical question: What is the difference between LY3471851 and placebo in the target patient population, in achieving successful response at Week 24 without regards to violation of concomitant medication rules?

For the supportive estimands, a **treatment policy estimand strategy** will be used to account for ICEs, and treatment effect will be assessed regardless of whether ICEs has occurred or not. That is, observed data after ICEs will be included as is in the analysis. Population, endpoints, and population-level summary are the same as described in Sections 6.5.1 and 6.5.2.

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6.6. Definition of Populations

The following populations are defined for this study:

Population	Description
Entered population	All participants who sign the informed consent form
Modified Intent-to-Treat (mITT) population	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 (PP) population	All randomized patients who do not commit an Important Protocol Deviation (IPD) that could potentially compromise efficacy results. IPDs are specified in the Trial Issue Management Plan.
Safety population	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and did not discontinue the study for the reason "lost to follow-up" at the first postbaseline visit. Participants will be analyzed according to the intervention they actually received within each study period.
Pharmacokinetic (PK) Analysis population	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention they actually received and have PK data available.

The mITT population will be used in analyses of efficacy and PRO, unless otherwise specified.

6.7. Participant Characteristics

6.7.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using the mITT population by treatment group. The summary will include descriptive statistics such as the number of patients (n), mean, SD, median, min, and max for continuous measures, and frequency counts and percentages for categorical measures. No formal statistical comparisons will be made among treatment groups, unless otherwise stated.

The continuous demographic and baseline characteristic variables outlined in Table KFAJ.6.1 will be summarized using descriptive statistics.

Table KFAJ.6.1. Continuous Demographic and Baseline Characteristic Variables

Variable	Quantitative	Categorical Summary	Subgroup Analysis
Demographic Characteristics			
Age [a]	Yes	<65, 65 to <75, ≥75	
Height	Yes		
Weight	Yes		
BMI [b]	Yes		
Sex	No	Female, Male	Yes
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	Yes
Country		Canada, United States, Puerto Rico, Argentina, Mexico, Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Romania, Spain, United Kingdom, South Korea, Taiwan, Japan, Australia, India, Israel, Russia, Ukraine	
Region (Table KFAJ.5.1)		North America, Latin America, Europe, Asia, Japan, Rest of World	Yes
Country GDP	No	Category 1 [Mexico, India, Ukraine] Category 2 [Argentina, Czech Republic, Hungary, Poland, Romania, Spain, Russia] Category 3 [Canada, United States, Puerto Rico, Belgium, France, Germany, Italy, United Kingdom, South Korea, Taiwan, Japan, Australia, Israel]	Yes
Ethnicity (only US sites)		Hispanic/Latino, Non-Hispanic/Non-Latino, Missing	Yes
Time since onset of lupus (years) [c]	Yes		
Concomitant Medication Use at Baseline			
Daily dose of prednisone (or equivalent) in mg/day [d]	Yes	<7.5 mg/day, ≥7.5 mg/day <10 mg/day, ≥10 mg/day	Yes
Immunosuppressant use	No	Yes, No	
Mycophenolate mofetil use	No		
Azathioprine use	No		
Methotrexate use	No		

Variable	Quantitative	Categorical Summary	Subgroup Analysis
Antimalarial use (for each drug)	No	Yes, No	
NSAID use	No		
Disease Severity at Baseline			
SLEDAI-2K	Yes	<10, ≥10	Yes
SLEDAI-2K organ system involvement at baseline	No	Yes, No	
British Isles Lupus Assessment Group (BILAG) organ system involvement at baseline (either A or B)	No	Yes, No	
BILAG A organ system involvement at baseline	No	Yes, No	Yes
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]		
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	Yes		
Physician's Global Assessment of Disease Activity score	Yes		
CCI [redacted]	[redacted]		
CCI [redacted]	[redacted]		
CCI [redacted]	[redacted]		

Variable	Quantitative	Categorical Summary	Subgroup Analysis
SLE Risk Probability Index (SLEPRI)	Yes	≤7, 7 to ≤11, 11 to ≤14, >14 (lower bounds are strictly greater than)	Yes
Prior Benlysta (belimumab) use	No	Yes, No	

Abbreviations: CCI [redacted]; GDP = gross domestic product; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; SLE = Systemic Lupus Erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

[a] Age will be calculated using an imputed date of birth of July 1st in the year of birth collected in the electronic case report form (eCRF). It will be calculated as: Age (in years) = (date of first dose – imputed date of birth)/365.25

[b] Body mass index (BMI) (kg/m2) at Visit 2. BMI (kg/m^2) = Weight [kg] / Height [m]^2

[c] Time since onset of lupus will be calculated using the date of onset of lupus (as recorded on the SLE History eCRF page) as follows: Time since onset of lupus (years) = (date of first dose - date of onset of lupus + 1) / 365.25.

CCI [redacted]

[d] Patients with a non-zero dose at Visit 2 will be included in this baseline summary, see Section 6.9.1 for details of prednisone (or equivalent) baseline dose.

6.7.2. Historical Illness and Preexisting Conditions

Historical illness/condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History eCRF page or on the Prespecified Medical History eCRF page with an end date prior to the date of informed consent. Preexisting condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History eCRF page or on the Prespecified Medical History 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. Notice if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on Adverse Events eCRF page from the date of worsening onwards. Historical illnesses and preexisting conditions will be classified using the latest version of the MedDRA. The number and percentage of patients with historical illnesses and preexisting conditions will be provided by treatment group, overall and by SOC and PT using the mITT population. Note that conditions with a partial or missing start date will be assumed to be "not preexisting" unless there is evidence, through comparison of partial dates, to suggest otherwise. Patients will only be counted once if same PT is listed in 2 or more different SOC categories.

6.8. Participant Disposition

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.

6.9. Concomitant Therapy

Previous and concomitant medications will be summarized by treatment group and will be presented by ATC drug classes using the latest version of the World Health Organization drug dictionary.

Under the composite estimand strategy described in Section 6.5.1, a patient will be considered a nonresponder after the first occurrence of a violation of any of the following concomitant medication rules, regardless of the patient's efficacy status or disposition status:

- no initiation or increase in dose from baseline of
  - nonsteroidal anti-inflammatory drug intended for treatment of signs and symptoms of SLE
  - prednisone (or equivalent)
  - antimalarial. and
  - immunosuppressant
- prednisone ≤10 mg/day (or equivalent) by Week 12

Violations of concomitant medication rules will be first identified via programming and then reviewed by a blinded medical to confirm the violations align with the criteria specified in the protocol. The confirmed list provided by the blinded medical will be used for analyses.

6.9.1. Corticosteroids

To allow for assessments of changes in doses of various corticosteroids, it was necessary to standardize all corticosteroid doses to an equivalent prednisone dose. Table KFAJ.6.2 provides a summary of frequent corticosteroids and their prednisone-equivalent dose. The dose of the drug listed in Column 1 is multiplied by the conversion factor in Column 2 to provide the prednisone equivalent dose (in milligrams). This dose of corticosteroid will be referred to as "prednisone (or equivalent)" throughout this document.

See Appendix 3 for a complete table showing conversion factors for each corticosteroid medication identified during the study, instructions for selecting corticosteroids, and the manual review process. References for this table can also be found in Appendix 3.

Baseline prednisone (or equivalent) dose will be the total daily dose of all corticosteroids being taken by a patient at Visit 2. This baseline dose will be used for baseline summaries and for comparisons to later visits. A daily dose of prednisone (or equivalent) will be calculated for each day between baseline and treatment discontinuation. The daily dose of prednisone (or equivalent) at each visit date will be used as the corticosteroid dose for that visit.

6.10. Treatment Compliance

Patient compliance with study medication will be assessed from the randomization visit (Week 0) to Visit 15 (Week 24) during the treatment period. Compliance will be summarized from randomization until end of treatment using the mITT population. A patient is considered noncompliant if 2 or more of the prescribed doses during the study are missed, not including doses withheld by the investigator. A patient who takes more than 12 of the prescribed doses during the treatment period is also considered noncompliant.

Compliance to study drug in the period of interest will be calculated as follows:

$$\frac{\text{actual total \# of doses}}{\text{Expected total \# of doses}} * 100.$$

If a patient has a dose temporarily interrupted by the investigator during the period, the total number of days that drug was withheld will be deducted from the total number of days in the calculation of the expected total number of doses used.

The summary statistics of the percent of compliance and noncompliance rate will be summarized by treatment group. The percent of compliance for Week 0 (Visit 2) through Week 24 (Visit 15) will be presented, along with the associated noncompliance rates.

6.11. Handling of Dropouts or Missing Data

Missing data imputation is handled separately from the estimand strategy. After intercurrent events are accounted for according to an estimand strategy described in Section 6.5, any remaining missing data will be handled using missing data imputation methods described in this section. Reasons for such missing data include, but are not limited to,

- intermittent missing visits, assessments, or some components of assessments
- temporary treatment interruptions, and
- early treatment discontinuation.

When NRI is used, missing binary data will be imputed as non-response.

When last observation carried forward is used, missing continuous data will be imputed with the last nonmissing postbaseline observation prior to the first occurrence of intercurrent events. For patients without at least one postbaseline observation, missing continuous data will not be imputed.

When baseline observation carried forward is used, missing continuous data will be imputed with baseline observation (last nonmissing data before the first injection). For patients without baseline observation, missing continuous data at postbaseline visits will not be imputed.

The missing data imputation methods for planned analyses are specified in Sections 6.14, 6.15, and 6.16.

6.12. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. The countries will be categorized into geographic regions, as described in Section 5.2. Geographic region will be included in a statistical model as a fixed effect, unless otherwise specified.

6.13. Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made for any analyses in this study.

6.14. Primary Endpoint/Estimand Analyses

The primary efficacy endpoint per composite estimand strategy (the primary estimand as described in Section 6.5.1) is

- SLEDAI-4 at Week 24 after accounting for violation of concomitant medication rules: (i) initiating or increasing in dose of corticosteroids, antimalarial, or immunosuppressant, or (ii) using prednisone >10 mg per day (or equivalent) after Week 12

Under the composite estimand strategy, participants will be considered nonresponders at all subsequent visits after the first violation of concomitant medication rules regardless of their discontinuation status.

The primary analysis for treatment comparison of each LY3471851 dose with placebo will be analyzed using a logistic regression model with treatment group, baseline disease activity (SLEDAI-2K <10; SLEDAI-2K ≥10), corticosteroid dose at baseline (<10 mg/day or ≥10 mg/day), and geographic region (North America, Latin America, Europe, Asia, Japan, Rest of World) in the model. The analysis will be based on the mITT population and missing data will be handled using NRI. P-values from the Fisher's exact test will also be reported as a sensitivity analysis, when logistic regression sample size requirements are not met (<5 subjects in any category for any factor).

As supplementary analyses,

- to determine the impact of important protocol deviations, the primary analysis detailed above will also be conducted on the per-protocol population

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6.15. Secondary Endpoints/Estimand Analyses

The secondary endpoints per composite estimand strategy (the primary estimand as described in Section 6.5.2) without violation of concomitant medication rules: (i) initiating or increasing in dose of corticosteroids, antimalarial, or immunosuppressant, or (ii) using prednisone >10 mg per day (or equivalent) after Week 12 are

- BICLA at Week 24
- SRI-4 at Week 24, and
- LLDAS at Week 24.

Under the composite estimand strategy, participants will be considered nonresponders at all subsequent visits after the first violation of concomitant medication rules regardless of their discontinuation status.

The analytical details specified in Section 6.14 will be followed. The supplementary analyses in Section 6.14 may also be considered for the secondary efficacy endpoints if deemed appropriate.

Description and derivation of secondary endpoints are described in a separate document, and the handling of missing data due to, for example, a missed visit is detailed in Appendix 1.


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6.19. Safety Analyses

All safety data will be descriptively summarized by treatment groups and analyzed based on the safety population. The safety population is defined as those patients who received at least 1 dose of study drug and did not discontinue the study for the reason "lost to follow-up" at the first postbaseline visit. The safety analyses include AEs, safety in special groups and circumstances, including adverse events of special interest, 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 IRs 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.

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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.

6.19.1. Extent of Exposure

Duration of exposure to study drug will be summarized for the safety population by treatment group. Exposure will be calculated as the date of last dose of study drug (or date of discontinuation) minus the date of first dose of study drug plus 1 day. Total PYs of exposure will be reported for each treatment group for overall duration of exposure. 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:

- ≥4 weeks, ≥12 weeks, and ≥24 weeks
- >0 to <4 weeks, ≥4 weeks to <12 weeks, ≥12 weeks to <24 weeks, and ≥24 weeks

Overall exposure will be summarized in total PYs, which are calculated according to the following:

> Exposure in PYs = sum of duration of exposure in days (for all patients in treatment group) / 365.25

No p-values will be reported in these tables as they are intended to describe the characteristics of the study sets.

6.19.2. Adverse Events

6.19.2.1. Adverse Events

AEs are recorded in the eCRF. Each AE will be coded to SOC and PT, using the MedDRA version that is current at the time of database lock. Severity of AEs is recorded as mild, moderate, or severe.

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 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 (that is, 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 (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. For events occurring on the day of the first dose of study treatment, the day and time 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 (that is, percentage; n/N*100).

In an AE overview table, the number and percentage of patients in the safety analysis set who experienced death, an SAE, any TEAE, permanent discontinuation from study drug due to an AE, temporary interruption of study drug due to an AE or laboratory abnormality, 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 CCI treatment group.
- by MedDRA PT with events ordered by decreasing frequency in the LY3471851 CCI treatment group.

AEs 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 CCI treatment group.

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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.

6.19.2.2. 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 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, or
- 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[redacted] 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.

[redacted]

CCI [redacted]

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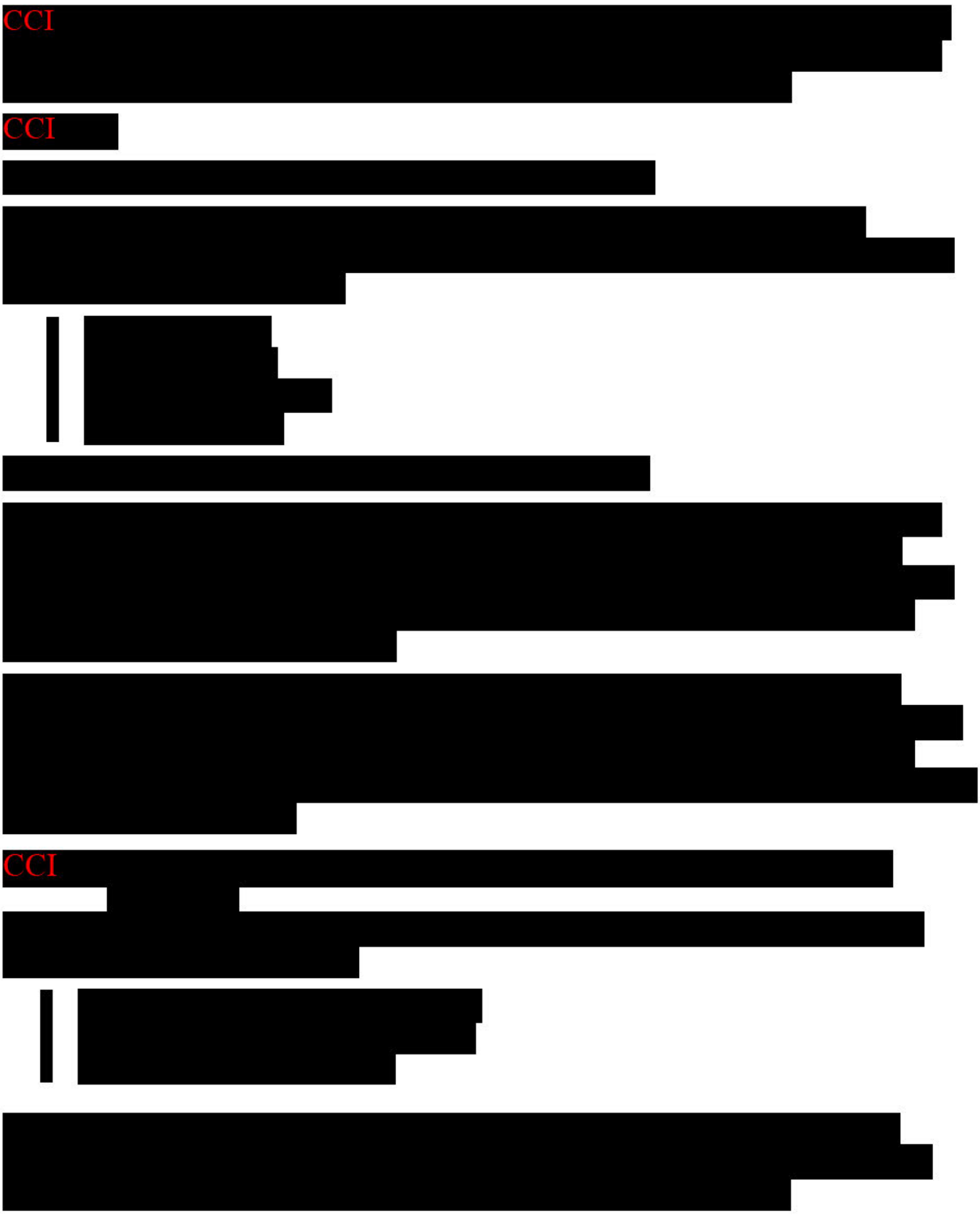

6.19.3.3. Malignancies

Malignancies will be identified using terms from the Malignant tumors SMQ (SMQ 20000194). Malignancies excluding 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), and
- 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 6.19) 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 report, disregarding the length of gap between the last treatment dose date and the event date will be included.

6.19.4. Injection Site Reaction

At every visit following the first dose and prior to any blinded study activity, an independent ISR assessor who is not involved with other study procedures will evaluate each participant for the presence of ISRs between the visits.

The number and percentage of patients who experienced an 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.

- anatomical location of the injection site reaction
- abdomen side
- directionality of the anatomical location of the administration
- arm side
- thigh side
- whether the subject have any injection site erythema (reddening) or not
- severity of the injection site erythema
- whether the subject have any injection site induration (hardening or thickening of tissue) or not
- severity of the injection site induration
- whether the subject have any injection site pain (including burning) or not

- severity of the injection site pain
- whether the subject have any injection site pruritus
- severity of the injection site pruritus
- whether the subject have any injection site edema (swelling or accumulation of fluid in tissues at height above normal skin) or not
- severity of the injection site edema, and
- when did the injection related event occur, in relationship to the study treatment.

The frequency of the maximum severity of ISRs will be summarized by treatment group.

CCI [redacted] It will not be considered a protocol violation if the planned sample size is not achieved due to an insufficient number of consenting and eligible participants.

6.19.5. Clinical Laboratory Evaluation

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 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 (Covance) reference ranges will be used. For the 4 key hepatic laboratory assessments (ALT, AST, total bilirubin, and ALP), central laboratory reference ranges (Covance) 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 6.19.5.1). Central laboratory reference ranges (Covance) will also be used to evaluate immunoglobulins and lymphocyte cell subsets (see Sections 6.19.5.3 and 6.19.5.7). See Appendix 6 for details of the reference range by laboratory analytes.

The 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 (for example, 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.

A listing of abnormal findings will be provided. The listing will include, but not be limited to, patient ID, treatment group, laboratory collection date, analyte name, and analyte finding.

6.19.5.1. 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 6.19.5. This section describes additional analyses for the topic. The central laboratory reference ranges (Covance) 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 ULN during the treatment and follow-up periods will be summarized for all patients with a postbaseline value and for subsets based on various levels of baseline.
    - The analysis of 3× ULN will contain 4 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN; patients whose maximum baseline is >1× ULN, but <3× ULN; patients whose maximum baseline value is ≥3× ULN; and patients whose baseline values are missing.
    - The analysis of 5× ULN will contain 5 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN; patients whose maximum baseline is >1× ULN, but <3× ULN; patients whose maximum baseline is ≥3× ULN, but <5× ULN; patients whose maximum baseline value is ≥5× ULN; and patients whose baseline values are missing.
    - The analysis of 10× ULN will contain 6 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN; patients whose maximum baseline is >1× ULN, but <3× ULN; patients whose maximum baseline is ≥3× ULN, but <5× ULN; patients whose maximum baseline is ≥5× ULN, but <10× ULN; patients whose maximum baseline value is ≥10× ULN; and patients whose baseline values are missing.
- The percentages of patients with an AST measurement greater than or equal to 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 and for subsets based on various levels of baseline. Analyses will be constructed as described above for ALT.
- The percentages of patients with a total bilirubin measurement greater than or equal to 2 × the central laboratory ULN during the treatment period will be summarized for all patients with a postbaseline value and subset into 4 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN; patients whose maximum baseline is >1× ULN but < 2× ULN; patients whose maximum baseline value is ≥2× ULN; and patients whose baseline values are missing.
- The percentages of patients with an ALP measurement ≥1.5× the central laboratory ULN during the treatment and follow-up periods will be summarized for all patients with a postbaseline value and subset into 4 subsets: patients whose nonmissing maximum baseline value is ≤1× ULN; patients whose maximum baseline is >1× ULN but <1.5× ULN; patients whose maximum baseline value is ≥1.5× ULN; and patients whose baseline values are missing.

Second, to further evaluate potential hepatotoxicity, an 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), and
- narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (SMQ 20000015)

6.19.5.2. Hematologic Changes

Hematologic changes will be defined based on clinical laboratory assessments. CLASI will be applied for laboratory tests potentially related to myelosuppressive events (refer to Appendix 7).

Treatment-emergent laboratory abnormalities potentially related to myelosuppression occurring at any time during the treatment and follow-up periods and shift tables of baseline to maximum grade during the treatment and follow-up periods will be tabulated. Planned and unplanned measurements will be included. Treatment emergence will be characterized using the following 5 criteria (as appropriate to the grading scheme):

- 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, and
- increase to Grade 4 at worst postbaseline.

Shift tables will show the number and percentage of patients based on baseline to maximum during the treatment and follow-up periods, with baseline depicted by the most extreme grade during the baseline period. With each shift table, a shift table summary displaying the number and percentage of patients with maximum postbaseline results will be presented by treatment group for each treatment period within the following categories:

- decreased; post-baseline category < baseline category
- increased; post-baseline category > baseline category, and
- same; postbaseline category = baseline category.

A laboratory-based treatment-emergent outcome related to increased platelet count will be summarized in a similar fashion. Treatment-emergent thrombocytosis as a laboratory-based abnormality will be defined as an increase in platelet count from a maximum baseline value ≤600 billion/L to any postbaseline value >600 billion/L. Planned and unplanned measurements

will be included. A listing of patients with treatment-emergent thrombocytosis will be provided for safety review.

6.19.5.4. 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 6.19.5.

TEAEs 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 Appendix 5. Frequency and relative frequency for each PT will be provided, ordered by decreasing frequency in the LY3471851 CCI treatment group.

6.19.5.5. Renal Function Effects

Effects on renal function will be assessed through analyses of creatinine, which are described in Section 6.19.5.

6.19.5.6. Elevations in Creatine Phosphokinase

Analyses of creatine phosphokinase are described in Section 6.19.5.

6.19.6. Vital Signs and Other Physical Findings

Vital signs and physical characteristics include systolic blood pressure, diastolic blood pressure, pulse, weight, body mass index, 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.

The planned analyses described for the laboratory analytes in Section 6.19.5 will be used to analyze the vital signs and physical characteristics.

Table KFAJ.6.1 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.

Table KFAJ.6.1. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

Parameter (Units of Measure)	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.

6.19.7. Additional Safety Sections

6.19.7.1. Symptoms of Depression (QIDS-SR16)

The QIDS-SR16 is a 16-item, self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV; APA 1994). Patients are asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a unique 4-point ordinal scale for each item with scores ranging from 0 to 3 reflecting increasing depressive symptoms as the item score increases. Additional information and the QIDS-SR16 questions may be found on the University of Pittsburgh Epidemiology Data Center website (http://www.ids-qids.org/index.html). A key reference for this instrument covers its psychometric properties for use in patients with chronic major depression (Rush et al. 2003). Quick Inventory of Depressive Symptomatology was developed at UT Southwestern.

The QIDS-SR16 total score is derived as the sum of the scores across the 9 scale domains. For scale domains that contain more than 1 item, the domain score is the highest item rating given across the items within that domain:

- sleep: the highest score on any 1 of the 4 sleep items (items 1 to 4)
- depressed mood: Item 5
- weight/appetite change: the highest score on any 1 of the 4 weight items (items 6 to 9)
- psychomotor changes: the highest score on either of the 2 psychomotor items (items 15 and 16)
- concentration: item 10
- worthlessness/Guilt: item 11
- suicidal ideation: item 12
- decreased interest: item 13, and
- decreased energy: item 14.

In the presence of missing data, the following rules will be employed to derive the total score. Firstly, considering the 3 multi-item domains (sleep, weight/appetite change, psychomotor changes), the domain score should be based on the maximum value across the appropriate items, and it should be missing only if each item is missing. Further, considering the 9 domain scores, the total score should be derived as missing if there are 3 or more domains that are missing; if 1 or 2 domain scores are missing, then the total score should be derived using a total score that is prorated to the full scale range (0 to 27) based on the available domain scores, retaining 1 decimal place in the total score derived in the presence of missing data.

The QIDS-SR16 total scores will also be categorized in the following severity classes as shown in Table KFAJ.6.3.

Table KFAJ.6.3. QIDS-SR16 Severity of Depressive Symptoms Categories Based on the QIDS-SR16 Total Score

QIDS-SR16 Severity of Depressive Symptoms Category	QIDS-SR16 Total Score
0 = None	0-5
1 = Mild	6-10
2 = Moderate	11-15
3 = Severe	16-20
4 = Very Severe	21-27

Abbreviation: QIDS-SR16 = Quick Inventory of Depressive Symptomatology Self-Rated.

Treatment differences in mean change QIDS-SR16 total score will be analyzed using the MMRM model described in Section 6.2. Only visits that occur on or before the date the patient discontinued treatment will be included in this analysis.

Using the QIDS-SR16 Severity of Depressive Symptoms Categories shown in Table KFAJ.6.3, shift tables will show the number and percentage of patients with total score in each category based on baseline to maximum category during the treatment period and up to 60 days after treatment discontinuation, with baseline depicted by the most extreme category during the baseline period, with further summarization of change from baseline in severity using categories of any improvement, no change, and any worsening, by treatment. Similarly, shift tables will be created for the QIDS-SR16 suicidal ideation item (Item 12) responses.

Treatment-emergent changes in QIDS-SR16 total score severity categories will be characterized as follows:

- Increase (from None) to Mild, Moderate, Severe, or Very Severe
- Increase (from None or Mild) to Moderate, Severe, or Very Severe
- Increase (from None, Mild, or Moderate) to Severe or Very Severe
- Increase (from None, Mild, Moderate, or Severe) to Very Severe

Treatment-emergent changes in QIDS-SR16 suicidal ideation item (Item 12) responses will be characterized as follows:

- Increase (from 0) to 1 to 3
- Increase (from 0 to1) to 2 to 3, and
- Increase (from 0 to 2) to 3.

6.19.7.2. Columbia Suicide Severity Rating Scale

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, based on the C-SSRS, will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (that is, if a patient's answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be displayed, even if not positive.

6.20. Other Analyses

6.20.1. Subgroup Analyses

Subgroup analysis will be conducted on SLEDAI-4 and SRI-4 at Week 24 with the composite estimand strategy based on the mITT population. Subgroup analysis may be conducted on BICLA at Week 24 with the composite estimand strategy for mITT population with at least 1 baseline BILAG A score or 2 baseline BILAG B scores. Missing data will be handled using NRI. Subgroups to be analyzed are listed in Section 6.7.1. Subgroup analyses on other efficacy endpoints may be performed as deemed appropriate.

Descriptive statistics will be provided for each treatment and stratum of a subgroup as outlined, regardless of sample size. Each categorical variable will be analyzed individually with a logistic model that contains the treatment, the subgroup variable, and subgroup by treatment interaction. The treatment-by-subgroup interaction will be tested at the 10% significance level to determine whether treatment differences are the same for each subgroup category. For the categorical variables, the number of responders and response rate will be reported for each subgroup.

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6.20.3. Annual Report Analyses

Annual report analyses will be stated in a separate document.

6.20.4. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset that will be converted to an XML file. Both SAEs and "other" AEs 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, and
  - the number of events experienced

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

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6.22. Data Monitoring Committee

Not applicable. An IAC will be used to conduct the interim analysis.

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

7. Unblinding Plan

A separate unblinding plan will be prepared.

8. References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Arlington (VA): American Psychiatric Association; 1994.

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9. Appendices

Appendix 1. Description and Derivation of Efficacy Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation/Comment	Definition of Missing
SLEDAI-2K	The SLEDAI-2K is a global disease activity instrument that focuses on high-impact disease manifestations across 9 organ domains: constitutional, mucocutaneous, musculoskeletal, vascular, cardiorespiratory, central nervous system, immunologic, renal, and hematologic.	SLEDAI-2K Total Score	Calculated by summing the weighted organ manifestation.	Any item scores are missing (not done, not assessed, NA or empty), but the visit occurred. • Baseline data for that item can be carried forward from the last non-missing data during the screening period. • Postbaseline data for that item can be carried forward from the last non-missing data if that data is obtained within the previous 34 days of that visit. After imputation, • If any item is still missing at the baseline visit, it will be imputed as 0. • For Renal domain, if urinary casts, hematuria and pyuria items are still missing for any post-baseline visit, they will be imputed as 0.
		Individual Organ Domain Improvement Defined by SLEDAI-2K	Patients with SLEDAI-2K score >0 within the organ domain at baseline, and able to decrease SLEDAI-2K (from baseline) within each organ domain score, separately.	Missing if any SLEDAI-2K item for that organ domain remains missing after instrument level imputation rules are applied.
		Individual Organ Domain No Worsening Defined by SLEDAI-2K	Among patients with at least one SLEDAI-2K item = 0 (not present) in the organ domain score at baseline, no increment of SLEDAI-2K organ domain score from baseline within each organ domain score, separately.	Missing if any SLEDAI-2K item for that organ domain remains missing after instrument level imputation rules are applied.

Measure	Description	Variable	Derivation/Comment	Definition of Missing
		No worsening from baseline in SLEDAI-2K	No increment from baseline of >0 points in SLEDAI-2K	Missing if any SLEDAI-2K item for that organ domain remains missing after instrument level imputation rules are applied.
SLEDAI-4	SLEDAI-4 is an index to measure overall improvement in disease activity (SLEDAI-2K)	SLEDAI-4 Responder	A ≥4-point reduction in SLEDAI-2K score from baseline.	Missing if SLEDAI-2K total score is missing after instrument level imputation rules are applied.
SRI-4	SRI-4 is a composite index to measure overall improvement in disease activity (SLEDAI-2K) while ensuring there is no worsening in other organ systems (BILAG and PGA)	SLE Responder Index 4	• A decrease in SLEDAI-2K ≥4 (from baseline) • No new BILAG A and no more than 1 new BILAG B disease activity score / organ domain (both compared with baseline), and • No worsening in PGA (defined as an increase of 0.3 points [10 mm] from baseline)	After each instrument level imputation rule is applied and there is still at least one missing component, • if the nonmissing components are all 'Y' then SRI-4 is missing. • if any of the nonmissing component is 'N' then the SRI-4 is 'N.'
BILAG-2004	BILAG2004 assesses 97 clinical signs, symptoms and laboratory parameters across 9 organ system domains: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and hematological	BILAG	A, B, C, D, or E score will be used in analyses for each of the 9 individual organ systems.	Within each organ domain (except renal and hematological), any missing data will be assumed to be 'Not present' if there is at least 1 nonmissing item in that organ. If all items in one organ domain are completely missing but the visit occurred, then the letter score of that organ from the previous visit will be pulled forward, provided data were obtained within 34 days of visit; otherwise missing except when the letter score from the last nonmissing visit is E, then E score will be pulled forward. For the renal and hematological domains,

Measure	Description	Variable	Derivation/Comment	Definition of Missing
				• If all item within this domain is 'NA', then items are coded as 'No.' • If any vital/lab item with "Yes" but vital and lab value is missing, then vital/lab values will be pulled forward from scheduled and unscheduled post-baseline visits, provided data were obtained within 34 days of visit; otherwise missing. • If all items in one organ domain are completely missing not 'NA' but the visit occurred, then the letter score of that organ from the previous visit will be pulled forward, provided data were obtained within 34 days of visit; otherwise missing except when the letter score from the last non-missing visit is E, then E score will be pulled forward.
		BILAG improvement	• Reduction of all baseline BILAG A to B/C/D and baseline BILAG B to C/D • No BILAG worsening in other organ systems, where worsening is defined as ≥1 new BILAG A or ≥2 new BILAG B	For the reduction part, missing if any of 9 domains at baseline or at the visit remains missing after instrument level imputation rules are applied except when the missing is at the baseline (any one or all domains) and the value at the visit is not A or B, then the other non-missing organ domains will be used to determine the response status.

Measure	Description	Variable	Derivation/Comment	Definition of Missing
				For the no worsening part, Missing if any of 9 domains at baseline or at the visit remains missing after instrument level imputation rules are applied except when the baseline (any one or all domains) is BILAG A and the value at the visit is missing, then the other non-missing organ domains will be used to determine the response status. If both components are missing or one component is missing and the other one is 'Y,' then missing. If at least one component is 'N', then 'N.'
		No BILAG worsening	No new BILAG A and no more than 1 new BILAG B disease activity score (both compared with baseline), where worsening is defined as ≥1 new BILAG A or ≥2 new BILAG B, both compared with the baseline. The baseline BILAG A improved to BILAG B at the visit will not be considered as the new BILAG B.	Missing if any of 9 domains at baseline or at the visit remains missing after instrument level imputation rules are applied except when the baseline (any one or all domains) is BILAG A and the value at the visit is missing, then the other nonmissing organ domains will be used to determine the response status.
		Individual Organ Domain Improvement Defined by BILAG	Among patients with BILAG A or B at baseline and able to reduce the baseline BILAG A to B/C/D and BILAG B to C/D for each organ domain, separately.	Missing if baseline or value remains missing after instrument level imputation rules are applied.

Measure	Description	Variable	Derivation/Comment	Definition of Missing
		Individual Organ Domain No Worsening Defined by BILAG	Among patients without BILAG A at baseline, no increment of baseline BILAG B/C/D/E to A and baseline BILAG C/D/E to B for each organ domain, separately.	Missing if baseline or value remains missing after instrument level imputation rules are applied.
PGA	The PGA is the physician's assessment of the patient's overall disease activity due to SLE. It is scored using a visual analog scale where 0 mm indicates no disease activity and 100 mm indicates the most severe disease activity possible. There are benchmarks of 0 (0 mm), 1 (33 mm), 2 (67 mm), and 3 (100 mm) on the line corresponding to no, mild, moderate, and severe SLE disease activity, respectively.	PGA score PGA category	Permitted range of values is from 0 to 100 mm. PGA categories are defined as: None (0) = '0 mm', Mild (>0 and <1.5) = ' >0 to < 50 mm', Moderate (≥1.5 to ≤2.5) = '≥ 50 mm to ≤83mm', Severe (>2.5) = '>83mm'.	If the visit occurred, data can be carried forward if obtained within 34 days of visit; otherwise missing.
		No worsening in PGA	Worsening is defined as an increase of ≥0.3 points (10 mm) from baseline. Therefore, no worsening is defined as any decrease, no change, or <0.3 points (10 mm) increase from baseline.	Missing if baseline or value remains missing after instrument level imputation rules are applied.
		PGA ≤1	PGA ≤33 mm	Missing if value remains missing at the visit after instrument level imputation rules are applied.

BICLA	BICLA is a composite index to measure overall improvement in disease activity (BILAG) while ensuring there is no worsening in other organ systems (SLEDAI and PGA)	BILAG Based Composite Lupus Assessment	• BILAG Improvement
			  ○ Reduction of all baseline BILAG A to B/C/D and baseline BILAG B to C/D
			  ○ No BILAG worsening in other organ systems, where worsening is defined as ≥1 new BILAG A or ≥2 New BILAG B
			• No worsening from baseline in SLEDAI-2K, where worsening is defined as an increase of >0 points from baseline in SLEDAI-2K
				After each instrument level imputation rule is applied and there is at least one component missing, if the non-missing components are all 'Y' then BICLA will be missing. If any of the non-missing component is 'N' then the BICLA is 'N.'

Measure	Description	Variable	Derivation/Comment	Definition of Missing
			No worsening from baseline in participants' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA VAS.	
[redacted]				
LLDAS	The LLDAS is a composite measure designed to identify patients achieving a state of low disease activity.	LLDAS	• SLEDAI-2K ≤ 4, with no activity in SLEDAI-2K major organ systems (CNS, Vascular, Renal, Cardiorespiratory and Constitutional), where "no activity" is defined as all items of SLEDAI-2K within these major organ systems equal to 0. • No new features of Lupus disease activity in SLEDAI-2K compared to previous occurred visit, where the "new feature" is defined as any of the SLEDAI-2K 24 items changed from 0 to greater than 0. • PGA ≤1 • Current prednisone or equivalent ≤7.5 mg/day	After each instrument level imputation rule is applied and there is at least one component missing, if the non-missing components are all 'Y' then LLDAS will be missing. If any of the nonmissing component is 'N' then the LLDAS is 'N.'

Measure	Description	Variable	Derivation/Comment	Definition of Missing
SLEDAI Flare Index	The SFI uses the SLEDAI score, disease activity scenarios, treatment changes, and PGA to define mild/moderate and severe flares.	SFI Flare	No derivation; used as entered.	The absence of a flare record, or 'Non Applicable,' both are indicative of no occurrence of flare.
		Time to first flare	Time to first flare will be derived as the first date of most recent flare minus date of first injection plus 1.	Not applicable


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Abbreviations: ACR = American College of Rheumatology; BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group - 2004; CCI CNS = central nervous system; CCI ; LLDAS = Lupus Low Disease Activity State; N = no; PGA = Physician Global Assessment; Q2W = every 2 weeks; SFI = Self-Report Family Instrument; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI-4 = a ≥4-point reduction in SLEDAI-2K score from baseline; CCI ; SRI-4 = Systemic Lupus Erythematosus Responder Index-4; VAS = Visual Analog Scale; Y = yes.

Appendix 2. Description of Efficacy Analyses

The table below provides the detailed analyses including estimand strategy, analysis method, missing data imputation, analysis population, and analysis type.

Measure	Endpoint	Estimand Strategy	Analysis Population	Comparison/ Timepoint	Analysis Method	Analysis Type
SLEDAI	SLEDAI-4	Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Logistic Regression with NRI for Week 24 – Primary Other – Exploratory
		Composite	Per-Protocol	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Exploratory
		Treatment Policy	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
	No worsening from baseline in SLEDAI-2K	Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
	SLEDAI Change from Baseline	Hypothetical	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	MMRM	Exploratory
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	MMRM with BOCF	Exploratory
	Individual Organ Domain Improvement Defined by SLEDAI-2K	Composite	mITT – Patients with SLEDAI-2K score > 0 within the organ domain at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
	Individual Organ Domain Worsening Defined by SLEDAI-2K	Composite	mITT – Patients with at least one baseline SLEDAI-2K = 0 in the organ domain at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory

Measure	Endpoint	Estimand Strategy	Analysis Population	Comparison/ Timepoint	Analysis Method	Analysis Type
	Resolution of Arthritis and/or Rash by SLEDAI-2K Components	Composite	mITT – Patients with SLEDAI-2K arthritis and/or rash 'Present' at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Logistic Regression with NRI for Week 24 – Secondary Other – Exploratory
SRI-4	SRI-4	Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Logistic Regression with NRI for Week 24 – Secondary Other – Exploratory
		Composite	Per-Protocol	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Exploratory
BICLA	BICLA	Composite	mITT – Patients with at least 1 BILAG A or 2 BILAG B scores at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Logistic Regression with NRI for Week 24 – Secondary Other – Exploratory
		Composite	Per-Protocol – Patients with at least 1 BILAG A or 2 BILAG B scores at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Exploratory
LLDAS	LLDAS	Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Logistic Regression with NRI for Week 24 – Secondary Other – Exploratory

Measure	Endpoint	Estimand Strategy	Analysis Population	Comparison/ Timepoint	Analysis Method	Analysis Type
BILAG	BILAG Improvement	Composite	mITT – Patients with at least 1 BILAG A or 2 BILAG B at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
	BILAG No Worsening	Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
	Individual Organ Domain - Improvement Defined by BILAG	Composite	mITT – Patients with BILAG A or B within the organ domain at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
	Individual Organ Domain - No Worsening Defined by BILAG	Composite	mITT – Patients with no BILAG A within the organ domain at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
PGA	PGA Change from Baseline	Hypothetical	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	MMRM	Exploratory

Measure	Endpoint	Estimand Strategy	Analysis Population	Comparison/ Timepoint	Analysis Method	Analysis Type
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	MMRM with BOCF	Exploratory
	No worsening in PGA	Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
	PGA ≤1	Composite	mITT – Patients with PGA > 1 at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory


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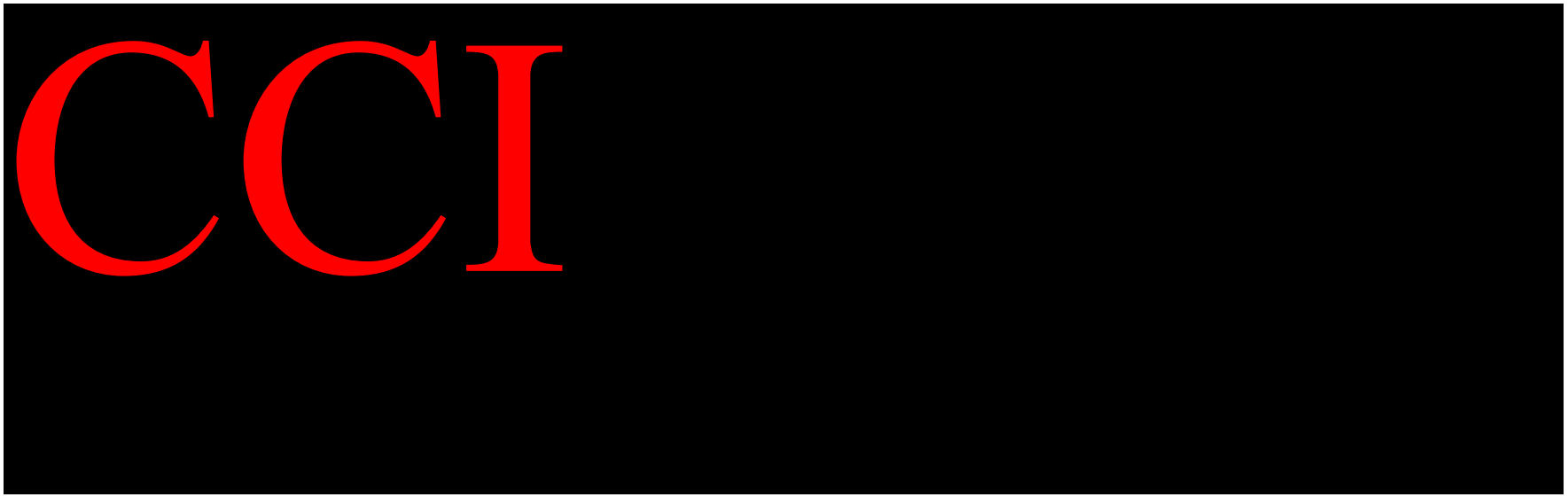

Abbreviations: Anti-dsDNA = anti-double stranded deoxyribonucleic acid; BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group - 2004; BOCF = baseline observation carried forward; CCI FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; LLDAS = Lupus Low Disease Activity State; mITT = modified intent-to-treat; MMRM = mixed models for repeated measures; NRI = nonresponder imputation; PGA = Physician Global Assessment; CCI SF = Short Form; SF-36 = 36-Item Short Form Health Survey; CCI SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI-4 = a ≥4-point reduction in SLEDAI-2K score from baseline; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; SRI-4 = Systemic Lupus Erythematosus Responder Index-4.

Appendix 3. Corticosteroid

All corticosteroid doses need to be converted to prednisone equivalent doses (as detailed in Section 6.9). If additional conversion factors are required, these will be added to the table below in a statistical analysis plan amendment prior to database lock.

The following table should be used for converting nonprednisone medications to prednisone equivalent:

> Multiply the dose of the corticosteroid taken by the patient (in milligrams) in Column 1 by the conversion factor in Column 2 to get the equivalent dose of prednisone (in milligrams).
>
> *Example: Patient is taking 16 mg of methylprednisolone po daily. To convert to prednisone: 16 mg methylprednisolone × 1.25 = 20 mg prednisone. 16 mg of methylprednisolone po daily is equivalent to 20 mg of prednisone po daily.*

Column 1	Column 2
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Appendix 4. 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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		Pneumonia proteus	10079867	Narrow
		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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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
	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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
	Human Polyomavirus infection including BK virus disease and PVAN (V), and Progressive Multifocal Leukoencephalopathy (IV)	BK virus infection	10055181	Narrow
		Human polyomavirus infection	10057366	
		JC virus granule cell neuronopathy	10074361	
		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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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
	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	

Category	Potential Opportunistic Infection	Preferred Term (MedDRA Version 22.1)	Preferred Term Code	Lilly Defined Classification
		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	
		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 (exclude COVID-19 and influenza 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.

Appendix 5. List of MedDRA Preferred Terms for Elevated or Increased Lipids from the Dyslipidemia SMQ (SMQ 20000026)

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

Preferred Term (MedDRA Version 20.0)	Preferred Term Code
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

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

Appendix 6. 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				
1	ALT/SGPT	Covance	Yes	Yes
2	AST/SGOT	Covance	Yes	Yes
3	Alkaline Phosphatase	Covance	Yes	Yes
4	Total Bilirubin	Covance	Yes	Yes
5	Direct Bilirubin	Covance	Yes	Yes
6	Albumin	LCTPB	Yes	Yes
7	Creatine Phosphokinase	LCTPB	Yes	Yes
8	Creatinine	Covance	Yes	Yes
9	Urea Nitrogen	LCTPB	Yes	Yes
11	estimated GFR	Covance	Yes	Yes
12	Creatinine Clearance	Covance	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	Covance	Yes	Yes
23	HDL Cholesterol – Direct	Covance	Yes	Yes
24	LDL/HDL Ratio – Calculated	None	Yes	No

Laboratory Group/Order	Laboratory Analyte	Reference Range Name	Analysis Type	
			Central Tendency	Outlier/Shift Analysis
Immunoglobulins				
1	Immunoglobulin A	Covance	Yes	Yes
2	Immunoglobulin G	Covance	Yes	Yes
3	Immunoglobulin M	Covance	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

Laboratory Group/Order	Laboratory Analyte	Reference Range Name	Analysis Type	
			Central Tendency	Outlier/Shift Analysis
CCI				

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; CD = cluster of differentiation; HDL = high-density lipoprotein; Ig = immunoglobulin; LCTPB = Lilly Large Clinical Trial Population Based; LDL = low-density lipoprotein; MCHC = mean corpuscular hemoglobin concentration; CCI UA = urinalysis.

Appendix 7. Common Terminology Criteria for Adverse Events (CTCAE) Related to Myelosuppressive Events

Event	Laboratory Test	Grade	Criteria in Système International (SI) Units	Criteria in Conventional (CN) Units
Anemia[a]	Hemoglobin	0 (normal)	≥7.27 mmol (Fe)/L for females and ≥8.18 mmol (Fe)/L for males	≥12 g/dL for females and ≥13.5 g/dL for males
		1	<7.27 mmol (Fe)/L for females and 8.18 mmol (Fe)/L for males and ≥6.2 mmol (Fe)/L	<12 g/dL for females and 13.5 g/dL for males and ≥10 g/dL
		2	<6.2 mmol (Fe)/L and ≥4.9 mmol (Fe)/L	<10 g/dL and ≥8.0 g/dL
		3	<4.9 mmol (Fe)/L and ≥4.0 mmol (Fe)/L	<8.0 g/dL and ≥6.5 g/dL
		4	<4.0 mmol (Fe)/L	<6.5 g/dL
Leukopenia[a]	White blood cell (WBC) count	0 (normal)	≥4.0 billion cells/L	≥4.0 thousand cells/uL
		1	<4.0 billion cells/L and ≥3.0 billion cells/L	<4.0 thousand cells/uL and ≥3.0 thousand cells/uL
		2	<3.0 billion cells/L and ≥2.0 billion cells/L	<3.0 thousand cells/uL and ≥2.0 thousand cells/uL
		3	<2.0 billion cells/L and ≥1.0 billion cells/L	<2.0 thousand cells/uL and ≥1.0 thousand cells/uL
		4	<1.0 billion cells/L	<1.0 thousand cells/uL
Neutropenia[a]	Absolute neutrophil count (ANC)	0 (normal)	≥2 billion cells/L	≥2 thousand cells/uL
		1	<2 billion cells/L and ≥1.5 billion cells/L	<2 thousand cells/uL and ≥1.5 thousand cells/uL
		2	<1.5 billion cells/L and ≥1.0 billion cells/L	<1.5 thousand cells/uL and ≥1.0 thousand cells/uL
		3	<1.0 billion cells/L and ≥0.5 billion cells/L	<1.0 thousand cells/uL and ≥0.5 thousand cells/uL
		4	<0.5 billion cells/L	<0.5 thousand cells/uL
Lymphopenia[a]	Lymphocyte count	0 (normal)	≥1.1 billion cells/L	≥1.1 thousand cells/uL
		1	<1.1 billion cells/L and ≥0.8 billion cells/L	<1.1 thousand cells/uL and ≥0.8 thousand cells/uL
		2	<0.8 billion cells/L and ≥0.5 billion cells/L	<0.8 thousand cells/uL and ≥0.5 thousand cells/uL
		3	<0.5 billion cells/L and ≥0.2 billion cells/L	<0.5 thousand cells/uL and ≥0.2 thousand cells/uL
		4	<0.2 billion cells/L	<0.2 thousand cells/uL
Thrombocytopenia[a]	Platelet count	0 (normal)	≥150 billions/L	≥150 thousands/uL
		1	<150 billions/L and ≥75 billions/L	<150 thousands/uL and ≥75 thousands/uL
		2	<75 billions/L and ≥50 billions/L	<75 thousands/uL and ≥50 thousands/uL
		3	<50 billions/L and ≥25 billions/L	<50 thousands/uL and ≥25 thousands/uL
		4	<25 billions/L	<25 thousands/uL

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events; Fe = iron.

[a] CTCAE grading was adjusted by replacing lower limit of normal (LLN) with a single value.

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