Statistical Analysis Plan J1V-MC-BT01 Version 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Two-Arm, Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of LY3361237 as a Treatment for Adults With At Least Moderately Active Systemic Lupus Erythematosus.

NCT05123586

Approval Date: 31-Aug-2023

Statistical Analysis Plan:
J1P-MC-BT01: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of LY3361237 as a Treatment for Adults with At Least Moderately Active Systemic Lupus Erythematosus

Master Protocol Title: A Master Protocol for a Randomized, Placebo-Controlled Clinical Trial of Multiple Interventions for the Treatment of Systemic Lupus Erythematosus

Master Protocol Number: J1V-MC-IMMA

Master Compound Number: LY900024

Master Protocol Short Title: A Master Protocol for a Randomized, Placebo-Controlled Clinical Trial of Multiple Interventions for the Treatment of Systemic Lupus Erythematosus

Sponsor Name: Eli Lilly and Company

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List of Intervention-Specific Appendices (ISAs):
ISA 1 for LY3361237 versus placebo (J1V-MC-BT01)

ISA Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Two-Arm, Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of LY3361237 as a Treatment for Adults with At Least Moderately Active Systemic Lupus Erythematosus

ISA Number: J1V-MC-BT01

ISA Compound Number: LY3361237

Study Phase: 2

ISA Short Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Two-Arm, Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of LY3361237 to Treat Adults with At Least Moderately Active Systemic Lupus Erythematosus

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Version History

This statistical analysis plan (SAP) for Study J1V-MC-BT01 (BT01) is based on the protocol dated 22 September 2021.

Study BT01 SAP version 3 was approved prior to the unblinding for a planned interim analysis of the first ISA (Study BT01). Changes in version 3 are documented. Minor corrections and/or additions may not be included.

Table 1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	9 Feb 2022	Not Applicable	Original version
2	15 Feb 2022	Update Table of Contents and minor editing	New comments in the SAP, link sections in the document
3	See date on Page 1	Update Sections 1, 4, and 6 and minor edits	Align with the analysis in previous studies and new comments

1. Introduction

This statistical analysis plan (SAP) is for Study J1V-MC-BT01 (BT01), an intervention-specific appendix (ISA) to the Master Protocol J1V-MC-IMMA (IMMA). This SAP has been developed after review of the Study BT01 Clinical Study Protocol (final version dated 21 June 2021), and Study BT01 Protocol Amendment (a) (final version dated 22 September 2021).

This SAP describes the planned analysis of the efficacy, safety, and pharmacokinetic (PK) and pharmacodynamic (PD) data from this study. A detailed description of the planned tables, figures, and listings (TFLs) to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical, PK and PD analyses of data. In general, the analyses are based on information from the protocol and there are no changes to the analyses described in the protocol. A limited amount of information concerning this study (for example, objectives, study design) is given to help the reader's interpretation. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

SAP BT01 elaborates on the statistical considerations identified in Protocol BT01 and SAP BT01 cannot modify the primary and secondary analyses described in Protocol BT01. If additional analyses are required to supplement the planned analyses described in SAP BT01, then these analyses may be performed and will be identified in each ISA's clinical study report (CSR) as post hoc analyses. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

1.1. Objectives and Estimands

Objectives	Estimands
Primary	
• To compare the efficacy of 450 mg LY3361237 Q2W versus placebo with respect to arthritis and/or rash remission in participants with SLE	The study will compare LY3361237 Q2W with placebo as randomized in participants with moderate to severe SLE who present with arthritis and/or rash at baseline. The primary comparison is the difference in proportions of participants who • achieve remission of arthritis and/or rash as defined by SLEDAI-2K at Week 24 • do not discontinue from treatment for any reason, and • do not violate concomitant medication rules.
Secondary	
• To compare 450 mg LY3361237 Q2W versus placebo with respect to SLE clinical signs and symptoms treatment response	The study will compare LY3361237 Q2W with placebo as randomized in participants with moderate to severe SLE who present with arthritis and/or rash at baseline. The comparisons include the following: • difference in proportions of participants who achieve SLEDAI-4 response at Week 24 and do not discontinue from treatment for any reason and not violate commitment medication rules, and • difference in proportions of participants who achieve SRI-4 response at Week 24 and do not discontinue from treatment for any reason and not violate commitment medication rules.

• To characterize the PK of 450 mg LY3361237 Q2W in participants with SLE	Steady-state trough serum concentration of LY3361237 at Week 24

Exploratory Objectives

The following are exploratory objectives for the evaluation of 450 mg LY3361237 Q2W:

- To compare the efficacy of LY3361237 Q2W versus placebo for the following measures:
  - corticosteroid sparing effect
  - individual organ system SLE disease manifestations using
    - SLEDAI-2K components
    - CLASI, and
    - joint counts
  - measures of SLEDAI-2K low-disease activity
    - LLDAS
  - BICLA
  - PGA
  - time to, and incidence of, any flare and first severe flare
  - serologic markers of SLE
  - interferon gene signature, and
  - SLICC/ACR Damage Index.
- To describe the observed safety of LY3361237 Q2W.
- To assess the potential development of anti-LY3361237 antibodies.
- To characterize the exposure-response of LY3361237 Q2W as related to biomarkers, RO, efficacy, and safety endpoints.
- To explore the effect of LY3361237 Q2W on exploratory biomarkers of SLE disease activity.

Note: The precise analysis for each estimand will be prospectively defined in the following sections of the statistical analysis plan and will include, at minimum, drug to be evaluated, dose/dosing regimen, population, indication under study, comparator, and timing of the analysis.

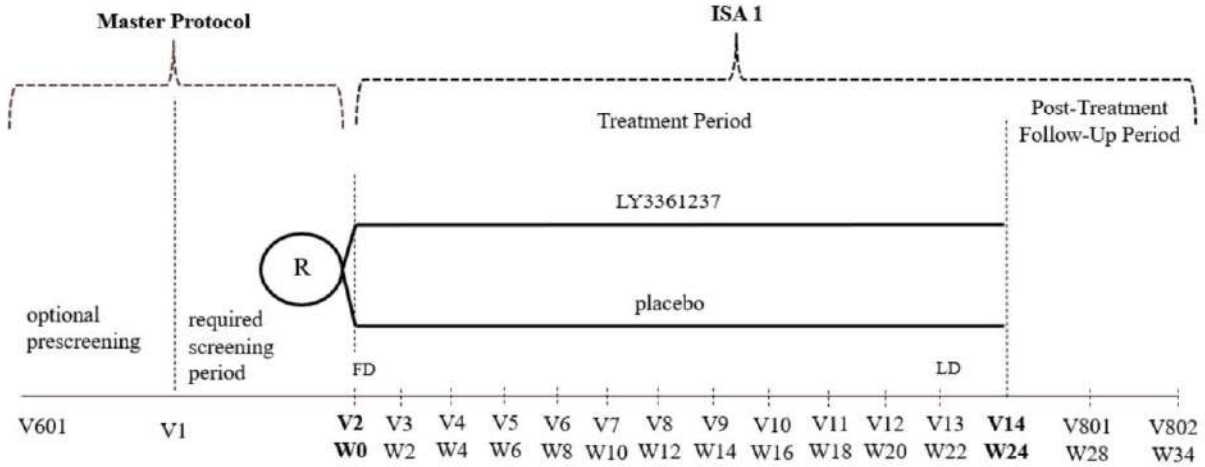
Abbreviations: ACR = American College of Rheumatology; BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; LLDAS = lupus low disease activity state; PGA = Physician's Global Assessment of Disease Activity; PK = pharmacokinetics; Q2W = every 2 weeks; RO = receptor occupancy; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI-4 = defined as 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.

1.2. Study Design

Study BT01 is an ISA to Master Protocol IMMA. It is a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2-arm Phase 2 study to evaluate the efficacy and safety of LY3361237 plus standard of care in adult study participants with at least moderately active systemic lupus erythematosus (SLE). This ISA has a required treatment period and a required post-treatment follow-up period. Master Protocol IMMA describes an optional prescreening period and a required screening period.

Number of Participants:

Approximately 90 participants will be randomly assigned in a 1:1 ratio to either LY3361237 or placebo. A schematic of the overall study design is presented in Figure 1.



Abbreviations: FD = first dose; ISA = intervention-specific appendix; LD = last dose; R = randomization to intervention groups of ISA; V = visit; W = week.

Figure 1. Schema of Study J1V-MC-BT01, a Phase 2 study to evaluate the efficacy and safety of LY3361237 in adults with at least moderately active systemic lupus erythematosus.

Optional prescreening period

The optional prescreening period is described in the Study IMMA SAP (Section 1.2.1).

Screening period

The screening period is described in the Study IMMA SAP (Section 1.2.1). The ISA specific informed consent forms will be signed before any Visit 2 study procedures are performed.

Participants found to be eligible according to all the study entry criteria of both Master Protocol IMMA and this ISA will be randomly assigned in a 1:1 ratio to receive 1 of the following study interventions:

- 450 mg LY3361237 once every 2 weeks (Q2W) plus standard of care, and
- placebo plus standard of care, given at matching intervals.

Participants will be stratified at randomization according to disease activity at baseline, corticosteroid dose at baseline, and geographic region (See Section 6.3 of Protocol BT01). Study interventions will be administered by subcutaneous (SC) 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 the Schedule of Activities (Section 1.3 of Protocol BT01). 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 (see Sections 5.2 and 6.5 of the Master Protocol IMMA) or unless changes are explicitly required by this Protocol BT01 (for example, dose adjustment for corticosteroids [see Section 6.5.1]). Safety and efficacy assessments and laboratory sample collections will be performed as specified in the Schedule of Activities (Section 1.3 of Protocol BT01) and as described in the Master Protocol IMMA.

Follow-up period

The posttreatment follow-up visit lasts approximately 10 weeks after the last visit of the 24-week treatment period. All participants will have posttreatment follow-up visits (Visit 801 and Visit 802; see Section 1.3 of Protocol BT01) for sample collections, including anti-drug antibodies (ADA) and PK, and for safety assessments.

Early discontinuation of study intervention

Participants who permanently discontinue the study intervention early are encouraged to remain in the study for safety monitoring through the end of the study treatment period and to participate in posttreatment follow-up visits. See Section 7 of the Master Protocol IMMA.

2. Statistical Hypotheses

The primary objective is to compare LY3361237 to placebo regarding remission of arthritis and/or rash at Week 24. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows:

- Null hypothesis: LY3361237 is not different from placebo with respect to the achievement of remission of arthritis and/or rash at Week 24.

The null hypotheses corresponding to the secondary estimands are as follows:

- LY3361237 is not different from placebo with respect to the achievement of Systemic Lupus Erythematosus Responder Index-4 (SRI-4) at Week 24, and
- LY3361237 is not different from placebo with respect to the achievement of a ≥4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score from baseline (SLEDAI-4) at Week 24.

Additionally, we will test some exploratory hypotheses for arthritis and rash respectively:

- Null hypothesis: LY3361237 is not different from placebo with respect to the change of arthritis status (improvement, no change, worsening) at Week 24, and
- Null hypothesis: LY3361237 is not different from placebo with respect to the change of rash status (improvement, no change, worsening) at Week 24.

2.1. Multiplicity Adjustment

No adjustments for multiplicity will be performed.

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined.

Participant Analysis Set	Description
Full analysis set	• All randomized participants. Participants will be included in the analyses according to the planned intervention.
mITT analysis set	• All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be included in the analysis set according to their randomly assigned intervention.
BICLA analysis set	• All mITT participants who meet the eligibility criteria for BICLA assessment. The eligibility criteria detail is in Section 4.7.6.
PP analysis set	• All randomized patients who do not commit an IPD that could potentially compromise efficacy results. IPDs are specified in the Trial Issue Management Plan.
Biomarker evaluable analysis set	• All randomized patients within the subset of participants from the exploratory analyses of dose and/or exposure relationship from whom a valid assay result has been obtained.
Safety analysis set	• All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received within each study period.
PK/PD analysis set	• All participants receiving at least 1 dose of study intervention and have PK and RO data available.

Abbreviations: BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; IPD = Important Protocol Deviation; mITT = modified intent-to-treat; PD = pharmacodynamic; PK = pharmacokinetic; PP = per-protocol; RO = receptor occupancy.

The safety analysis set is used to analyze the endpoints and assessments related to safety, and the modified intent-to-treat (mITT) and the per-protocol (PP) populations will be used in analyses of efficacy and patient-reported outcomes (PRO), unless otherwise specified. All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

4. Statistical Analyses

4.1. General Considerations

This SAP is intended to describe the analyses of all objectives, as well as safety assessments, for Study BT01.

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

See Master Protocol IMMA (Section 9.3.1) and Master Study IMMA SAP for platform trial considerations, such as borrowing of placebo data.

Considerations specific to this ISA include the following:

- All efficacy analyses will be tested at a two-sided alpha level of .10 for frequentist analyses.
- The primary and secondary estimand that will be used to analyze the primary and secondary endpoints is composite strategy estimand where comparisons will not include data collected after intercurrent events (ICE) including any concomitant medication violation or treatment discontinuation. Participants who discontinue or who are noncompliant with concomitant medication rules are defined as non-responders. Endpoint definition effectively gives complete data which will be analyzed as described in Sections 4.4 and 4.5.
- The p-values will be rounded up to 3 decimal places. For example, any p-value strictly >.049 and ≤.05 will be displayed as .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 .001 will always be understood to mean ≤.001. Likewise, any p-value displayed as 1.000 will be understood to mean >.999 and ≤1.

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.

The primary analysis method for treatment comparisons of binary efficacy and health outcome variables is CCI [redacted]. For treatment group and placebo group comparison, an estimate of the unconditional difference with corresponding 90% confidence interval (CI), the unconditional odds ratio with corresponding 90% CI and p-value will be presented. The p-value for all other explanatory variables will also be presented. CCI [redacted]
The treatment response rates, treatment differences versus placebo, and their corresponding 90% CIs will be provided.

The primary analysis method for both unconditional treatment difference of continuous efficacy and health outcome variables will be G-computation using a linear regression model with treatment group (LY or placebo), baseline disease activity (SLEDAI-2K <10 or SLEDAI-2K ≥10), corticosteroid dose at baseline (<10 mg/day or ≥10 mg/day), geographic region (USA, Europe, or rest of the world) in the model. The mean for each treatment group along with the estimate of the difference between treatments (difference between LY group and placebo), standard error (SE), p-value, and the 90% 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 linear regression analyses. However, the data will still be used in other analyses. In addition, if an ICE happens, including but not limited to rescue medication use, the data collected before that event will be used and any data afterward will be excluded in the linear regression model.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-event variables. CCI [redacted] Treatment comparisons will use the hazard ratios and corresponding p-values from the Cox regression. Patients completing the treatment period without event will be censored at the date of completion. Patients 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.

Descriptive statistics will be used to summarize for all adverse events (AE), discontinuation, and other categorical safety data. Continuous vital signs and laboratory values will be analyzed using descriptive summaries and may also by a linear regression model with treatment and baseline values in the model. Statistics to be presented are the same as those for linear regression analyses stated above. For document writing purposes for safety, tests with two-sided p-values less than .10 will be referred to as having significant statistical evidence for a treatment difference, unless otherwise noted.

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

Changes to the data analysis methods

SAP BT01 elaborates on the statistical analysis specified in Protocol BT01. Any change to the data analysis methods described in SAP BT01, and the justification for making the change, will be described in the CSR and should be considered post hoc, regardless of whether the change occurred before unblinding or not. Furthermore, additional exploratory analyses of the data will be conducted as deemed appropriate and will be considered post hoc.

4.2. Participant Characteristics

4.2.1. Demographics and Baseline Characteristics

Refer to Section 4.4.1 in Study IMMA SAP for summaries of participant demographics and baseline characteristics. Additional ISA specific analysis is described in Table 4.1.

Table 4.1. ISA Specific Patient Characteristics

Variable	Continuous	Categorical Summary	Subgroup Analysis
Disease Severity at Baseline			
Total SLICC/ACR Damage Index score	Yes	None	

Abbreviations: ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics.

4.3. Participant Disposition

Please refer to Section 4.5 of Study IMMA SAP for Participant Disposition.

4.4. Primary Estimand

Remission of arthritis and/or rash at Week 24

The primary clinical question of interest is: What is the difference between LY3361237 and placebo in the target patient population, in the proportion of participants who achieve remission of arthritis and/or rash as defined by the SLEDAI-2K after 24 weeks of intervention without violating concomitant medication rules and do not discontinue study intervention?

The ICEs of interest – "intervention discontinuation for any reason" and "any concomitant medication violation" – will be handled through the endpoint definition (composite variable strategy) and will be considered non-responders. All remaining ICEs are handled using the treatment policy strategy.

The estimand is described by the following attributes:

Population: participants with moderate to severe SLE who present with arthritis and/or rash at baseline. Further details can be found in Protocol BT01 Section 5.

Endpoint: responders at Week 24 defined as achieving all 3 of the following criteria:

- achieves remission of arthritis and/or rash at Week 24 as measured by SLEDAI-2K and defined in Protocol BT01 Section 8.1.1
- does not permanently discontinue study intervention for any reason prior to Week 24, and
- does not violate any concomitant medication rules (Protocol BT01 Section 6.5 and Section 6.8 of this SAP) prior to Week 24.

Treatment condition: study interventions as randomized with restricted use of concomitant medications. Further details on study interventions and concomitant medications can be found in Protocol BT01 Section 6.

Population-level summary: Unconditional difference in proportions of responders at Week 24 between treatment conditions (LY3361237 vs. placebo).

The rationale for this estimand is that if a participant discontinues treatment, the burden of treatment outweighs its benefits. It also assumes that if a participant violates the concomitant medication rules, the participant is not receiving sufficient benefit from treatment. Therefore, being a responder requires a positive response as well as completing treatment and not violating concomitant medication rules.

4.4.1. Main Analytical Approach

The primary endpoint analysis will use the mITT population. The primary endpoint will be analyzed using a G-computation with logistic regression model as working model to test the treatment difference between LY3361237 450 mg versus placebo in the proportion of patients who achieve remission of arthritis and/or rash at Week 24 with the stratification at randomization variables including the baseline disease activity, corticosteroid dose at baseline, and geographic region as model covariates.

The unconditional odds ratio and 90% CIs will be reported. The unconditional treatment difference and 90% CIs will be reported. In addition, we will report the 95% CIs and the p-values with respect to the alpha threshold .05.

Stratification at randomization

The randomization will be stratified based on the following factors:

- disease activity at baseline (SLEDAI-2K <10; SLEDAI-2K ≥10)
- corticosteroid dose at baseline (<10 mg; ≥10 mg), and
- geographic region (United States; Europe; rest of the world).

4.4.1.1. Missing Data Imputation

CCI

[redacted]

CCI [redacted]

4.5. Secondary Estimand(s)

SLEDAI-4 at Week 24

The clinical question of interest for a secondary objective regarding reduction in other SLE clinical signs and symptoms is: What is the difference in the percentage of participants who achieve SLEDAI-4 after 24 weeks of intervention without violating concomitant medication rules and do not discontinue study intervention?

The same ICE strategies used for constructing the primary estimand will be used for constructing this estimand.

The estimand is described by the following attributes:

Population: participants with moderate to severe SLE who present with arthritis and/or rash at baseline. Further details can be found in Protocol BT01 Section 5.

Endpoint: responder at Week 24 defined as achieving all 3 of the following criteria:

- achieves SLEDAI-4 response at Week 24 as defined in the Protocol BT01 Section 8.1.2.1
- does not permanently discontinue study intervention for any reason prior to Week 24, and
- does not violate any concomitant medication rules (Protocol BT01 Section 6.5 and Section 6.8 of this SAP) prior to Week 24.

Treatment condition: study interventions as randomized with restricted use of concomitant medications. Further details on study interventions and concomitant medications can be found in Protocol BT01 Section 6.

Population-level summary: unconditional difference in proportions of responders at Week 24 between treatment conditions (LY3361237 vs. placebo).

The rationale for this estimand is the same as the primary estimand.

SRI-4 at Week 24

The clinical question of interest for another secondary objective regarding reduction in other SLE clinical signs and symptoms is: What is the difference between the proportion of participants who achieve SRI-4 after 24 weeks of intervention without violating concomitant medication rules and do not discontinue study intervention?

The same ICE strategies used for constructing the primary estimand will be used for constructing this estimand.

The estimand is described by the following attributes:

Population: participants with moderate to severe SLE who present with arthritis and/or rash at baseline. Further details can be found in Protocol BT01 Section 5.

Endpoint: responder at Week 24 defined as achieving all 3 of the following criteria:

- achieves SRI-4 response at Week 24 as defined in Protocol BT01 Section 8.1.2.2.
- does not permanently discontinue study intervention for any reason prior to Week 24, and
- does not violate any concomitant medication rules (Protocol BT01 Section 6.5 and Section 6.8 of this SAP) prior to Week 24.

Treatment condition: study intervention as randomized with restricted use of concomitant medications. Further details on study interventions and concomitant medications can be found in Protocol BT01 Section 6.

Population-level summary: Unconditional difference in proportions of responders at Week 24 between treatment conditions (LY3361237 vs. placebo).

The rationale for this estimand is the same as the primary estimand. The missing data will be handled similarly to the process described in Section 4.4.1.1.

4.5.1. Additional Analysis

The number and percentage of responders and non-responders at each visit will be presented by treatment group. The proportion of responders to SRI-4 at treatment completion will be analyzed using a logistic regression model as specified for the primary analysis in Section 4.4.1. Moreover, the number and percentage of patients who sustain responses will be summarized by treatment group. Specifically, 1 type of sustained response will be included:

- respond by Week 12 and maintain response until Week 24.

A table for reasons of non-response, based on NRI, will also be tabulated at Week 24. Reasons are study treatment non-completers, concomitant medication violation (increase), SLEDAI not reduced by ≥4 points, British Isles Lupus Assessment Group (BILAG) criteria not met, Physician's Global Assessment (PGA) criteria not met, or missing data. If a patient is a non-responder by more than 1 reason, then count only the first reason in the list. For example, if a patient didn't meet SLEDAI criteria and BILAG criteria, then the patient would be counted in the SLEDAI count.

Similarly, the proportion of responders to SLEDAI-4 at treatment completion will be analyzed using logistic regression model as specified for the primary analysis in Section 4.4.1.

4.6. Supplementary Estimands 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 LY3361237 and placebo in the target patient population, in achieving successful response at Week 24 without regards to violation of concomitant medication rules?

The primary and secondary objective will be additionally assessed, under a situation when the use of concomitant medications may violate the specified rules, but best effort is made to

comply, through a supplementary estimand. Multiple ICE strategies will be applied to construct this supplementary estimand. The ICE – "intervention discontinuation for any reason" – will be handled through the endpoint definition using the composite variable strategy, and all other ICEs including "any concomitant medication violation" will be handled using the treatment policy strategy. The supplementary estimand for primary objective is described by the following attributes:

Population: participants with moderate to severe SLE who present with arthritis and/or rash at baseline. Further details can be found in Protocol BT01 Section 5.

Endpoint: responder at Week 24 defined as achieving both of the following criteria:

- achieves remission of arthritis and/or rash at Week 24 as measured by SLEDAI-2K and defined in Protocol BT01 Section 8.1.1, and
- does not permanently discontinue study intervention for any reason prior to Week 24.

Treatment condition: study intervention as randomized with best effort to manage use of concomitant medication. Further details on study interventions and concomitant medications can be found in Protocol BT01 Section 6.

Population-level summary: unconditional difference in proportions of responders at Week 24 between treatment conditions (LY3361237 vs. placebo).

The analytical approach followed will be similar to Section 4.4.1 after taking into account the ICE strategy described above. The secondary estimands described in Section 4.5 may also be considered for analysis using the aforementioned estimand strategy.

4.7. Exploratory Estimands

CCI [redacted]

4.7.1. Rash and Arthritis

The change of rash status in patients, as defined by the SLEDAI-2K, at Week 24 will be listed. Specifically, the number of patients with improvement of rash, no change in rash, and worsening of rash will be reported respectively. A Cochran-Mantel-Haenszel test will be used to test between the status of rash (improvement, no change, or worsening) and the treatment group (LY or placebo), with stratification factors based on

- CCI [redacted]
- CCI [redacted]

- CCI [redacted]

For sensitivity analysis, Fisher's exact test will be used to test between the status of arthritis (improvement, no change, or worsening) and the treatment group (LY or placebo).

The change of arthritis status in patients, as defined by the SLEDAI-2K, at Week 24 will be listed. Specifically, the number of patients with improvement of arthritis, no change of arthritis, and worsening of arthritis will be reported respectively. A Cochran-Mantel-Haenszel test will be used to test between the status of arthritis (improvement, no change, or worsening) and the treatment group (LY or placebo), with stratification factors based on:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

For sensitivity analysis, Fisher's exact test will be used to test between the status of arthritis (improvement, no change, or worsening) and the treatment group (LY or placebo).

4.7.2. Rash and/or Arthritis with Intercurrent Events Handled Using Treatment Policy Strategy

The analysis for the proportion of patients with rash and/or arthritis at Week 24 with the stratification at randomization variables, will be performed as described in the section above for mITT patient population with the ICEs handled using treatment policy strategy as described in Section 4.6. That is, all mITT patients will be analyzed without considering rescue medication use, corticosteroid tapering requirement, or any other possible ICEs.

4.7.3. Corticosteroid-Sparing Effect

The proportion of patients receiving ≥10 mg/day prednisone at baseline able to reduce prednisone (or equivalent) dose to ≤7.5 mg for 12 consecutive weeks between Week 12 and Week 24 will be compared between LY3361237 treatment group and placebo. The number and percentage of responders and non-responders at each visit will be presented by treatment group. The number of responders and non-responders will be compared using a chi-square test with respect to the treatment group (LY or placebo). If the number of patients in 1 categorical group in 1 treatment group is less than 5, a Fisher's exact test will be used instead.

4.7.4. Individual Organ System Systemic Lupus Erythematosus Disease Manifestations Using Systemic Lupus Erythematosus Disease Activity Index 2000 Components, Cutaneous Lupus Erythematosus Disease Area and Severity Index, and Joint Counts

For SLEDAI-2K, within each organ system and each individual item (as detailed in Section 6.3), the proportion of patients who go from "present" at baseline to "absent" at Week 12 and Week 24 will be compared between treatment group and placebo with a Fisher's exact test. No statistical comparison will be performed for the summaries by individual items.

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) consists of the disease activity and damage scores. Activity is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and nonscarring alopecia.

Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. The scores are calculated by simple addition based on the extent of the symptoms. Note that when calculating the total damage score, the dyspigmentation score is multiplied by 2 if dyspigmentation usually lasts >12 months. Both disease activity and damage scores will be summarized by treatment and visit separately.

CLASI change from baseline in the activity and damage scores will be summarized and analyzed at Week 4 through Week 24 by linear regression method as described in Section 4.1. In addition, the change from baseline in proportion of patients with ≥50% reduction in the disease activity score and damage scores at Week 12 and Week 24 will be analyzed by a logistic regression model, as described in Section 4.1. This analysis (proportion of patients with ≥50% reduction) will be repeated for those patients who had a baseline CLASI activity score of 10 or higher.

The number of tender and swollen joints will be determined by examination of 28 joints (14 joints on each side of the patient's body). These 28 joints will be assessed and classified as no symptoms, tender only, swollen only, tender and swollen, or not evaluable. The number of tender and swollen joints ranges from 0 to 28, respectively.

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. Any positive response on pressure, movement, or both will then be translated into a single tender versus nontender dichotomy. Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthrosis will be assessed as not swollen, unless there is unmistakable fluctuation. The change from baseline in the number of 28 tender and swollen joint counts affected by SLE arthritis at Week 4 through Week 24 will be summarized and analyzed by linear regression as described in Section 4.1. The proportion of patients with ≥50% reduction in the number of tender/swollen joints affected by SLE arthritis at Week 12 and Week 24 will also be performed by logistic regression as described in Section 4.1. This analysis (proportion of patients with ≥50% reduction) will be repeated for those patients who had a baseline count of tender joints ≥8 and a baseline count of swollen joints ≥8.

Imputation rules for SLEDAI-2K and joint count are described in Sections 6.3 and 6.5, respectively.

4.7.5. Lupus Low Disease Activity State

A lupus low disease activity state (LLDAS) response is defined as a low level of disease activity attained with or without use of low-dose steroids and/or tolerated standard maintenance doses of standard of care immunosuppressant medications[4]. In detail, the definition of LLDAS is

1. SLEDAI-2K ≤4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity
2. no new lupus disease activity compared with the previous assessment
3. a Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI PGA (scale 0-3) ≤1
4. a current prednisolone (or equivalent) dose ≤7.5 mg daily, and

5. well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents.

The proportion of patients who achieve LLDAS at Week 24 will be compared between LY3361237 treatment group and placebo. The number and percentage of responders and non-responders at each visit will be presented by treatment group. The proportion of responders will be compared using a logistic regression model as specified in Section 4.1.

4.7.6. British Isles Lupus Assessment Group-Based Composite Lupus Assessment

The proportion of patients who meet criteria for response as defined by BILAG-based Composite Lupus Assessment (BICLA) at Week 24 will be compared between LY3361237 treatment group and placebo. The eligibility criteria for BICLA assessment for the mITT patients are:

- BILAG 2004 index level A disease activity in ≥1 organ system at baseline, or
- BILAG 2004 index level B disease activity in ≥2 organs systems if no level A disease activity was present at baseline.

The BICLA is a composite index used to assess disease activity in SLE. A BICLA response is defined as follows:

- reduction of all baseline BILAG-2004 A to B or C or D; and baseline BILAG-2004 B to C or D; and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
- no worsening from baseline in SLEDAI-2K, where worsening is defined as any increase from baseline in SLEDAI-2K, and
- no worsening from baseline in participants' lupus disease activity, where worsening is defined by an increase ≥0.3 points on PGA of Disease Activity.

The number and percentage of responders and non-responders at each visit will be presented by treatment group. The proportion of responders will be compared using a logistic regression model as specified in Section 4.1.

4.7.7. Physician's Global Assessment of Disease Activity

PGA scores will be summarized by treatment group and visit using descriptive statistics (n, mean, SD, median, minimum, and maximum). Similarly, the change from baseline in PGA scores will be summarized at all scheduled postbaseline visits. The change from baseline score to each scheduled visit will be analyzed using an linear regression model as described in Section 4.1.

4.7.8. Time to, and Incidence of, Any Flare and First Severe Flare

Cox regression model will be used for the time-to-event analyses.CCI [redacted] The Kaplan-Meier estimate of the proportion of patients experiencing severe/mild/moderate flare will be presented for each severity. The Kaplan-Meier estimate of the proportion of patients experiencing flare regardless of the severity

will also be presented. Estimates and 90% CIs for the 25th percentile, median, and 75th percentile will be provided, if estimable, by treatment group.

4.7.9. Serologic Markers of Systemic Lupus Erythematosus

In patients with elevated anti-double stranded DNA (anti-dsDNA) at baseline, proportion of patients with normal/high at Week 12 and Week 24 will be analyzed using Fisher's exact test.

In patients with elevated anti-dsDNA at baseline, change in anti-dsDNA level at Week 4 through Week 24 compared to baseline will be analyzed using linear regression model as described in Section 4.1.

In patients with low complement 3 (C3) at baseline, proportion of those who become normal/high at endpoint (Week 12 and Week 24) will be analyzed using Fisher's exact test.

In patients with low complement 4 (C4) at baseline, proportion of those who become normal/high at endpoint (Week 12 and Week 24) will be analyzed using Fisher's exact test.

In patients with low C3 and C4 at baseline, change in C3 and C4 levels at Week 4 through Week 24 compared to baseline will be analyzed using linear regression model as described in Section 4.1.

4.7.10. Interferon Gene Signature

Interferon Signature Genes (ISGs) are a large set of genes that are induced in target cells by type 1 interferons. CCI

[redacted]

4.7.11. Systemic Lupus Erythematosus International Collaborating Clinics Damage Index

The change from baseline to Week 24 will be analyzed using linear regression with LOCF as the imputation method as described in Section 4.1. Details of the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) Damage Index score are provided in Section 6.6.

4.8. Safety Analyses

See Master Study IMMA SAP (Section 4.10) for safety assessments and safety monitoring activities required for all ISAs. Procedures specified in the following subsections of this ISA must be followed in addition to those described in Master Protocol IMMA.

All safety data will be descriptively summarized by treatment groups (LY and placebo) and analyzed based on the safety population described in Section 3. The safety analyses include AEs, safety in special groups and circumstances, laboratory analytes, the 16-Item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16), the Columbia Suicide Severity Rating Scale (C-SSRS), electrocardiograms, and vital signs. The duration of exposure will also be summarized. The categorical safety measures will be summarized using descriptive measures and may be 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 linear regression, with treatment and baseline values in the model. More details are provided in subsequent sections.

For infections, an IR per 100 patient-years of observation (PYO), will be provided. PYO will be calculated as the sum of all patient observation time in the treatment group. For a patient with an event, the observation time will end at the first event date; for a patient without the event, the observation time will be censored at the patient's last treatment dose date plus 30 days or the patient's last visit, whichever occurs first. Only events that occur within 30 days after the patient's treatment discontinuation date will be considered.

See formula as follows:

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

IR will be calculated as follows:

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

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

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

4.8.1. 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 patient-years (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, and
- >0 to <4 weeks, ≥4 weeks to <12 weeks, ≥12 weeks to <24 weeks, and ≥24 weeks.

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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.

4.8.2. Adverse Events

4.8.2.1. 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.

Treatment-emergent adverse events (TEAEs) are defined as events that either first occurred or worsened in severity after the first dose of study drug and the earliest of the visit study drug disposition date or the last visit date during the treatment period, whichever occurred first, and up to 30 days after study treatment discontinuation. The MedDRA Lowest Level Term (LLT) will be used in defining which events are treatment-emergent. The maximum severity for each LLT during the baseline period until the first dose of the study medication will be used as baseline. If an event is preexisting during the baseline period, but it has missing severity, and the event persists during the treatment period or up to 30 days after treatment discontinuation, then the baseline severity will be considered mild for determining any postbaseline treatment-emergence (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, a serious adverse event (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 the 2 formats listed below:

- by MedDRA PT nested within SOC with SOCs ordered alphabetically, and events ordered within each SOC by decreasing frequency in the LY3361237 450 mg treatment group, and

- by MedDRA PT with events ordered by decreasing frequency in the LY3361237 450 mg treatment group.

For events that are gender specific, the denominator and computation of the percentage will only include patients from the given gender.

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 LY3361237 450 mg treatment group.

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

Common TEAEs are defined as TEAEs that occurred in ≥2% (before rounding) of patients in any treatment group including placebo. The number and percentage of patients with common TEAEs will be summarized by treatment using MedDRA PT ordered by decreasing frequency in the LY3361237 450 mg treatment group.

The number and percentage of patients with TEAEs will be summarized by maximum severity by treatment using MedDRA PT ordered by decreasing frequency for the common TEAEs and by treatment group using MedDRA PT nested within SOC, respectively. Events will be ordered by decreasing frequency within SOC in the LY3361237 450 mg treatment group. For each patient and TEAE, the maximum severity for the MedDRA level being displayed is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA PT.

4.8.2.2. Serious Adverse Events

An individual listing of all SAEs 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, an 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 LY3361237 450 mg treatment group. In addition, the SAEs will be summarized by treatment group using MedDRA PT without SOC. An individual listing of all SAEs will be provided.

4.8.3. Adverse Events of Special Interest

4.8.3.1. Infections

Completion of the Infection eCRF page is required for each infection reported as an AE or SAE.

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

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

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

For infections of special interest (herpes zoster, and herpes simplex), serious infections, and potential opportunistic infections (POIs) the IR and 95% CI will be calculated (for detail, see Section 4.8).

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

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

Potential opportunistic infections

The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al. (2015). See also Master Protocol IMMA (Appendix 10.5).

POIs will be identified in 2 ways[3]:

1. POIs will be identified from TEAEs based on a Lilly-defined list of MedDRA PTs shown in Section 6.9. The list is maintained outside Study BT01 SAP and can be updated without an amendment to Study BT01 SAP. These PTs are a subset of terms from the Infections and Infestations SOC.
2. Medical will review the list of POIs, including the details captured on the infection-specific eCRF, and determine whether the infection is a 'confirmed opportunistic infection'.

The summary analysis of opportunistic infections identified using the 2 approaches above will be provided. Events will be ordered by decreasing frequency of pathogen nested under pathogen species (mycobacteria, bacteria, fungal, viral, and parasites). The order of frequency will be determined using the LY3361237 450 mg group.

Herpes zoster

A summary table of herpes zoster will be provided. Herpes zoster will be defined based on the MedDRA PTs as listed under Herpes zoster (any form) (II) in Section 6.9, excluding Varicella virus test (10070444). The summary table will also include event maximum severity, seriousness, whether resulting in temporary study drug interruption, whether resulting in study drug discontinuation, whether treated with antiviral medication, and event outcome.

If a patient has more than 1 event of herpes zoster, the event with the maximum severity will be used in these summary tables. If more than 1 event of herpes zoster occurs with the same severity, the event with the longest duration will be used in the summary table.

Herpes simplex

A summary analysis of herpes simplex will be provided. Herpes simplex will be defined based on the MedDRA PTs as listed under Herpes simplex (invasive disease only) (IV) in Section 6.9. The summary table will include event maximum severity, seriousness, whether resulting in temporary study drug interruption, whether resulting in study drug discontinuation, and whether treated with antiviral medication. Antiviral medication will be selected based on Anatomical Therapeutic Chemical code level 2 "antiviral for systemic use."

If a patient has more than 1 event of herpes simplex, the event with the maximum severity will be used in these summary tables. If more than 1 event of herpes simplex occurs with the same severity, the event with the longest duration will be used in the summary table.

Hepatitis B virus DNA

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

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

- HBsAb- / HBcAb-
- HBsAb+ / HBcAb-
- HBsAb+ / HBcAb+, and
- HBsAb- / HBcAb+.

Association between infection and neutropenia/lymphopenia

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

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

4.8.3.2. Systemic Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when the study participants are receiving the study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

Sample collection at time of systemic hypersensitivity events

In the case of generalized urticaria or anaphylaxis, additional samples should be collected as described in Protocol BT01 Attachment 10.1.2. Laboratory results are provided to the sponsor via the central laboratory.

There are two time periods:

- **time period A, potential immediate hypersensitivity:** analysis of TEAEs occurring on the day of study drug administration, and
- **time period B, potential non-immediate hypersensitivity:** analysis of TEAEs occurring strictly after the day of study drug administration (but prior to subsequent drug administration).

Analyses of both time periods use current Standardised MEDdra Queries (SMQs), published by the Maintenance and Support Services Organization, to search for relevant events. The TEAEs are characterized as follows:

- Anaphylactic reaction SMQ (20000021; narrow, algorithm per SMQ guide, and broad)
- Hypersensitivity SMQ (20000214; narrow and broad), and
- Angioedema SMQ (20000024; narrow and broad).

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

4.8.4. Injection Site Reaction

The number and percentage of patients who experienced injection site reactions (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:

- anatomical location of the ISR

- abdomen side
- directionality of the anatomical location of the administration
- arm side
- thigh side
- whether the subject has any injection site erythema (reddening)
- severity of the injection site erythema
- whether the subject has any injection site induration (hardening or thickening of tissue)
- severity of the injection site induration
- whether the subject has any injection site pain (including burning)
- severity of the injection site pain
- whether the subject has any injection site pruritus
- severity of the injection site pruritus
- whether the subject has any injection site edema (swelling or accumulation of fluid in tissues at height above normal skin)
- severity of the injection site edema, and
- injection related event occur, in relationship to the study treatment (time to onsite of ISR)

If an ISR is reported by a participant or site staff, the ISR CRF will be used to capture additional information about this reaction (for example, injection-site pain, degree and area of erythema, induration, pruritis, and edema).

4.8.5. Clinical Laboratory Evaluations

Please refer to Section 4.10.4 in Study IMMA SAP.

4.8.6. Vital Signs and Other Physical Findings

Please refer to Section 4.10.5 in Study IMMA SAP.

4.8.7. Depression and Suicide

Please refer to Section 4.10.6 in Study IMMA SAP.

4.9. Other Analyses

4.9.1. Concomitant Therapy

Previous and concomitant medications will be summarized by treatment for each ISA and will be presented by Anatomical Therapeutic Chemical drug classes using the WHO Drug Dictionary version WHODDMAR19B3 (Uppsala Monitoring Centre 2019). Details can be found in Master Protocol IMMA Section 6.5 and Protocol BT01 Section 6.5. When the primary estimand is used for analyses, participants who require initiation or increase in dosage of corticosteroids, antimalarials, or immunosuppressants after randomization will be analyzed as non-responders from the day of initiation or increase in medication.

This describes how, for the efficacy analyses with primary estimand, the participant's responder/non-responder status will be handled in cases of such medication changes.

If the following medication is started after baseline or is increased in dosage after baseline...	**Then the participant's status for the efficacy analyses, from the time of change onward, will be:**
Corticosteroid	Non-responder
Antimalarial	Non-responder
Immunosuppressant (from the list in the protocol)	Non-responder

4.9.2. Treatment Compliance

Treatment compliance with study intervention will be summarized by treatment group. A participant will be considered significantly noncompliant if he or she fails to receive the study intervention within the required treatment window as defined in Protocol BT01 Section 1.3, Figure 1. Overall compliance with therapy is defined to be missing no more than 20% of the expected injections and not missing 2 consecutive dosing visits.

Treatment compliance with study medication will be assessed from the randomization visit (Week 0) to Visit 14 (Week 24) during the treatment period. Compliance will be summarized from randomization until end of treatment using the mITT population. Compliance to study drug in the period of interest will be calculated as follows:

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

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 14) will be presented, along with the associated noncompliance rates.

4.9.3. Immunogenicity Assessments

The frequency and percentage of participants with preexisting ADAs and with treatment-emergent ADAs (TE ADAs) to LY3361237 will be tabulated and listed.

For participants who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution (1:10) of the assay (treatment-induced ADAs). For participants who are ADA positive at baseline, TE ADAs are defined as

those with a 4-fold (2 dilution) increase in titer compared to baseline (treatment-boosted ADAs). For the TE ADA positive participants, the distribution of maximum titers will be described.

The relationship between the presence of antibodies to LY3361237 and the LY3361237 serum concentrations and receptor occupancy (RO) response, including safety and efficacy of LY3361237, may be assessed to show participants with ADA titers versus those without titers.

4.9.4. Patient-Reported Outcomes

For analysis of QIDS-SR16 data, see the methods described for safety data in Section 9.3.5 of the Master Protocol IMMA. If additional PROs are considered, dichotomous variables will be analyzed using logistic regression analyses, whereas linear regression will be the primary method of analysis for continuous endpoints. The analyses will be based on the mITT population, unless otherwise specified.

4.9.5. Subgroup Analyses

Subgroup analyses may be conducted for the primary endpoint rash and/or arthritis remission at Week 24 using the mITT population. Subgroups that may be evaluated include interferon gene signature status, original genetic sex, race, geographic region, baseline anti-dsDNA status, baseline SLEDAI-2K, complement status, previous therapies, and disease duration.

In detail, the following subgroups (but not limited to only these) may be evaluated:

- gender (male; female)
- baseline anti-dsDNA status (positive; negative)
- baseline interferon signature (positive; negative)
- baseline complement (low C3 and/or low C4; normal/high C3; normal/high C4)
- race (Asian; Black/African American; White; other)
- disease severity at baseline (SLEDAI-2K): (<10; ≥ 10)
- region (United States; Europe; rest of the world), and
- corticosteroid dose at baseline: (<10 mg; ≥ 10 mg).

If the number of participants is too small (less than 5 participants) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. Descriptive statistics will be provided for each treatment and stratum of a subgroup. Categorical variables 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 continuous variables, if the subgroup analyses are conducted only at Week 24 (Visit 14), linear regression model with LOCF will be used, in which the treatment, the baseline values, the subgroup variable, and subgroup by treatment interaction will be included as covariates in the model. For the categorical variables, the number of responders and response rate may be reported for each subgroup.

4.10. CCI

Additional analyses may be performed as deemed necessary. If applicable, any early access will be detailed in the Unblinding Plan.

4.10.1. Assessment Committee

If an interim analysis is conducted, it will be performed by an internal assessment committee (AC). Details of the planned interim data analyses and the AC data review process are included in the Study BT01 AC charter.

4.11. Pharmacokinetic Assessment

CCI

4.12. Pharmacodynamic Assessment

CCI

4.13. Data Monitoring Committee

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

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

4.14. Changes to Protocol-Planned Analyses

There were no changes from the protocol specified statistical analysis.

5. Sample Size Determination

In this ISA, approximately 180 patients will be screened to achieve 90 participants randomly assigned to study intervention (45 per treatment group).

The sample size calculation is based on the primary efficacy endpoint, remission of rash and/or arthritis as assessed by SLEDAI-2K at Week 24. Approximately 90 participants will be randomized in a 1:1 ratio to LY3361237 450 mg and placebo treatment groups. CCI

6. Supporting Documentation

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

Table APP.1.1. 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, CNS, 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 nonmissing data during the screening period. • Postbaseline data for that item can be carried forward from the last nonmissing 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 postbaseline 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	Among patients with at least one SLEDAI-2K item = 0 (not present) in the organ domain score at	Missing if any SLEDAI-2K item for that organ domain remains missing after

		Defined by SLEDAI-2K	baseline, no increment of SLEDAI-2K organ domain score from baseline within each organ domain score, separately.	instrument level imputation rules are applied.
		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	BILAG-2004 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 • If all items 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 postbaseline 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 nonmissing 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 nonmissing organ domains will be used to determine the response status.

				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 nonmissing 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.
		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	PGA score PGA category	Permitted range of values is from 0 to 100 mm.	If the visit occurred, data can be carried forward if

	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 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 ≤83 mm', Severe (>2.5) = '>83 mm'.	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
			  o Reduction of all baseline BILAG A to B/C/D and baseline BILAG B to C/D
			  o 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
			• 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.
				After each instrument level imputation rule is applied and there is at least one component missing, if the nonmissing components are all 'Y' then BICLA will be missing. If any of the nonmissing component is 'N' then the BICLA is 'N.'

CLASI	The CLASI is a validated instrument to assess cutaneous	Total Activity Score	Calculated within tablet system with edit checks; no additional derivation.	Within tablet system: If any item scores, but not all are

	manifestations of SLE consisting of 2 scores: • Activity • Damage			missing then impute a score of 0 for the missing item(s). For completely missing questionnaires, data can be carried forward if obtained within 34 days of visit; otherwise missing.
		Total Damage Score	Calculated within tablet system with edit checks; no additional derivation.	Within tablet system: if any item scores, but not all are missing then impute a score of 0 for the missing item(s). For completely missing questionnaires, data can be carried forward if obtained within 34 days of visit; otherwise missing.
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 nonmissing components are all 'Y' then LLDAS will be missing. If any of the nonmissing component is 'N' then the LLDAS is 'N.'
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

SLICC/ACR	SLICC/ACR Damage Index assesses damage to 12 organ systems regardless of its cause.	SLICC/ACR Damage Index Score	Calculated as the sum of all available entries with a maximum score of 47.	

Abbreviations: ACR = American College of Rheumatology; BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group - 2004; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CNS = central nervous system; LLDAS = Lupus Low Disease Activity State; MCS = Mental Component Summary; N = no; NA = not applicable; PCS = Physical Component Summary; PGA = Physician's Global Assessment; PROMIS SF = Patient-Reported Outcomes Measurement Information System Short Form; 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; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; SRI-4 = Systemic Lupus Erythematosus Responder Index-4; VAS = Visual Analog Scale; Y = yes.

6.2. 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.

Table APP.2.1. Description of Efficacy Analyses

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	linear regression	Exploratory
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
	Individual Organ Domain Improvement	Composite	mITT – Patients with SLEDAI-2K score > 0 within the	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI	Exploratory

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	Defined by SLEDAI-2K		organ domain at baseline		Fisher's Exact Test with NRI	
	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
	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
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	linear regression	Exploratory
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression 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
CLASI	Total Activity Score, Change from Baseline	Hypothetical	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression with BOCF	Exploratory
	Total Damage Score, Change from Baseline	Hypothetical	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression with BOCF	Exploratory
	≥50% Reduction in CLASI Total Damage Score	Composite	mITT – Patients with CLASI Total Damage Score ≥10 at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI; Fisher's Exact Test with NRI	Exploratory
	≥50% Reduction in CLASI Total Activity Score	Composite	mITT – Patients with CLASI Total Activity Score ≥10 at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
Corticosteroid-Sparing Effect	Reduction of prednisone (or equivalent) dose to ≤7.5 mg for 12 consecutive weeks between Week 12 and Week 24	Composite	mITT – Patients with prednisone (or equivalent) >10 mg at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory

	Prednisone (or equivalent) dose, change from baseline	Hypothetical	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Hypothetical	Per-Protocol	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression with BOCF	Exploratory
TJC	TJC, change from baseline	Hypothetical	mITT – Patients with tender joints affected by SLE arthritis at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Composite	mITT – Patients with tender joints affected by SLE arthritis at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression with BOCF	Exploratory
	≥50% Reduction in TJC	Composite	mITT – Patients with tender joints affected by SLE arthritis at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
		Composite	mITT – Patients with ≥8 TJC at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
SJC	SJC, change from baseline	Hypothetical	mITT – Patients with swollen joints affected by SLE arthritis at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Composite	mITT – Patients with swollen joints affected by SLE arthritis at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Linear regression with BOCF	Exploratory

	≥50% Reduction in SJC	Composite	mITT – Patients with swollen joints affected by SLE arthritis at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
		Composite	mITT – Patients with ≥8 SJC at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Logistic Regression with NRI Fisher's Exact Test with NRI	Exploratory
Serologic Markers of SLE	Anti-dsDNA, change from baseline	Hypothetical	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression with BOCF	Exploratory
		Hypothetical	mITT – Patients with elevated anti-dsDNA level (>120 IU/mL)	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
	C3 level, change from baseline	Hypothetical	mITT – Patients with low C3 level at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory
		Composite	mITT – Patients with low C3 level at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Linear regression with BOCF	Exploratory
	Normal/high C3 level	Composite	mITT – Patients with low C3 at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Fisher's Exact Test	Exploratory
	C4 level, change from baseline	Hypothetical	mITT – Patients with low C4 level at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory

		Composite	mITT – Patients with low C4 level at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression with BOCF	Exploratory
	Normal/high C4 level	Composite	mITT – Patients with low C4 at baseline	LY3471851 vs Placebo at postbaseline visits in the treatment period	Fisher's Exact Test	Exploratory
Flare	Time to first flare	Hypothetical (censored at the time of first violation of concomitant medication rules if flare not occurred beforehand)	mITT	LY3471851 vs Placebo during the treatment period	Cox regression Kaplan-Meier plot	Exploratory
Severe Flare	Time to first severe flare	Hypothetical (censored at the time of first violation of concomitant medication rules if flare not occurred beforehand)	mITT	LY3471851 vs Placebo during the treatment period	Cox regression Kaplan-Meier plot	Exploratory
SLICC Damage Index	SLICC Damage Index, change from baseline	Composite	mITT	LY3471851 vs Placebo at postbaseline visits in the treatment period	linear regression	Exploratory

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; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; LLDAS = Lupus Low Disease Activity State; MCS = Mental Component Summary; mITT = modified intent-to-treat; NRI = non-responder imputation; PCS = Physical Component Summary; PGA = Physician's Global Assessment; SF = Short Form; SJC = Swollen Joint Count; 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; TJC = Tender Joint Count.

6.3. Appendix 3: SLEDAI-2K

The total SLEDAI score is a weighted sum of those questions that have been answered as "present" on the CRF. The weights are listed below. For example, if a patient's CRF was marked present on psychosis, arthritis and rash then their score would be 8+4+2=14.

For the SLEDAI questionnaire, if any, but not all, of the 24 item scores is missing then impute a score of 0 for the missing item(s) when calculating the total score. In addition, any item with missing data will be imputed as 'not present' for any other analyses if at least one of the 24 items is nonmissing. If all 24 item scores are missing, then the total score will be missing, as well as any other analysis by organ system or individual descriptor.

Weight	SLEDAI SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38°C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.
TOTAL SLEDAI SCORE	_____		

For the purposes of analyses by organ system, the following list shows what descriptors are part of each organ system:

1. **Central Nervous System**: Seizure, Psychosis, Organic Brain Syndrome, Visual Disturbance, Cranial Nerve Disorder, Lupus Headache, CVA
2. **Vascular**: Vasculitis
3. **Musculoskeletal**: Arthritis, Myositis
4. **Renal**: Urinary Casts, Hematuria, Proteinuria, Pyuria
5. **Mucocutaneous**: Rash, Alopecia, Mucosal Ulcers
6. **Cardiovascular and Respiratory**: Pleurisy, Pericarditis
7. **Immunologic**: Low complement, Increased DNA Binding
8. **Constitutional**: Fever
9. **Hematologic**: Thrombocytopenia, Leukopenia

6.4. Appendix 4: BILAG 2004

The BILAG 2004 index is a validated global disease activity index designed on the basis of the physician's intent-to-treat, focusing on changes in disease manifestations (not present, improving, same, worse, or new) occurring in the last 4 weeks compared with the previous 4 weeks. The instrument assesses 97 clinical signs, symptoms, and laboratory parameters across 9 organ system domains: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematology.

For BILAG, any item that appears 'Not done' will be assumed to be 'Not present'. Any missing data will be assumed to also be 'Not present' if at least there is a nonmissing item in the whole questionnaire.

- The BILAG A disease activity score is severe disease activity requiring high-dosage oral or intravenous corticosteroids, immunomodulators, or high-dosage anticoagulation along with high-dosage corticosteroids or immunomodulators.
- The BILAG B disease activity score is moderate disease activity requiring low-dosage oral corticosteroids, intramuscular or intra-articular corticosteroid injections, topical corticosteroids or immunomodulators, antimalarials, or symptomatic therapy.
- The BILAG C corresponds to stable, mild disease.
- The BILAG D is inactive disease that was active previously.
- The BILAG E indicates the system was never involved.

Calculation of the BILAG A and B Disease Activity Scores for Each Domain

Constitutional

Category A:

Pyrexia recorded as 2 (same), 3 (worse), or 4 (new), **and**

Any 2 or more of the following recorded as 2 (same), 3 (worse), or 4 (new):

Weight loss

Lymphadenopathy/splenomegaly

Anorexia

Category B:

Pyrexia recorded as 2 (same), 3 (worse), or 4 (new), **or**

Any 2 or more of the following recorded as 2 (same), 3 (worse), or 4 (new):

Weight loss

Lymphadenopathy/splenomegaly

Anorexia

but do not fulfill criteria for Category A

Category C

Pyrexia recorded as 1 (improving) or

One or more of the following recorded as >0:

Weight loss

Lymphadenopathy/Splenomegaly

Anorexia

but does not fulfill criteria for category A or B

Category D

Previous involvement

Category E

No previous involvement

MUCOCUTANEOUS

Category A

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Skin eruption - severe

Angio-oedema - severe

Mucosal ulceration - severe

Panniculitis/Bullous lupus - severe

Major cutaneous vasculitis/thrombosis

Category B

Any Category A features recorded as 1 (improving) or

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Skin eruption - mild

Panniculitis/Bullous lupus - mild

Digital infarcts or nodular vasculitis

Alopecia - severe

Category C

Any Category B features recorded as 1 (improving) or

Any of the following recorded as >0:

Angio-oedema - mild

Mucosal ulceration - mild

Alopecia - mild

Periungual erythema/chilblains

Splinter haemorrhages

Category D

Previous involvement

Category E

No previous involvement

NEUROPSYCHIATRIC

Category A

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Aseptic meningitis

Cerebral vasculitis

Demyelinating syndrome

Myelopathy

Acute confusional state

Psychosis
Acute inflammatory demyelinating polyradiculoneuropathy
Mononeuropathy (single/multiplex)
Cranial neuropathy
Plexopathy
Polyneuropathy
Status epilepticus
Cerebellar ataxia

Category B

Any Category A features recorded as 1 (improving) or

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Seizure disorder
Cerebrovascular disease (not due to vasculitis)
Cognitive dysfunction
Movement disorder
Autonomic disorder
Lupus headache - severe unremitting
Headache due to raised intracranial hypertension

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

MUSCULOSKELETAL

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Severe Myositis

Severe Arthritis

Category B

Any Category A features recorded as 1 (improving) or

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Mild Myositis

Moderate Arthritis/Tendonitis/Tenosynovitis

Category C

Any Category B features recorded as 1 (improving) or

Any of the following recorded as >0:

Mild Arthritis/Arthralgia/Myalgia

Category D

Previous involvement

Category E

No previous involvement

CARDIORESPIRATORY

Category A

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Myocarditis/Endocarditis + Cardiac failure

Arrhythmia
New valvular dysfunction
Cardiac tamponade
Pleural effusion with dyspnoea
Pulmonary haemorrhage/vasculitis
Interstitial alveolitis/pneumonitis
Shrinking lung syndrome
Aortitis
Coronary vasculitis

Category B

Any Category A features recorded as 1 (improving) or

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Pleurisy/Pericarditis
Myocarditis - mild

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

GASTROINTESTINAL

Category A

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Peritonitis

Lupus enteritis/colitis
Intestinal pseudo-obstruction
Acute lupus cholecystitis
Acute lupus pancreatitis

Category B

Any Category A feature recorded as 1 (improving) or

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Abdominal serositis and/or ascites
Malabsorption
Protein losing enteropathy
Lupus hepatitis

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

OPHTHALMIC

Category A

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Orbital inflammation/myositis/proptosis
Keratitis - severe
Posterior uveitis/retinal vasculitis - severe
Scleritis - severe

Retinal/choroidal vaso-occlusive disease

Optic neuritis

Anterior ischaemic optic neuropathy

Category B

Any Category A features recorded as 1 (improving) or

Any of the following recorded as 2 (same), 3 (worse), or 4 (new):

Keratitis - mild

Anterior uveitis

Posterior uveitis/retinal vasculitis - mild

Scleritis - mild

Category C

Any Category B features recorded as 1 (improving) or

Any of the following recorded as >0:

Episcleritis

Isolated cotton-wool spots (cytoid bodies)

Category D

Previous involvement

Category E

No previous involvement

RENAL

Category A

Two or more of the following providing 1, 4, or 5 is included:

1. Deteriorating proteinuria (severe) defined as

   a. urine dipstick increased by ≥2 levels (used only if other methods of urine protein estimation not available); or
   b. 24-hour urine protein >1 g that has not decreased (improved) by 25%; or
   c. urine protein-creatinine ratio >100 mg/mmol that has not decreased (improved) by 25%; or
   d. urine albumin-creatinine ratio >100 mg/mmol that has not decreased (improved) by 25%.
2. Accelerated hypertension.
3. Deteriorating renal function (severe) defined as
   a. plasma creatinine >130 mol/L and having risen to >130% of previous value; or
   b. GFR <80 mL/min per 1.73 m^2 and having fallen to <67% of previous value; or
   c. GFR <50 mL/min per 1.73 m^2 and last time was > 50 ml/min per 1.73 m^2 or was not measured.
4. Active urinary sediment
5. Histological evidence of active nephritis within last 3 months
6. Nephrotic syndrome

Category B

One of the following:

1. One of the Category A features
2. Proteinuria (that has not fulfilled Category A criteria)
   a. urine dipstick which has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); or
   b. 24-hour urine protein ≥0.5 g that has not decreased (improved) by 25%; or
   c. urine protein-creatinine ratio ≥50 mg/mmol that has not decreased (improved) by 25%; or
   d. urine albumin-creatinine ratio ≥50 mg/mmol that has not decreased (improved) by 25%
3. Plasma creatinine > 130 mol/L and having risen to ≥115% but ≤130% of previous value.

Category C

One of the following:

1. Mild/Stable proteinuria defined as

a. urine dipstick ≥1+ but has not fulfilled criteria for Category A and B (used only if other methods of urine protein estimation not available); or

b. 24-hour urine protein >0.25 g but has not fulfilled criteria for Category A and B; or

c. urine protein-creatinine ratio >25 mg/mmol but has not fulfilled criteria for Category A and B; or

d. urine albumin-creatinine ratio >25 mg/mmol but has not fulfilled criteria for Category A and B

2. Rising blood pressure (providing the recorded values are >140/90 mm Hg) which has not fulfilled criteria for Category A and B, defined as

a. systolic rise of ≥30 mm Hg; and

b. diastolic rise of ≥15mm Hg

Category D

Previous involvement

Category E

No previous involvement

Note: although albumin-creatinine ratio and protein-creatinine ratio are different, we use the same cut- off values for this index.

HEMATOLOGICAL

Category A

TTP recorded as 2 (same), 3 (worse), or 4 (new) or

Any of the following:

Haemoglobin	<8 g/dL
White cell count	$<1.0 \times 10^9$/L
Neutrophil count	$<0.5 \times 10^9$/L
Platelet count	$<25 \times 10^9$/L

Category B

TTP recorded as 1 (improving) or

Any of the following:

Haemoglobin	8 - 8.9 g/dL
White cell count	1 - 1.9 × 10^9/L
Neutrophil count	0.5 - 0.9 × 10^9/L
Platelet count	25 - 49 × 10^9/L
Evidence of active haemolysis	

Category C

Any of the following:

Haemoglobin	9 - 10.9 g/dL
White cell count	2 - 3.9 × 10^9/L
Neutrophil count	1 - 1.9 × 10^9/L
Lymphocyte count	<1.0 × 10^9/L
Platelet count	50 - 149 × 10^9/L
Isolated Coombs' test positive	

Category D

Previous involvement

Category E

No previous involvement

Numerical Categorization for BILAG A-E

For each organ system domain, BILAG 2004 numeric score of A to E will be assigned according to the following rule (Yee et al. 2010)

- BILAG A disease activity score = 12 points
- BILAG B disease activity score = 8 points
- BILAG C disease activity score = 1 point
- BILAG D disease activity score = 0 points
- BILAG E disease activity score = 0 points

For each complete BILAG assessment, the points score from each of the nine BILAG organ system domains will be summed to obtain a BILAG 2004 numeric score. The numeric score will only be calculated if each of the 9 disease activity scores are nonmissing.

6.5. Appendix 5: Joint Assessment

The 28 joints will be evaluated for tenderness and 28 joints will be evaluated for swelling (hips are excluded for swelling) at the specified visits as shown in the schedule of events of the protocol. The 28 joint count will be performed at Week 0 (V2/baseline), Week 2 (V4) to Week 24 (V14), end of treatment, and at follow-up visit.

The following joint count imputation rules will be applied.

1. Joints that had any of the following procedures or disease conditions that occur at the screening (Visit 1), up to and including baseline (Visit 2), will be imputed as follows:
    a. Arthroplasty, fusion, synovectomy, ankylosis, amputation, injury, fracture, infection and other condition: these will be considered "nonevaluable" from baseline up to end of the study. Joints that include "nonevaluable" joints will be prorated from baseline up to end of the study. For example, the swollen joint count score for 6 swollen plus 2 "nonevaluable" joints is calculated as [6/(28-2)]*28 = 6.46.
    b. Injection and other procedure: joints that have received intra-articular and bursal injections will be collected in the data but set to painful/ tender or swollen after the injection for 6 months (up to Week 24 (V15) [Visit 9]).
2. Joints that had any of the following procedures or disease conditions that occur postbaseline (any time during treatment with the study drugs) will be imputed as follows:
    a. Amputation: amputation that occurs postbaseline will be considered "nonevaluable" from the visit after amputation up to end of the study. Joints that include "nonevaluable" joints will be pro-rated from the visit after amputation up to end of the study. For example, the swollen joint count score for 6 swollen plus 2 "nonevaluable" joints is calculated as [6/(28-2)]*28 = 6.46.
    b. Arthroplasty, fusion, synovectomy, and ankylosis: if any of these procedures occur postbaseline, joints will be set to tender and swollen from the visit after the procedure up to the end of the study.
    c. Infection, injury, and fracture or other condition: if any of these conditions occur postbaseline, joints will be set to tender and swollen from the visit after the condition until the condition is resolved.
    d. Injection and other procedure: joints that have received intra-articular and bursal injections postbaseline will be collected in the data but set to tender and swollen after the injection for 6 months or the end of the study (whichever comes first).

The number of tender and swollen joints will be calculated by summing all joints respectively. For patients who have an incomplete set of joints evaluated, the joint count will be adjusted to a 28-joint count for tenderness and a 28-joint count for swelling by dividing the number of affected joints by the number of evaluated joints and multiplying by 28 for tenderness and 28 for swelling.

6.6. Appendix 6: SLICC/ARC Damage Index

The total score is a simple sum of all 39 items on the CRF. Note that while most items are scored either 0 (not present) or 1 (present), there are some items that are weighted heavier. Note for example that the following items can have a response of either 0, 1 or 2 on the CRF. If "2" is selected that is what should be included in the sum

- Cerebrovascular accident,
- myocardial infarction,
- significant tissue loss
- infarction or resection of bowel
- avascular necrosis
- malignancy

Also note for end stage renal failure, it is either 0 (not present) or 3 (present). If it is present, then the score of 3 is added to the total.

6.7. Appendix 7: Corticosteroid Conversion

All corticosteroid doses need to be converted to prednisone equivalent doses (as detailed in Section 6.8). 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.*

Table APP.7.1. Corticosteroid Conversion

Column 1	Column 2
Corticosteroid Preferred Term	Conversion factor for converting to an equivalent prednisone dose
Prednisone	1
Prednisone acetate	1
Prednisolone	1
Prednisolone acetate	1
Prednisolone sodium phosphate	1
Methylprednisolone	1.25
Methylprednisolone acetate	1.25
Methylprednisolone sodium succinate	1.25
Triamcinolone	1.25
Triamcinolone acetonide	1.25
Triamcinolone hexacetonide	1.25
Cortisone	0.2
Cortisone acetate	0.2
Hydrocortisone	0.25
Hydrocortisone acetate	0.25
Hydrocortisone sodium succinate	0.25
Betamethasone	6.25
Betamethasone acetate	6.25
Betamethasone dipropionate	6.25
Betamethasone sodium phosphate	6.25
Dexamethasone	6.25
Dexamethasone acetate	6.25
Dexamethasone phosphate	6.25
Dexamethasone sodium phosphate	6.25
Paramethasone	2.5
Deflazacort	0.83
Celestona bifas	6.25
Depo-medrol med lidokain	1.25
Diprospan	6.25
Fluocortolone	1
Meprednisone	1.25

6.8. Appendix 8: Corticosteroid Management

Key elements of corticosteroid management in this study include the following:

- Enrolled participants are restricted to prednisone ≤20 mg per day (or equivalent) at randomization (Visit 2), having been on stable doses for at least 2 weeks prior to randomization.
- Following randomization, the dose of prednisone (or equivalent) should not be increased above the participant's background level (dose at baseline).
- Participants on ≥10 mg per day are required to taper their dose to taper their dose to <10 mg per day by Week 12, and maintain a dose <10 mg to Week 24 to be considered **responders**.
- Participants with intolerable or exacerbating disease are allowed access to standard of care therapy, including increasing the dose of prednisone (or equivalent). Such participants are allowed to remain in the study but will be permanently discontinued from study intervention (see the Master Protocol IMMA [Section 7.1]).

6.9. Appendix 9: List of MedDRA Preferred Terms for Potential Opportunistic Infections

Table APP.9.1. MedDRA Preferred Terms for 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	

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		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	
		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
		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	
		Pneumonia salmonella	10035733	
		Salmonella bacteraemia	10058924	
		Salmonella sepsis	10058878	
		Typhoid fever	10045275	
		Salmonella test positive	10070127	Broad
		Salmonellosis	10039447	
		Salmonella test	10079854	
Bacteria		Shigella sepsis	10074481	Narrow

	Shigellosis (invasive disease only) (V)	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 acinctobactcr	10079866	Narrow
		Pneumonia proteus	10079867	
		Pneumonia serratia	10079868	
Fungal	Aspergillosis (invasive disease only) (II)	Aspergillosis oral	10003489	
		Cerebral aspergillosis	10051597	
		Meningitis aspergillus	10073245	
		Oro-pharyngeal aspergillosis	10053029	
		Aspergillus infection	10074171	
		Aspergillus test	10070450	
		Aspergillus test positive	10070448	
		Bronchopulmonary aspergillosis	10006473	
		Sinusitis aspergillus	10051016	
	Blastomycosis (IV)	Blastomycosis	10005098	Narrow
		Epididymitis blastomyces	10015001	
		Osteomyelitis blastomyces	10031255	
		Pneumonia blastomyces	10035671	
		None		Broad
	Candidiasis (invasive disease, or oral not limited to the tongue) (II)	Candida endophthalmitis	10059449	Narrow
		Candida osteomyelitis	10064699	
		Candida pneumonia	10053158	
		Candida retinitis	10068612	
		Candida sepsis	10053166	
		Candida urethritis	10081262	
		Candidiasis of trachea	10064459	
		Cerebral candidiasis	10078126	
		Endocarditis candida	10014669	
		Gastrointestinal candidiasis	10017938	
		Hepatic candidiasis	10049653	
		Hepatosplenic candidiasis	10051590	
		Meningitis candida	10027205	
		Oesophageal candidiasis	10030154	
		Oral candidiasis	10030963	
		Oropharyngeal candidiasis	10050346	
		Peritoneal candidiasis	10056562	

		Splenic candidiasis	10051725	
		Systemic candida	10042938	
		Bladder candidiasis	10058523	Broad
		Candida infection	10074170	
		Candida test	10070453	
		Candida test positive	10070451	
		Mucocutaneous candidiasis[1]	10028080	
		Respiratory moniliasis	10038705	
	Coccidioidomycosis (II)	Coccidioides encephalitis	10054214	Narrow
		Coccidioidomycosis	10009825	
		Cutaneous coccidioidomycosis	10068747	
		Meningitis coccidioides	10027207	
		None		Broad
	Cryptococcosis (II)	Cryptococcal cutaneous infection	10054216	Narrow
		Cryptococcal fungaemia	10067112	
		Cryptococcosis	10011490	
		Disseminated cryptococcosis	10013439	
		Gastroenteritis cryptococcal	10011485	
		Meningitis cryptococcal	10027209	
		Neurocryptococcosis	10068368	
		Pneumonia cryptococcal	10067565	
		Cryptococcus test	10070456	Broad
		Cryptococcus test positive	10070455	
	Histoplasmosis (II)	Acute pulmonary histoplasmosis	10001027	Narrow
		Chronic pulmonary histoplasmosis	10009115	
		Endocarditis histoplasma	10014676	
		Histoplasmosis	10020141	
		Histoplasmosis cutaneous	10049142	
		Histoplasmosis disseminated	10020144	
		Meningitis histoplasma	10027243	
		Pericarditis histoplasma	10034489	
		Retinitis histoplasma	10038912	
		Presumed ocular histoplasmosis syndrome	10063664	Broad
	Microsporidiosis (IV)	Microsporidia infection	10053982	Narrow

		None		Broad
	Other invasive fungi: Mucormycosis (=zygomycosis) [Rhizopus, Mucor, and Lichtheimia], *Scedosporium/ 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	
		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	
		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	
		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	
		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	
		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	
		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	None		Narrow

		Delftia acidovorans infection	10081339	
		Sphingomonas paucimobilis bacteraemia	10081563	
Non-specific terms		Central nervous system immune reconstitution inflammatory response	10080100	Broad
		Abscess fungal	10000269	
		Alternaria infection	10054207	
		Arthritis fungal	10060966	
		Biliary tract infection fungal	10065203	
		Central nervous system fungal infection	10072805	
		Cerebral fungal infection	10049657	
		Encephalitis fungal	10065170	
		Erythema induratum	10015213	
		Eye infection fungal	10015933	
		Fungaemia	10017523	
		Fungal abscess central nervous system	10017524	
		Fungal endocarditis	10017529	
		Fungal labyrinthitis	10065174	
		Fungal oesophagitis	10049656	
		Fungal peritonitis	10061138	
		Fungal pharyngitis	10076516	
		Fungal retinitis	10068613	
		Fungal sepsis	10058872	
		Fungal urethritis	10081163	
		Hepatic infection fungal	10065217	
		Meningitis fungal	10027236	
		Mycotic endophthalmitis	10063202	
		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; POI = potential opportunistic infections; PT = Preferred Term; PVAN = Polyomavirus-associated nephropathy; SMQ = Standardized MedDRA Query.

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

Table APP.10.1. 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
Flow Cytometry				
1	CD3+ T Cells – %	Covance	Yes	Yes
2	CD3+ T Cells – Absolute	Covance	Yes	Yes
3	CD3+CD4+ T cells (CD4) – %	Covance	Yes	Yes
4	CD3+CD4+ T cells (CD4) – Absolute	Covance	Yes	Yes
5	CD3+CD8+ T cells (CD8) – %	Covance	Yes	Yes
6	CD3+CD8+ T cells (CD8) – Absolute	Covance	Yes	Yes
7	CD56+/CD16+ NK cells – %	Covance	Yes	Yes
8	CD56+/CD16+ NK cells – Absolute	Covance	Yes	Yes
9	CD19+ B cells – %	Covance	Yes	Yes
10	CD19+ B cells – Absolute	Covance	Yes	Yes
11	CD4+CXCR3+CCR6- Th1 cells - %	None	Yes	No
12	CD4+CXCR3+CCR6- Th1 cells - Absolute	None	Yes	No
13	CD4+CXCR3-CCR6+ Th17 cells - %	None	Yes	No
14	CD4+CXCR3-CCR6+ Th17 cells - Absolute	None	Yes	No
15	CD3+CD4+CD127-/loCD25+FoxP3+ (CD4+) T regulatory cells - %	None	Yes	No
16	CD3+CD4+CD127-/loCD25+FoxP3+ (CD4+) T regulatory cells - Absolute	None	Yes	No
17	CD3+CD4+CD127-/loCD25+ (CD4+) IL2-producing naïve and central memory Helper T cells - %	None	Yes	No

Laboratory Group/Order	Laboratory Analyte	Reference Range Name	Analysis Type	
			Central Tendency	Outlier/Shift Analysis
18	CD3+CD4+CD127-/loCD25+ (CD4+) IL2-producing naïve and central memory Helper T cells - Absolute	None	Yes	No
19	CD20+ B cells – %	None	Yes	No
20	CD20+ B cells – Absolute	None	Yes	No
21	CD19+CD27-IgD+ mature naïve B cells – %	None	Yes	No
22	CD19+CD27-IgD+ mature naïve B cells – Absolute	None	Yes	No
23	CD19+CD27+IgD- switched memory B cells – %	None	Yes	No
24	CD19+CD27+IgD- switched memory B – Absolute	None	Yes	No
25	CD19+CD27+IgD+ non-switched memory B cells – %	None	Yes	No
26	CD19+CD27+IgD+ non-switched memory B – Absolute	None	Yes	No
27	CD19+CD27-IgD- Immature/transitional B cells – %	None	Yes	No
28	CD19+CD27-IgD- Immature/transitional B – Absolute	None	Yes	No
29	CD4/CD8 Ratio – Calculated	None	Yes	No
--	CD4+CD45RA-CCR7- effector memory T cells	None	No	No
--	CD4+CD45RA+CCR7- effector memory T cells	None	No	No
--	CD4+CD45RA+CCR7- naïve T cells	None	No	No
--	CD4+CD45RA-CCR7+ central memory T cells	None	No	No
--	CD8+CD45RA+CCR7+ naïve T cells	None	No	No
--	CD8+CD45RA-CCR7+ central memory T cells	None	No	No
--	CD8+CD45RA-CCR7- effector memory T cells	None	No	No
--	CD8+CD45RA+CCR7- effector memory T cells	None	No	No

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

6.11. Appendix 11: Common Terminology Criteria for Adverse Events Related to Myelosuppressive Events

Table APP.11.1. 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

Event	Laboratory Test	Grade	Criteria in Système International (SI) Units	Criteria in Conventional (CN) Units
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

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

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

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