Statistical Analysis Plan J1V-MC-IMMA Version 2

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.

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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

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

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List of Intervention-Specific Appendices (ISAs):

ISA 1 for LY3361237 versus placebo (J1V-MC-BT01)

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Version History

This statistical analysis plan (SAP) for Study J1V-MC-IMMA is based on Protocol J1V-MC-IMMA, dated 22 Sept 2021.

SAP Version 2 was approved prior to the first unblinded interim analysis of the first Intervention Specific Appendix (ISA) (BT01). Changes in Version 2 are documented in the following table. Minor corrections and/or additions may not be included.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version
2		Updated Section 1.2 Study Design Added detail to assignment to treatment, informed consent, and screening processes. Updated Section 4 Statistical Analyses Changes to layout Additional detail included in 4.10.2.2, Serious Adverse Events. Updated 4.10.3.1 Abnormal Hepatic Tests	Ease of reading

1. Introduction

This SAP is for Master Protocol Study J1V-MC-IMMA (IMMA). SAP IMMA has been developed after review of the J1V-MC-IMMA Clinical Study Protocol (final version dated 21 June 2021), and J1V-MC-IMMA Protocol Amendment (a) (final version dated 22 September 2021).

SAP IMMA describes the planned analysis of the efficacy and safety from this Master Protocol and its ISAs.

The intent of this document is to provide guidance for the statistical analyses of data. In general, the analyses are based on information from Protocol BT01 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.

SAP IMMA elaborates on the statistical considerations identified in Protocol IMMA and SAP IMMA cannot modify the primary and secondary analyses described in Protocol IMMA. If additional analyses for each ISA are required to supplement the planned analyses described in SAP IMMA and the ISA's SAP, these analyses may be performed and will be identified in each ISA's clinical study report (CSR) as post hoc analyses.

SAP IMMA 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 (EMA 1998) and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports (EMA 1995).

1.1. Objectives and Estimands

The purpose of Master Protocol IMMA is to create a framework to evaluate the efficacy and safety of various investigational interventions for systemic lupus erythematosus (SLE) as hypotheses emerge. The clinical research objectives and estimands for specific investigations are detailed in the relevant ISA. In general, each ISA assesses 1 or more interventions relative to placebo with respect to

- efficacy as measured by global disease activity, organ-specific disease activity, and, if applicable, patient-reported outcomes, and
- safety, using standard assessments and measures such as physical examinations, clinical safety laboratory tests, suicidality and depression evaluations, and collection of vital signs and spontaneously reported adverse events (AEs).

1.2. Study Design

1.2.1. Overall Design

This is a multinational, multicenter, randomized, double-blind, placebo-controlled, platform-type clinical trial to investigate the efficacy and safety of multiple interventions for SLE simultaneously or sequentially. Figure 1.1 illustrates the general schema.

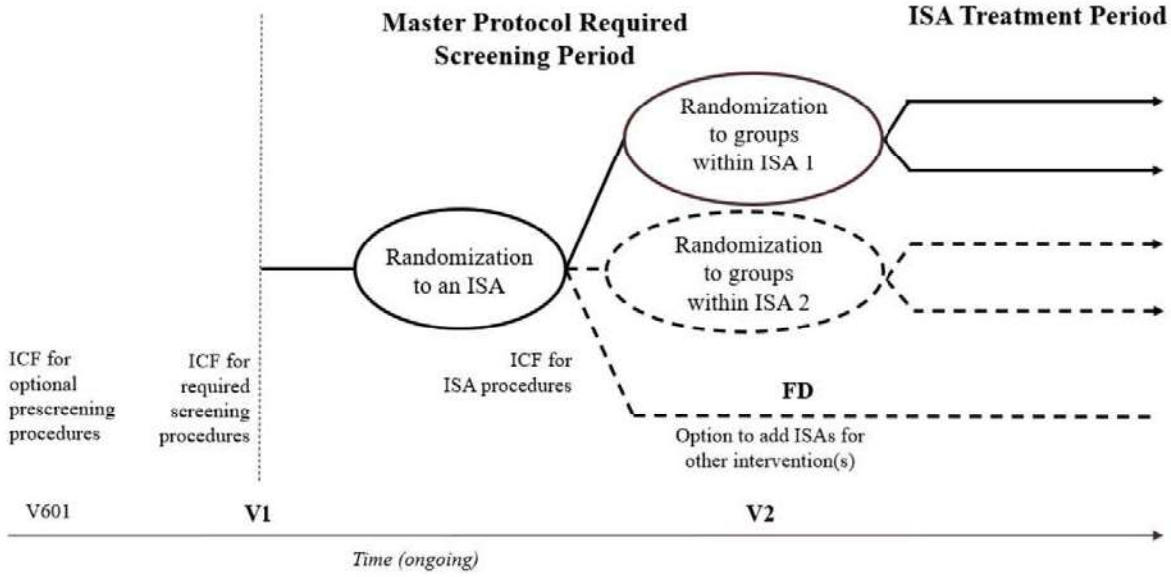
Master protocol and ISAs

The overall protocol design consists of 2 components which, used together, define the investigations to be conducted in this platform trial:

- Master Protocol IMMA explains the platform study concept, overall structure, and governance, giving primary focus to screening activities, study entry and discontinuation criteria, safety monitoring activities, and statistical analysis methods applicable to all ISAs, and
- Individual ISAs provide information on the investigation of specific interventions, including intervention-specific background information, benefit and risk, dose justification; intervention-specific research objectives and estimands; intervention-specific study entry and discontinuation criteria; and intervention-specific outcomes measurements and statistical analysis methods. Each ISA includes a schedule of activities (SoA) applicable from the time of a participant's random assignment through the time of the participant's last planned study visit.

More details can be found in Master Protocol IMMA Section 4.

Figure 1.1 illustrates the general schema for this master protocol. Schemas for interventions studied under Master Protocol IMMA are provided in the ISAs.



Abbreviations: FD = first dose; ICF = informed consent form; ISA = intervention-specific appendix; V = eCRF visit.

Figure 1.1 Schema of Master Protocol J1V-MC-IMMA for a randomized, placebo-controlled clinical trial of multiple interventions for the treatment of systemic lupus erythematosus.

Informed consent process

To participate in this trial, a participant must provide informed consent for the procedures described both in Master Protocol IMMA and in the relevant ISA. This could mean signing more than one informed consent form (ICF), as illustrated in Figure 1.1.

- an ICF for the optional prescreening
- an IMMA ICF, which describes the study purpose and high-level design, the required screening procedures, and general information about the investigational interventions to which the participant might be randomly assigned, and
- an ISA-specific ICF, which describes the study purpose and design, the intervention risk and benefit information, required study treatment and posttreatment procedures, and the approximate probability of the participant's being randomized to the placebo control group.

CCI [redacted]

Screening period:

The required screening period begins at Visit 1. Visit 1 must occur at least 3 days, but no more than 35 days, before the planned randomization visit (Visit 2). CCI [redacted] A participant identification number will be assigned at Visit 1 if one was not assigned at Visit 601. Participant eligibility will be reviewed and confirmed by an eligibility review committee prior to random assignment to an ISA.

Study entry criteria

Participants found to be eligible according to all study entry criteria (See Sections 5.1 and 5.2 of Protocol IMMA) will be randomly assigned to one of the ISAs and will be randomly assigned to a treatment group within the designated ISA. The participant's within-ISA randomization treatment group assignment will be blinded. For some ISAs, additional entry criteria might be required prior to the second randomization. If so, these additional entry criteria will be specified in the relevant ISAs.

Randomization to ISAs

At the inception of this platform trial, only 1 ISA will be active. Eligible participants at the inception of the platform trial will be assigned only to that 1 active ISA.

As subsequent interventions enter the platform trial, the plan for randomization to active ISAs will be updated and explained in the new ISAs and/or other study documents. CCI [redacted]

Treatment and posttreatment periods

For investigations conducted under Master Protocol IMMA, the study treatment period begins at Visit 2. After the last visit in the treatment period, participants will have 1 or more posttreatment follow-up visits, as specified in the relevant ISA. See the ISAs for procedures conducted at Visit 2 and at subsequent visits in these study periods.

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 Protocol IMMA Section 7).

1.2.2. Method of Assignment to Treatment

Assignment to the ISAs and to the treatment groups within the ISAs will be determined by a computer-generated random sequence using an interactive web response system (IWRS). The randomization ratios are specified in the individual ISAs. At the inception of Protocol IMMA, there is a single ISA in which there is randomization to treatment groups in a 1:1 ratio. Subsequent ISAs will have randomization ratio details which will depend on anticipated timing of ISA entry, number of active ISAs, required number of participants to be assigned to an active treatment group in the ISA, and desired number of placebo participants to maintain the blind and minimize bias. The within-ISA allocation to active and placebo treatment arms will be constructed so that the likelihood of random assignment to placebo for the platform trial is 25% to 50%.

2. Statistical Hypotheses

For each ISA of this master protocol, the primary null hypothesis is that there is no difference between the intervention and placebo on primary objective. Intervention-specific details regarding hypotheses and statistical testing are in the respective ISAs.

2.1. Multiplicity Adjustment

There is no plan to implement any multiple testing strategy in Master Protocol IMMA. If a multiple testing strategy is required at an ISA level, it will be detailed in the ISA SAP.

3. Analysis Sets

Analysis set is a broad term used to define a set of definitions for the population and treatment conditions that are essential attributes for defining an estimand. Table 3.1 describes the analyses sets defined for all ISAs, unless otherwise specified in the ISA. Additional intervention-specific analyses sets may be described in the respective ISAs.

Table 3.1. Analysis Sets

Analysis Set	Population	Treatment Condition	Used to Analyze
Modified intent-to-treat (mITT)	All randomly assigned participants receiving at least 1 dose of study intervention.	Intervention randomly assigned to participants.	• Efficacy objectives • Patient-reported outcomes, if applicable
Safety Analysis Set	All randomly assigned participants receiving at least 1 dose of study intervention.	Intervention participants actually received.	• Safety
Pharmacokinetics (PK)	All randomly assigned participants receiving at least 1 dose of study intervention and who have PK data available.	Intervention participants actually received.	• PK

4. Statistical Analyses

4.1. Sample Size Determination

At the inception of Master Protocol IMMA, there will be a single ISA (BT01). Approximately 90 participants will be randomly assigned to a treatment group in this single ISA. Approximately 45 of these participants will be randomly assigned to the placebo group.

In subsequent ISAs, borrowing of placebo data may be used in safety, health outcomes, and efficacy analyses, including the primary analysis according to the approach defined in Section 4.2. If borrowing occurs at time of primary database lock for the intervention of interest, the intervention data will be compared to all placebo data available, as appropriate.

Details of sample size and power assumptions and calculations for each intervention are in the respective ISAs.

4.2. General Considerations

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.

Not all displays described in SAP IMMA will necessarily be included in the CSR. Not all displays will necessarily be created as a static display. Some displays may be incorporated into interactive display tools such as Spotfire instead of, or in addition to, a static display. Any display described in SAP IMMA and not included in the CSR will be available upon request.

Unless otherwise indicated in ISA-specific analyses, these general considerations apply to the analyses.

- ***p-values***

  Unless otherwise indicated in ISA-specific analyses, the primary and secondary endpoint analyses will be tested at a two-sided alpha level of 0.05 for frequentist analyses.

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

- ***Multiplicity adjustments***

No adjustments for multiplicity will be performed.

- ***Intercurrent events of interest***

Intercurrent events of interest (ICE) and associated estimand strategy will be described in the SAP of each ISA.

- ***Statistical analysis of efficacy and health outcomes***

Statistical analysis efficacy and health outcomes are ISA specific, please refer to respective ISA SAP for guidance.

- ***Handling missing data***

Missing data will be handled separately from the estimand strategy. After intercurrent events are accounted for according to estimand strategies, any remaining missing data will be handled by methods specified in the respective ISAs.

CCI

Changes to the data analysis methods

SAP IMMA elaborates on the statistical analysis specified in Protocol IMMA. Any change to the data analysis methods described in SAP IMMA, and the justification for making the change, will be described in the CSR for each ISA 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.

4.3. Definition of Baseline and Postbaseline Measures

Baseline will be defined as the last available value before the first dose of the study intervention for both the efficacy and safety analyses, unless otherwise specified in the ISAs. In most cases, this will be the measure recorded at Visit 2.

The treatment period begins after the first study drug administration at Visit 2, unless otherwise specified in the ISAs. The end of the treatment period is specified in the ISAs. After the last visit in the treatment period, participants will have 1 or more posttreatment follow up visits, as specified in the ISAs. See the ISAs for procedures conducted at Visit 2 and at subsequent visits in these study periods.

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

4.4. Participant Characteristics

4.4.1. Demographics and Baseline Characteristics

Patient characteristics, including demographics, will be summarized using the modified intent-to-treat (mITT) population by treatment group. The summary will include descriptive statistics such as the number of patients (n), mean, standard deviation (SD), median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures. No formal statistical comparisons will be made among treatment groups, unless otherwise stated. Table 4.1 itemizes the specific baseline measures and patient characteristics to be presented and how they will be summarized. Changes to Table 4.1, including the summary of additional patient characteristics, will not require an amendment to SAP IMMA. Additional ISA-specific characteristics will be detailed in the respective ISA-specific SAP.

Table 4.1 Summary Tables Related to Demographics and Patient Characteristics

Variable	Quantitative	Categorical Summary	Subgroup Analysis
Demographic Characteristics			
Age[a]	Yes	<65, 65 to <75, ≥75	
Height	Yes		
Weight	Yes		
BMI[b]	Yes		
Sex	No	Female, Male	Yes
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	Yes
Country	No	By country	
Geographic Region	No	North America, Europe, Rest-of-world	Yes
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino, Not Applicable	Yes
Ethnicity (only US sites)		Hispanic/Latino, Non-Hispanic/Non-Latino, Missing	Yes
Time since onset of lupus (years)[d]	Yes		
Concomitant Medication Use at Baseline			
Daily dose of corticosteroid (mg/day)[e]	Yes	• Yes/No • <7.5 mg/day or ≥7.5 mg/day • <10 mg/day or ≥10 mg/day	Yes
Immunosuppressant use	No	Yes/No	
Mycophenolate mofetil use	No	Yes/No	
Azathioprine use	No	Yes/No	
Methotrexate use	No	Yes/No	
Antimalarial use (for each drug)	No	Yes/No	
NSAID use	No	Yes/No	
Disease Severity at Baseline			
SLEDAI-2K	Yes	<10 or ≥10	Yes
Prevalence of SLEDAI-2K organ system involvement (for each organ system domain)	Yes		

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Variable	Quantitative	Categorical Summary	Subgroup Analysis
SLEDAI-2K organ system involvement (for each organ system domain)	No	Yes/No	
British Isles Lupus Assessment Group (BILAG) A or B organ system involvement (for each organ system domain)	No	Yes/No	
BILAG A organ system involvement (for each organ system domain)	No	Yes/No	Yes
Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) Total Activity Score	Yes	<4, ≥4	Yes
CLASI Total Damage Score	Yes	None	
Number of tender joints (from 28-tender joint count)	Yes	<6, ≥6	Yes
Number of swollen joints (from 28-swollen joint count)	Yes	<6, ≥6	Yes
Physician's Global Assessment of Disease Activity Score	Yes	None	
Patient's Global Impression of Severity – 7 Days (Lupus)	Yes	None	
Serological Marker at Baseline			
CCI			

Variable	Quantitative	Categorical Summary	Subgroup Analysis
CCI			

Abbreviations: ANA = anti-nuclear antibodies; CCI
CCI BMI = body mass index;
CCI eCRF = electronic case report form;
NSAID = nonsteroidal anti-inflammatory drug; SLE = systemic lupus erythematosus;
SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

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

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

[c] Puerto Rico is considered part of US.

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

In case of partial date of SLE diagnosis, the following imputation rules will be utilized:

- if both month and day are missing, impute July 1.
- if month is missing and day is not missing, impute July 1.
- if only day is missing, impute 15.

[e] Patients with a non-zero dose at Visit 2 will be included in this baseline continuous summary. See Appendix 1 for details of prednisone (or equivalent) baseline dose.

4.4.2. Historical Illness and Preexisting Conditions

Historical illness or condition is defined as the condition or event recorded on the Pre-Existing Conditions and Medical History electronic case report form (eCRF) page or on the Prespecified Medical History eCRF page with an end date prior to the date of informed consent and no end

date (that is, the event is ongoing) or an end date on or after the date of informed consent. Notice if a preexisting condition worsens in severity on or after the date of informed consent, will be recorded as an AE on the Adverse Events eCRF page from the date of worsening onwards. Historical illnesses and preexisting conditions will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with historical illnesses and preexisting conditions will be provided by treatment group, overall and by System Organ Class (SOC) and Preferred Terms (PT) using the mITT population. Note that conditions with a partial or missing start date will be assumed to be "not preexisting" unless there is evidence, through comparison of partial dates, to suggest otherwise. Patients will only be counted once if the same PT is listed in 2 or more different SOC categories.

4.5. Participant Dispositions

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants who were screened and randomly assigned to the study, and the number and percentage of participants who complete the study or discontinue early, both overall and by reason for discontinuation for each ISA at the end of the study. Intervention-specific analyses are described in the respective ISAs. A summary of important protocol deviations will be provided for each ISA.

4.6. Primary Estimand(s) and Analyses

The primary estimand and analyses are described in respective ISA-specific SAPs.

4.6.1. Sensitivity Analyses

No sensitivity analyses are planned for the initial ISA (BT01). Sensitivity analyses in subsequent ISAs regarding placebo borrowing may include methods described in Section 4.2.

4.7. Secondary Estimands(s) and Analyses

The secondary estimand and analyses are detailed in the relevant SAP for each ISA.

4.8. Exploratory Estimand(s) and Analyses

Intervention-specific exploratory estimands and analyses are described in the respective ISAs.

4.9. Supplementary Estimand(s) and Analyses

Supplemental analyses may be performed for the primary objective by assessing alternative estimands constructed under different strategies for handling treatment discontinuations due to different reasons, prohibited medication use, or other intercurrent events of interest. Details of supplementary analyses, alternative estimands, and corresponding statistical methods are specified in the respective ISAs.

4.10. Safety Analyses

All safety data will be descriptively summarized by treatment conditions and analyzed based on the safety analysis set defined in Section 3. The safety analyses include AEs, safety in special groups and circumstances, including Adverse Events of Special Interest (AESI), laboratory analytes, Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16 [Rush et al. 2003]), Columbia-Suicide Severity Rating Scale (C-SSRS), electrocardiograms (ECGs), and vital signs. The duration of exposure will also be summarized. Categorical safety measures will be summarized using descriptive measures and may be analyzed using Fisher's exact test. The mean change in continuous safety measures, including vital signs, QIDS-SR16, physical characteristics, and laboratory values, will be summarized by visits and may be analyzed by ANCOVA with treatment and baseline covariates in the model. More details are provided in subsequent sections.

In safety analyses, tests with two-sided p-values ≤ 0.05 will be referred to as having strong statistical evidence for a treatment difference, unless otherwise noted or indicated in the respective ISAs. IIowever, p-values should not be over-interpreted for these safety analyses. Except in the case of prespecified hypotheses, p-values will be used primarily as a flagging mechanism.

Safety analyses described in this IMMA SAP apply to all ISAs, unless otherwise indicated in ISA-specific safety analyses. In general, safety analyses are performed for each ISA, and additional master protocol-level safety analyses may be performed as part of the integrated safety analyses.

4.10.1. Extent of Exposure

Master Protocol IMMA will include both small and large molecules. As such, exposure is considered an intervention-specific topic and will be described in the respective ISA SAPs or appendices.

4.10.2. Adverse Events

4.10.2.1. Adverse Events

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

A treatment-emergent adverse effect (TEAE) is defined as an event that first occurs or worsens in severity after baseline, with baseline defined as all preexisting conditions recorded at Visit 1 and any AEs recorded before the first dose of study intervention (that is, between Visits 1 and 2 and recorded with the time of onset before the first dose of study intervention) 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. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the baseline period, the event will be treated as mild in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as

severe and treatment-emergence will be determined by comparing with baseline severity. 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. Note that conditions with a partial or missing start date will be assumed to be "not preexisting" unless there is evidence, through comparison of partial dates, to suggest otherwise. Patients will only be counted once if same PT is listed in 2 or more different SOC categories.

The planned summaries for AEs are provided in Table 4.2. For events that are gender-specific, the denominator and computation of the percentage will only include participants from the given gender. MedDRA PTs are assigned to a SOC through primary mappings (as defined by MedDRA). Thus, MedDRA PTs will appear in only 1 SOC. Unless otherwise specified, the planned summaries for AEs will be provided for the treatment period. A listing of AEs that occur more than 30 days after study treatment discontinuation will also be provided.

Table 4.2. Summary Tables Related to Adverse Events

Analysis	Details
AE overview	Number and percentages of patients who experienced death, an SAE, any TEAE, and permanent discontinuation from study treatment due to an AE. Statistical comparisons will be included.
TEAEs by PT within SOC	Number and percentages of patients with TEAEs using MedDRA PT nested within SOC. SOCs will be ordered alphabetically, and events within each SOC will be ordered by decreasing frequency. Statistical comparisons will be applied at both the SOC and PT levels.
Maximum severity TEAEs by PT	The number and percentages of participants with TEAEs by maximum severity using MedDRA PT. For each participant and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. The maximum severity will be determined based on the non-missing severities. If all severities are missing for the defined postbaseline period of interest, it will show as missing in the table. Events will be ordered by decreasing frequency.
Common TEAEs by PT	Number and percentages of patients with TEAEs using MedDRA PT for the common TEAEs. Common TEAEs are defined as TEAEs that occurred in ≥2% (before rounding) of participants in any treatment group including placebo. Events will be ordered by decreasing frequency.
SAEs by PT within SOC	Number and percentage of patients who experienced a SAE (including death and SAEs temporally associated or preceding deaths) using MedDRA PT nested within SOC. SOCs will be ordered alphabetically, and events within each SOC will be ordered by decreasing frequency. Statistical comparisons will be applied at both the SOC and PT levels.
SAEs listing	A listing of SAEs. SAEs resulting in death will be identified through a flag in the listing.
Treatment discontinuations due to AE by PT within SOC	Number and percentage of patients who permanently discontinued from study treatment due to an adverse event (including Aes that led to death) using MedDRA PT nested within SOC. SOCs will be ordered alphabetically, and events within each SOC will be ordered by decreasing frequency. Statistical comparisons will be applied at both the SOC and PT levels.
Treatment and study discontinuations listing	A listing of treatment discontinuations and study discontinuations.

Abbreviations: AE = adverse event; LLT = Lowest Level Term;
MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event;
SOC = System Organ Class; TEAE = treatment-emergent adverse event.

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4.10.2.2. Serious Adverse Events

According to 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 the MedDRA PT nested within the SOC. An individual listing of all SAEs will be provided.

4.10.2.3. Adverse Events of Special Interest (AESI)

AESI are considered an intervention-specific topic and will be described in the respective ISA SAPs/appendices.

4.10.3. Clinical Laboratory Evaluations

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

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

- ***Box plots for observed values***

Values at each visit (starting at randomization) and change from baseline to each visit and to last postbaseline measure will be displayed in box plots for patients who have a baseline and at least 1 postbaseline visit. For visits included in the treatment period, patients will be included only if the visit occurs on or before the date of treatment discontinuation or completion. The follow-up visit will be the first visit that occurred during the follow-up period. Individual measurements outside of the reference limits will also be displayed using distinct symbols overlaying the box plot. Original-scale data will be used for the display but for some analytes (for example, immunoglobulins) a logarithmic scale will be used to aid in viewing measures of central tendency and dispersion. Unplanned measurements will be excluded. Descriptive summary statistics will be included in a table below the box plot. These box plots will be used to evaluate trends over time and to assess the potential impact of outliers on central tendency summaries. No inferential statistics will be provided.

- ***Treatment-emergent high/low analyses***

The number and percentage of patients with treatment-emergent high and low laboratory results at any time will be summarized by treatment conditions. Planned and unplanned measurements will be included. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all baseline visits, to a value greater than the high limit at any time

during the treatment period, and up to 60 days after treatment discontinuation. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits, to a value less than the low limit at any time during the treatment period, and up to 60 days after treatment discontinuation. No inferential statistics will be provided.

- ***Listing of abnormal findings***

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

4.10.3.1. Abnormal Hepatic Tests

Analyses for abnormal hepatic tests involve 4 laboratory analytes: alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBL), and serum alkaline phosphatase (ALP). Analyses for the change from baseline to the last visit that occurred on or before the date of treatment discontinuation and shift tables are described in Section 4.10.3. This section describes additional analyses for the topic.

The number and percentage of patients with the following abnormal elevations in hepatic laboratory tests will be summarized by treatment conditions. Fisher's exact test may be used to compare study interventions with placebo. Table 4.3 summarizes the analysis and period of analysis on Safety Analysis Set.

Table 4.3 Summary Tables and Figures Related to Hepatic Safety

Analysis	Analysis Period
Abnormal Postbaseline Categories – Hepatic Safety Parameters • ALT: The number and percentage of participants with a measurement greater than or equal to 1 time (1X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) the performing lab upper limit of normal (ULN) during the treatment period for all participants with a postbaseline value. • AST: The number and percentage of participants with a measurement greater than or equal to 1 time (1X), 3 times (3X), 5 times (5X), 10 times (10X), and 20 times (20X) the performing lab upper limit of normal (ULN) during the treatment period for all participants with a postbaseline value. • ALP: The number and percentage of participants with a measurement greater than or equal to 2 times (2X), and 3 times (3X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline. • TBL: The number and percentage of participants with a measurement greater than or equal to 2 times (2X), 5 times (5X), and 8 times (8X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value. • GGT: The number and percentage of participants with a measurement greater than or equal to 2 times (2X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.	Placebo-controlled treatment period and follow up period
Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs ALT or AST)	Placebo-controlled treatment period
Hepatocellular Drug-Induced Liver Injury Screening Table	Placebo-controlled treatment period
Cholestatic Drug-Induced Liver Injury Screening Plot (TBL vs ALP)	Placebo-controlled treatment period
Cholestatic Drug-Induced Liver Injury Screening Table	Placebo-controlled treatment period

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; TBL = total bilirubin; ULN = upper limit of normal.

Participant profiles will be created for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the IMMA protocol) and are in Safety analysis set.

Participant profiles will include demographics, disposition, information collected on the hepatic safety CRFs (where applicable) and a display of study drug exposure, adverse events, medications, blood pressure, heart rate, and the liver -related measurements over time.

4.10.4. Vital Signs and Other Physical Findings

Vital signs and physical characteristics include systolic blood pressure, diastolic blood pressure, pulse, weight, body mass index, and body temperature. Original-scale data will be analyzed. The planned analyses described for the laboratory analytes in Section 4.10.3 will be used to analyze the vital signs and physical characteristics. Unless otherwise specified, the planned summaries of AEs will be provided for the treatment period. The criteria for identifying subjects with treatment-emergent abnormalities are based on Table 4.4.

Table 4.4. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg)	≤90 (low limit) and decrease from lowest value during baseline ≥20 if >90 at each baseline visit	≥140 (high limit) and increase from highest value during baseline ≥20 if <140 at each baseline visit
Diastolic BP (mm Hg)	≤50 (low limit) and decrease from lowest value during baseline ≥10 if >50 at each baseline visit	≥90 (high limit) and increase from highest value during baseline ≥10 if <90 at each baseline visit
Pulse (beats per minute)	<50 (low limit) and decrease from lowest value during baseline ≥15 if ≥50 at each baseline visit	>100 (high limit) and increase from highest value during baseline ≥15 if ≤100 at each baseline visit
Weight (kg)	(Loss) decrease ≥7% from lowest value during baseline	(Gain) increase ≥7% from highest value during baseline
Temperature (°F)	<96 (low limit) and decrease from lowest value during baseline ≥2 if ≥96 at each baseline visit	≥101 (high limit) and increase from highest value during baseline ≥2 if <101 at each baseline visit

Abbreviations: BP = blood pressure.

4.10.5. Depression and Suicide

During the study, suicidal ideation and behavior, and depression will be assessed prospectively by the investigator via signs and symptoms and using QIDS-SR16 and the C-SSRS.

4.10.5.1. Symptoms of Depression 16-Item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16)

The QIDS-SR16 (Rush et al. 2003) is a 16-item, self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (APA 1994). Patients are asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a unique 4-point ordinal scale for each item, with scores ranging from 0 to 3 reflecting increasing depressive symptoms as the item score increases. The QIDS-SR16 total score is derived as the sum of the scores across the 9 scale domains. For scale domains that contain more than 1 item, the domain score is the highest item rating given across the items within that domain:

- Sleep: the highest score on any 1 of the 4 sleep items (Items 1 to 4)
- Depressed mood: Item 5

- Weight/appetite change: the highest score on any 1 of the 4 weight items (Items 6 to 9)
- Concentration: Item 10
- Worthlessness/Guilt: Item 11
- Suicidal ideation: Item 12
- Decreased interest: Item 13
- Decreased energy: Item 14
- Psychomotor changes: the highest score on either of the 2 psychomotor items (Items 15 and 16)

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

The QIDS-SR16 total scores will also be categorized in the severity classes shown in Table 4.5.

Table 4.5. Severity of Depressive Symptoms Categories Based on the QIDS-SR16 Total Score

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

Abbreviations: QIDS-SR16 = Quick Inventory of Depressive Symptomatology Self Report.

Treatment differences in mean change in the QIDS-SR16 total score will be analyzed using the linear regression method described in Section 4.2. Only visits that occur on or before the date the participant discontinued treatment will be included in the analysis.

Using the QIDS-SR16 Severity of Depressive Symptoms categories shown in Table 4.5, shift tables will be used to show the number and percentage of participants in each category based on the QIDS-SR16 Total Score at every postbaseline visit in contingent to the baseline. Further summarization of change from baseline in severity using categories of any improvement, no change, and any worsening, by treatment conditions may also be tabulated.

The number and percentage of participants with treatment-emergent changes in QIDS-SR16 total score severity categories at any time during the treatment period, based on any increase to mild and above, moderate or above, severe or above, very severe, will also be summarized.

4.10.5.2. Columbia Suicide Severity Rating Scale (C-SSRS)

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

4.11. Other Analyses

4.11.1. Concomitant Therapy

Previous and concomitant medications including corticosteroids, anti-malarials and immunosuppressants will be summarized for each ISA and will be presented by Anatomical Therapeutic Chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Details can be found in Master Protocol IMMA Section 6.5 and each ISA-SAP.

To allow for assessments of changes in doses of various corticosteroids, all corticosteroid doses will be standardized to an equivalent prednisone dose. Table 4.6 provides a summary of frequent corticosteroids and their prednisone-equivalent dose. The dose of the drug listed in Column 1 of Table 4.6 is multiplied by the conversion factor in Column 2 to provide the prednisone equivalent dose (in milligrams). This dose of corticosteroid will be referred to as "prednisone (or equivalent)" throughout this document. See Appendix 1 for a complete table showing conversion factors for each corticosteroid medication identified during the study, instructions for selecting corticosteroids, and the manual review process.

A daily dose of corticosteroid will be derived using the prednisone-equivalent dose for each study day from baseline to the treatment discontinuation day for patients who discontinue treatment early, or to the day before for treatment completers. For immunosuppressant and antimalarial medications, a daily dose will be calculated for each medication by preferred name.

Table 4.6. Conversion Factors for Calculating Prednisone (or Equivalent) Doses

Column 1	Column 2
Corticosteroid Preferred Term	**Conversion Factor for Converting to an Equivalent Prednisone Dose**
Prednisone	1
Prednisolone	1
Methylprednisolone	1.25
Triamcinolone	1.25
Cortisone	0.2
Hydrocortisone	0.25
Betamethasone	6.25
Dexamethasone	6.25
Paramethasone	2.5
Deflazacort	0.83

4.11.2. Treatment Compliance

Treatment compliance with the investigational product will be summarized by treatment for each ISA. Intervention-specific analyses are described in the respective ISAs.

4.11.3. Pharmacokinetics/Pharmacodynamics

Intervention-specific pharmacokinetic (PK)/pharmacodynamic (PD) analyses are described in the respective ISAs, in a separate PK/PD analysis plan, or in both.

4.11.4. Immunogenicity

When applicable, the frequency and percentage will be tabulated for each ISA for

- participants with preexisting antidrug antibodies (ADA), and
- participants with TE-ADA to the active study intervention.

A subject is evaluable if there is at least one non-missing test result for ADA for both the baseline period and the postbaseline period. All percentages are relative to the total number of ADA evaluable subjects. A TE-ADA evaluable subject is considered to be TE-ADA positive (TE-ADA+) if the subject has at least one postbaseline titer that is 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or is a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE-ADA+ participants, the distribution of maximum titers will be described. If assessed, the frequency of neutralizing antibodies may also be tabulated in TE-ADA+ participants.

The relationship between the presence of antibodies and study intervention concentrations, and the PK parameters and PD response including safety and efficacy, may also be assessed. Additional details may be provided in the respective ISAs and ISA-SAPs.

4.11.5. Patient-Reported Outcomes

Intervention-specific analyses of patient-reported outcomes, if applicable, are described in the respective ISAs.

4.11.6. Subgroup analyses

Intervention-specific subgroup analyses are described in the respective ISAs.

4.12. CCI

4.13. Assessment Committee (AC) or Other Review Board

Eligibility Review Committee

An eligibility review committee, also called adjudication panel, will review study entry data to ensure that prospective study participants meet the study entry criteria, particularly SLE disease activity criteria, prior to random assignment. In addition, the committee will help ensure that high quality data are entered into the EDC system for lupus assessments. The committee may include members of a third-party organization, members of the study team, and external SLE consultants as needed. Membership, responsibilities, operations, and measures to maintain confidentiality will be described in a committee charter.

Assessment Committee (AC)

In addition to safety reviews routinely performed by the sponsor as described in Master Protocol IMMA Section 8.2, the AC will review the safety data in an unblinded fashion periodically, or on an ad hoc basis during the study, and will determine whether any changes (for example, dose reductions or other protocol modifications) should be made. If an efficacy interim analysis is specified in an ISA, the AC will also be responsible for review of the available efficacy data. The AC reviewing the interim data will include, at a minimum, a Lilly medical physician, a statistician, and a representative from the Lilly Global Patient Safety Organization, and may include Lilly study team members. Details about the AC membership, purpose, responsibilities, and operation will be described in an AC charter, which will be approved prior to the first unblinding. Investigator sites will receive information about interim analysis results only if they need to know for the safety of their study participants.

4.14. Changes to Protocol-Planned Analyses

There were no changes from the protocol specified statistical analysis.

5. References

[APA] *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. American Psychiatric Association; 1994.

[EMA] European Medicines Agency. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9). Published 5 February 1998. Accessed July 07, 2023.

[EMA] European Medicines Agency. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3). Published 30 November 1995. Accessed July 07, 2023.

[FDA] United States Food and Drug Administration. Adjusting for covariates in randomized clinical trials for drus and biological products: guidance for industry. May 2023. Accessed July 17, 2023. https://www.fda.gov/media/148910/download

Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573-583. https://doi.org/10.1016/s0006-3223(02)01866-8

The Columbia Lighthouse Project. Columbia-Suicide Severity Rating Scale (C-SSRS). Columbia University; 2007.

Appendix 1. Corticosteroid

All corticosteroid doses need to be converted to prednisone equivalent doses (as detailed in Section 4.11.1). If additional conversion factors are required, these will be added to Table S1 in a SAP 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 per os daily is equivalent to 20 mg of prednisone po daily.*

Table S1. Complete Conversion Factors for Calculating Prednisone (or Equivalent) Doses

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

Column 1	Column 2
Corticosteroid Preferred Term	**Conversion factor for converting to an equivalent prednisone dose**
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

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