Master Protocol J1V-MC-IMMA(a)

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: 22-Sep-2021

Title Page

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 Protocol Amendment Number: A

Compound: Multi-molecule code LY900024

Study Phase: 2

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

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 155806

List of Intervention-Specific Appendices (ISAs):

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

Approval Date: Protocol Amendment Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 22-Sep-2021 GMT

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*21 Jun 2021*

Amendment A

This amendment occurred before any study participant was consented or dosed at any study site, and before the protocol was submitted to any European Union member state.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to address regulatory comments regarding discontinuation of participants from study intervention, study stopping rules, and use of EULAR/ACR 2019 classification criteria for SLE.

Section # and Name	Description of Change	Brief Rationale
1.2. Schema	Revised schema, removing a redundant phrase "optional prescreening"	To clarify distinction between required screening and optional prescreening
1.3. Schedule of Activities	Revised comment for chest x-ray row, adding text about pericardial and pleural effusion evaluation	To implement EULAR/ACR 2019 classification criteria, per regulatory request
1.3. Schedule of Activities	Deleted "ACR Revised 1997 Criteria" and added "EULAR/ACR 2019 Criteria" under Clinician-administered assessments (electronic) row	Regulatory request
1.3. Schedule of Activities	Added reticulocytes to "Hematology" row	To implement EULAR/ACR 2019 classification criteria, per regulatory request
1.3. Schedule of Activities	Added a row called "Antiphospholipid antibody panel" with assessment at Visit 1	To implement EULAR/ACR 2019 classification criteria, per regulatory request
4.2. Scientific Rationale for Study Design	Removed the phrase about ACR Revised 1997 Criteria and added "based on documentation of meeting EULAR/ACR 2019 classification criteria for SLE (Aringer et al. 2019)." Stated that SLEDAI-2K clinical features score ≥4 is at screening rather than randomization	Regulatory request, and internal document consistency
5.1. Inclusion Criteria, Criterion #4	Removed phrase about "ACR Revised 1997 Criteria" and added having "a total score of 10 or more points on EULAR/ACR 2019 classification criteria for SLE (Aringer et al. 2019)"	Regulatory request
5.1. Inclusion Criteria, Criterion #6	Specified that "clinical SLEDAI-2K score ≥4 (not including any items related to laboratory values)" must be met at screening (Visit 1) instead of at Visit 2	To facilitate introduction of future ISAs by separating BT01 Visit 2 requirement from IMMA inclusion criterion

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria, Criterion #22	Changed "Have participated" to "Have been dosed"	For consistency with Criterion #46
5.4.1. Allowed Retesting of Screening Investigations	In bulleted list, revised to make the listed lab tests into a nonexhaustive set of examples	To improve flexibility
7.1. Discontinuation of Study Intervention	Changed values for abnormal hematology laboratory tests (hemoglobin, WBC, ANC, and ALC)	Regulatory request
7.1. Discontinuation of Study Intervention	Removed "Clinically significant ECG finding" from bulleted list and added "ECG finding" to paragraph about AEs, SAEs, and laboratory values that are criteria for permanent discontinuation of study intervention. Deleted "clinically significant" from same paragraph.	Regulatory request
7.1. Discontinuation of Study Intervention	Deleted "related to study drug administration" from paragraph about systemic hypersensitivity reaction	Regulatory request
7.1. Discontinuation of Study Intervention	Added "Serious and opportunistic infections, as defined in Section 5.2" to reasons for permanent discontinuation of study intervention. It was previously a reason for temporary discontinuation.	Regulatory request
7.1. Discontinuation of Study Intervention	Added "Participant with intolerable or exacerbating disease" to reasons for permanent discontinuation	Regulatory request
7.1.1. Temporary Discontinuation (Withholding) of Study Intervention	Deleted "Serious or opportunistic infections, as defined in Section 5.2" from reasons for temporary discontinuation of study intervention. It is now a reason for permanent discontinuation.	Regulatory request
8.2.4. Chest Radiography	Added text to the "Note" indicating that chest x-ray is used for pericardial and pleural effusion evaluation, as well as for TB evaluation	To implement EULAR/ACR 2019 classification criteria, per regulatory request
10.2.1. Clinical Laboratory Tests Performed at Visit 1	In "Hematology," added reticulocytes to cell morphology	To implement EULAR/ACR 2019 classification criteria, per regulatory request
10.2.1. Clinical Laboratory Tests Performed at Visit 1	In "Clinical Chemistry," added indirect bilirubin, haptoglobin, and lactate dehydrogenase (LDH)	To implement EULAR/ACR 2019 classification criteria, per regulatory request
10.2.1. Clinical Laboratory Tests Performed at Visit 1	In "Serology," added antiphospholipid antibody panel	To implement EULAR/ACR 2019 classification criteria, per regulatory request
10.4.1. Definitions	Deleted "tubal ligation" from examples of conditions defining woman not of childbearing potential	For consistency with stated pregnancy testing requirements

Section # and Name	Description of Change	Brief Rationale
10.10. Appendix 10: Abbreviations and Definitions	Added EULAR definition	Editorial changes based on changes in other sections
11. References	Added Aringer et al. 2019 Deleted Hochberg 1997 and Tan et al. 1982	Editorial changes based on changes in other sections

Table of Contents

1. Protocol Summary

1.1. Synopsis

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

Rationale: Study J1V-MC-IMMA (IMMA) is designed as a platform trial to investigate the efficacy and safety of multiple investigational interventions for SLE simultaneously and/or sequentially as hypotheses emerge. This platform trial employs an overarching infrastructure to harness the benefits of shared data and to enable operational efficiencies in a patient population that is difficult to recruit and has high unmet medical need. This master protocol (IMMA) together with its ISAs describes the specific clinical investigations to be conducted in this platform trial.

Objectives and Endpoints: The clinical research objectives and endpoints for this trial were selected to evaluate the efficacy of each intervention relative to placebo for global SLE disease activity, organ-specific disease activity, and, if applicable, patient-reported outcomes. These objectives and endpoints are evaluated using validated clinical instruments and assessments, such as SLEDAI-2K, CLASI, BILAG 2004, and tender and swollen joint counts. The specific objectives and endpoints for each intervention are detailed in each ISA.

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 and/or sequentially.

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/risk, dose justification; intervention-specific research objectives, endpoints, and estimands; intervention-specific study entry and discontinuation criteria; and intervention-specific outcomes measurements and statistical analysis methods. Each ISA includes an SoA applicable from the time of a participant's randomization through the time of the participant's last planned study visit.

Disclosure Statement: This is a treatment platform protocol for the study of multiple interventions (multiple arms) and blinding of participants and investigators.

Number of Participants: Participant numbers are specified in the individual ISAs.

Intervention Groups and Duration: Intervention groups and durations are specified in the ISAs. This platform trial has one ISA (ISA 1: J1V-MC-BT01) at its inception. The enrollment

period for this ISA is estimated to be approximately 12 months. Adding the planned treatment and follow-up periods to the enrollment period results in a total ISA duration of approximately 22 months.

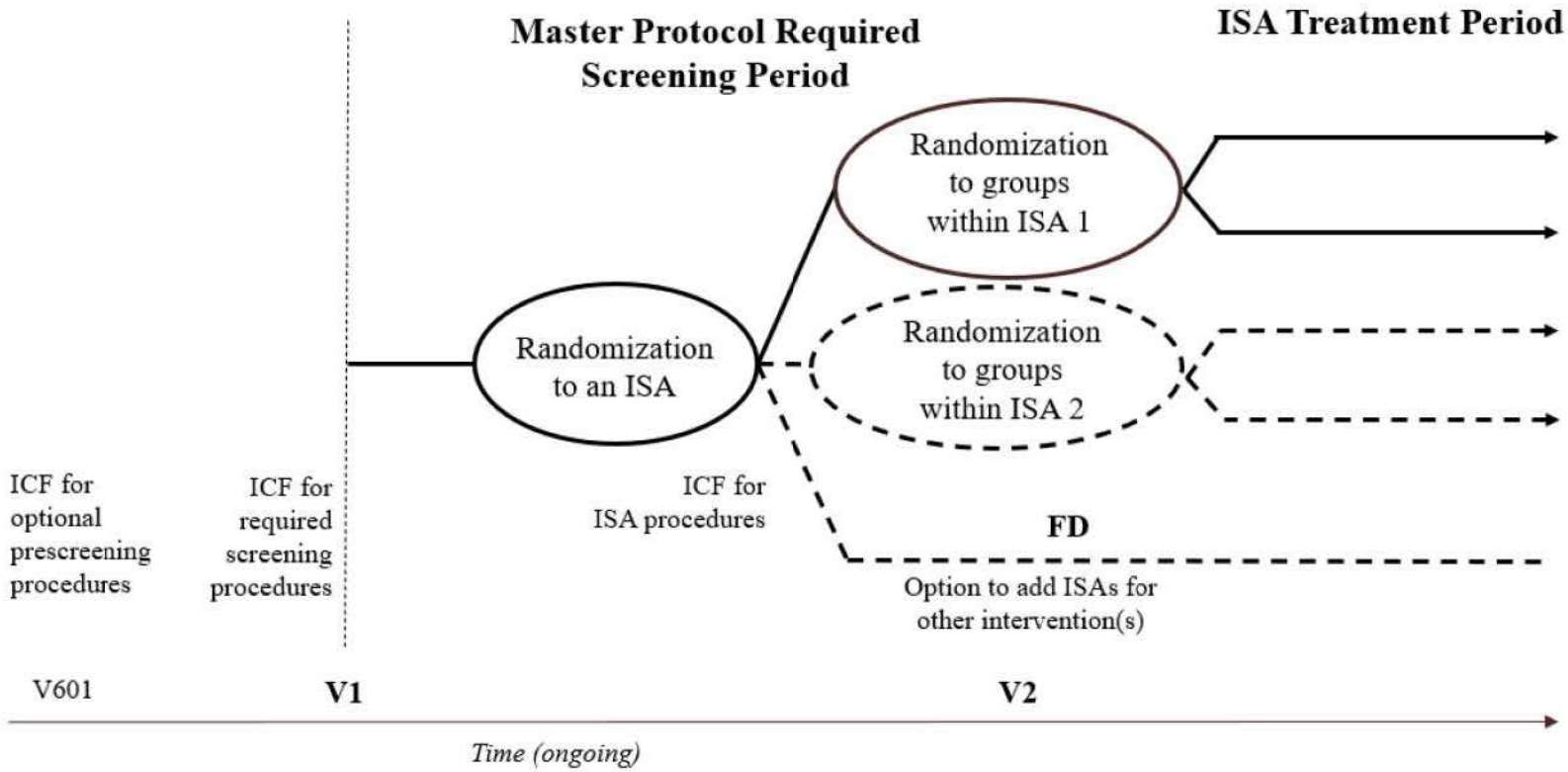
This platform trial is designed to enable interventions to be added to the platform over time through the introduction of new ISAs. CCI [redacted]

Data Monitoring Committee: Yes (Internal Assessment Committee)

1.2. Schema

Figure 1 illustrates the general schema for this master protocol.

Schemas for interventions studied under this master protocol are provided in the ISAs.



Note: 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.

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

Figure 1. Schema of the J1V-MC-IMMA master protocol for a randomized, placebo-controlled clinical trial of multiple interventions for the treatment of systemic lupus erythematosus.

1.3. Schedule of Activities (SoA)

This SoA describes screening activities applicable to all interventions studied under this master protocol.

For activities conducted at randomization and postrandomization visits, see the relevant ISA.

Prescreening and Screening Periods of Master Protocol J1V-MC-IMMA Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.			
	Prescreening (optional)	Screening (required)	Comment
Visit number	V601	V1	
Weeks before randomization at Visit 2	—	≤5	
Study day	—	—	
Visit interval tolerance (days)	—	≤35 to –3 days before Visit 2	
Fasting visit			No fasting in this period
Option for remote visit	X		The specified visit may be conducted remotely (that is, by mobile health care and/or telemedicine) if written approval is provided by the sponsor and according to the preferences of the participant and the study site.
Prescreening informed consent form (ICF)	X		Central prescreening of ANA, anti-dsDNA, and/or anti-Sm is permitted after signing the prescreening ICF and can be performed before the participant signs the main ICF. See Section 4.1.
ICF(s) for IMMA protocol		X	The ICF(s) must be signed before any protocol-specific test/procedures are performed.
Inclusion and exclusion criteria, review and confirm		X	
Demographics		X	
Preexisting conditions and medical history, including relevant surgical history		X	
Prespecified medical history (indication and history of interest)		X	
Prior treatments for indication		X	Includes all SLE-specific therapies since date of diagnosis, such as immunosuppressive agents and antimalarials.
Substance use (alcohol, caffeine, tobacco use)		X	

Prescreening and Screening Periods of Master Protocol J1V-MC-IMMA Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.			
	Prescreening (optional)	Screening (required)	Comment
Visit number	V601	V1	
Weeks before randomization at Visit 2	—	≤5	
Study day	—	—	
Visit interval tolerance (days)	—	≤35 to –3 days before Visit 2	
Fasting visit			No fasting in this period
Option for remote visit	X		The specified visit may be conducted remotely (that is, by mobile health care and/or telemedicine) if written approval is provided by the sponsor and according to the preferences of the participant and the study site.
Concomitant medications		X	
Adverse events (AEs)		X	See Section 8.3.1 for timing of AE collection relative to signing of ICF.
Physical evaluation			
Height		X	Participant should remove shoes.
Weight		X	
Vital signs		X	Includes pulse rate, blood pressure, respiratory rate, and body temperature. Measured after participant has been sitting at least 5 minutes. See Section 8.2.1.
Physical examination		X	The complete physical examination will exclude pelvic, rectal, and breast examinations, unless clinically indicated. The SLE symptom physical assessment is captured in the electronic tablet. See Section 8.2.2. Assess for tuberculosis (TB) risk factors, and for signs and symptoms of active TB, including check of peripheral lymph nodes; see Section 8.2.6.
12-lead ECG (local)		X	See Section 8.2.3.
Chest x-ray (posterior-anterior view) (local)		X	Interpreted and reported by a radiologist or pulmonologist. Chest x-ray is not required if one was performed within 6 months prior to Visit 1 and if sufficient documentation exists for the TB evaluation and for pericardial and pleural effusion evaluation per EULAR/ACR 2019 criteria. See Sections 8.2.4 and 8.2.6.

Prescreening and Screening Periods of Master Protocol J1V-MC-IMMA Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.			
	Prescreening (optional)	Screening (required)	Comment
Visit number	V601	V1	
Weeks before randomization at Visit 2	—	≤5	
Study day	—	—	
Visit interval tolerance (days)	—	≤35 to –3 days before Visit 2	
Fasting visit			No fasting in this period
Option for remote visit	X		The specified visit may be conducted remotely (that is, by mobile health care and/or telemedicine) if written approval is provided by the sponsor and according to the preferences of the participant and the study site.
Patient-reported outcomes (electronic)			
QIDS-SR16		X	Administer before any clinical assessments. See Sections 8 and 8.2.10.
Clinician-administered assessments (electronic)			
EULAR/ACR 2019 Criteria		X	Collected via an electronic tablet device.
BILAG 2004 (Historical)		X	Collected via an electronic tablet device.
BILAG 2004 (Index)		X	Collected via an electronic tablet device.
SLEDAI-2K		X	Collected via an electronic tablet device.
28 tender and swollen joint counts		X	Collected via an electronic tablet device.
Clinician-administered assessments (paper)			
C-SSRS Screening/Baseline		X	Adapted for the assessment of ideation and behavior categories only.
Laboratory tests and sample collections			
Hematology, with reticulocytes		X	
Clinical chemistry		X	
Urinalysis		X	
Serum pregnancy		X	Only for women of childbearing potential (WOCBP) and females with a history of tubal ligation. See Section 8.2.5.1, Appendix 10.2, and Appendix 10.4.

Prescreening and Screening Periods of Master Protocol J1V-MC-IMMA Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.			
	Prescreening (optional)	Screening (required)	Comment
Visit number	V601	V1	
Weeks before randomization at Visit 2	—	≤5	
Study day	—	—	
Visit interval tolerance (days)	—	≤35 to –3 days before Visit 2	
Fasting visit			No fasting in this period
Option for remote visit	X		The specified visit may be conducted remotely (that is, by mobile health care and/or telemedicine) if written approval is provided by the sponsor and according to the preferences of the participant and the study site.
Follicle-stimulating hormone (FSH)		X	Optional; performed as needed to confirm postmenopausal status. See Section 8.2.5.1, Appendix 10.2, and Appendix 10.4.
Thyroid-stimulating hormone (TSH)		X	
Tuberculosis (TB) test		X	Lilly-designated laboratory preferred; may be completed locally; see Appendix 10.2. Participants who had a tuberculin skin test (TST) will return from 48 to 72 hours after placement to have their test results read. Purified protein derivative (PPD) does not need to be read at the site but must be read by a trained medical professional and results must be presented to the site prior to randomization.
HIV screening tests		X	
Hepatitis C virus (HCV) screening tests		X	See Section 8.2.8.
Hepatitis B virus (HBV) screening tests		X	See Section 8.2.7.
HBV DNA		X	Performed only for participants who test positive for anti-HBc at screening. See Section 8.2.7.
Urinary protein/creatinine ratio (UPCR)		X	
Urinary albumin/creatinine ratio (UACR)		X	
Estimated glomerular filtration rate (eGFR)		X	Calculated using Modification of Diet in Renal Disease (MDRD) method.
CCI			

Prescreening and Screening Periods of Master Protocol J1V-MC-IMMA Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.			
	Prescreening (optional)	Screening (required)	Comment
Visit number	V601	V1	
Weeks before randomization at Visit 2	—	≤5	
Study day	—	—	
Visit interval tolerance (days)	—	≤35 to –3 days before Visit 2	
Fasting visit			No fasting in this period
Option for remote visit	X		The specified visit may be conducted remotely (that is, by mobile health care and/or telemedicine) if written approval is provided by the sponsor and according to the preferences of the participant and the study site.
CCI			
Visit registration			
Register the visit in IWRS		X	

Abbreviations: ACR = American College of Rheumatology; CCI ; CCI ; anti-HBc = antibody to hepatitis B core antigen; anti-Sm = anti-Smith antibodies; BILAG 2004 = British Isles Lupus Assessment Group 2004; C-SSRS = Columbia – Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EULAR = European League Against Rheumatism; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IWRS = interactive web-response system; QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology – Self Report; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; V = visit.

2. Introduction

Systemic lupus erythematosus is a chronic, debilitating, autoimmune disease characterized by the presence of autoreactive B cells and elevated levels of autoantibodies. The disease can affect multiple cell types, organ systems, and follows an unpredictable clinical course. Patients may present with arthralgia, arthritis, skin rash, alopecia, oral ulcers, pleuritis, pericarditis, nephritis, vasculitis, stroke, seizure, leukopenia, thrombocytopenia, anemia, photosensitivity, and the presence of autoantibodies directed to nuclear antigens. The disease predominately affects adult females, and people of Black ethnicity have a higher incidence and prevalence globally than other ethnic groups (Rees et al. 2017).

The standard-of-care for SLE varies widely and currently includes the use of corticosteroids, NSAIDs, antimalarial medication, cytotoxic agents, and immunosuppressants. Unfortunately, the morbidity of the disease remains substantial, as measured by various tools for evaluating health-related quality of life, loss of work productivity, pain, and fatigue (Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue 2007; Özel and Argon 2015). More than 60% of patients with SLE will develop clinically detectable organ damage about 4 years after the diagnosis, as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (Cooper et al. 2007). A meta-analysis involving more than 27,000 patients showed that SLE patients had a 3-fold increase in risk of death compared with the general population (Yurkovich et al. 2014).

2.1. Study Rationale

Patients with SLE need improved treatment options with acceptable safety profiles. The new treatment options should reduce disease activity and flares, delay organ damage, lessen the use of corticosteroids and cytotoxic agents, and improve overall morbidity and mortality.

In recent decades, multiple new therapeutic interventions have progressed into Phase 3 trials for SLE, but with limited success. Only 1, belimumab, has received regulatory approvals for marketing worldwide. The costly failures of large late-phase clinical development programs and missed opportunities to bring new interventions into proof-of-concept clinical trials have prompted reflection on the problems inherent in the design and conduct of SLE studies. Among the problems identified by Merrill et al. (2018) are

- large and unwieldy designs
- lack of study sites
- difficulty recruiting patients
- lack of reliability in study endpoints
- heterogeneity in the disease itself, and
- inconsistencies in clinical practice for SLE treatment.

Proposed solutions include more frequent use of smaller and shorter pilot trials, investment in training sites and improving patient access to clinical trials globally, as well as adaptive approaches for demonstrating efficacy and safety.

Such solutions lend themselves to an approach called a master protocol. As described by Woodcock and LaVange (2017), a platform study uses a master protocol to establish an overarching governance structure, a screened patient population, and randomization plans to test a shared hypothesis across multiple investigational interventions. A platform study can have treatment arms that begin independently of one another as new interventions become ready for testing. Individual interventions may be ended independently, either when a particular intervention has concluded or as interim analyses show that a particular intervention's criteria for futility or success have been met. Studies employing master protocols have been utilized in diseases for which significant drug development challenges exist, including oncology (I-SPY-2 [Barker et al. 2009]; Lung-MAP [Herbst et al. 2015]; AGILE [Alexander et al. 2018]) and Alzheimer's disease (EPAD [Ritchie et al. 2016]; DIAN-TU [Bateman et al. 2017]).

This platform trial for the clinical investigation of SLE treatments employs a master protocol with uniform screening activities and study entry criteria, and with ISAs, for the goal of accomplishing the following efficiencies:

- Establish a network of trained clinical investigative sites that will benefit from streamlined and coordinated trial logistics and consistency in data collection methods;
- Improve data quality through consistency in the training of raters and through increases in rater experience via continuous conduct of the same assessments over time;
- Use of a shared placebo control group, thereby reducing the overall number of study participants who receive placebo; and
- Enable continuous, efficient, and flexible development of promising interventions for SLE while maintaining appropriate scientific rigor and oversight by ethics committees and regulatory authorities.

Rationales for investigation of particular interventions are provided in the associated ISAs.

2.2. Background: Intervention Selection and Governance of the Platform Trial

2.2.1. Intervention Selection (Adding, Stopping Treatment Arms)

This master protocol is designed to permit the evaluation of multiple investigational interventions for SLE.

Testing of some interventions may be stopped early based on medical, safety, regulatory, futility, lack of benefit/efficacy, or other reasons consistent with applicable laws, regulations, and GCP. End-of-study definitions are provided in Section 4.4.

Testing of new interventions may be added to this master protocol. Minimum criteria to determine inclusion of new ISAs or testing of new interventions include:

- adequate safety, tolerability, and PK properties supportive of an intervention's entry into development for an SLE indication (see Section 2.2.2), and
- regulatory and ERB or IRB approval to add the new ISAs and new interventions to the platform trial.

If new interventions are selected to be added, this master protocol will be amended, and sites will be informed as necessary.

2.2.2. Governance

Eli Lilly and Company will be responsible for the selection of interventions to be added to, or removed from, clinical development on this platform trial. Lilly or a designee will provide the interventions to the study sites.

An IAC will be established for the purpose of making periodic prespecified or ad hoc assessments of safety data in an unblinded fashion and to make recommendations for protocol modifications or other actions. This internal committee will be independent of the Lilly study team.

In addition, an internal or external (independent) CEC may be established, if so specified in an ISA, for the purpose of adjudicating defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study.

These and other governance considerations are further described in Appendix 10.1, Section 10.1.5.

2.3. Benefit/Risk Assessment

Intervention-specific benefit/risk information is provided in the relevant ISA.

In addition, information about the known and expected benefits and risks and reasonably expected AEs of the intervention may be found in the IB for each intervention.

3. Objectives, Endpoints, and Estimands

The purpose of this master protocol is to create a framework to evaluate the efficacy and safety of various investigational interventions for SLE as hypotheses emerge. The clinical research objectives and endpoints 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 AEs.

4. Study Design

4.1. 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 and/or sequentially. Figure 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/risk, dose justification; intervention-specific research objectives, endpoints, and estimands; intervention-specific study entry and discontinuation criteria; and intervention-specific outcomes measurements and statistical analysis methods. Each ISA includes an SoA applicable from the time of a participant's randomization through the time of the participant's last planned study visit.

Informed consent process

To participate in this trial, a participant must provide informed consent for the procedures described both in this master protocol and in the relevant ISA. This could mean signing more than one ICF, as illustrated in Figure 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.

The content of these ICFs might be combined into a single ICF, depending on operational considerations, such as having only one active ISA when the participant enters Study IMMA.

The ICF(s) must meet the regulatory and ethical requirements stated in Appendix 10.1 of this master protocol.

Optional prescreening

CCI [redacted]

CCI [redacted]

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 randomization to an ISA.

Study entry criteria

Participants found to be eligible according to all study entry criteria (Sections 5.1 and 5.2) 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, those 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 this master protocol, 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 Section 7).

4.2. Scientific Rationale for Study Design

The following are rationales for key elements of this master protocol design. Rationales for endpoints, trial duration, and other key elements of the study design are provided in the ISAs.

Appropriateness of study population

Adult patients with at least moderately active SLE are an appropriate study population for a novel investigational product with immunomodulating properties. The study entry criteria will enable enrollment of participants who are representative of the general population of patients with at least moderately active SLE, based on documentation of meeting EULAR/ACR 2019 classification criteria for SLE (Aringer et al. 2019), with positivity for auto-antibodies (ANA, anti-dsDNA, or anti-Sm) at screening, a SLEDAI-2K score ≥6 at screening, and a SLEDAI-2K clinical features score ≥4 at screening.

Use of placebo control

A double-blind, placebo-controlled design limits bias for both investigator assessments and patient-reported outcomes and enables a clearer interpretation of the effects of an active intervention. The use of placebo instead of an active comparator is warranted because there are few approved therapies for SLE and because participants will be allowed to receive concomitant standard-of-care therapies.

Optional prescreening

Optional prescreening was included in the study design to reduce the number of screen failures. In previous studies of SLE, the absence of autoantibodies, as assessed by the central laboratory during the screening period, has been a major reason for screening failures.

Race and ethnicity

In this study, collection of demographic information includes ethnicity (in the United States only) and race. The scientific rationale is based on the need to assess response in safety and/or efficacy based on race or ethnicity. Such a need can be addressed only if the relevant data are collected.

Concomitant medications

This master protocol includes an integrated set of rules intended to minimize the confounding effect of concomitant medications while maintaining participant safety; see Section 6.5 of this master protocol and the relevant ISA(s). The program for management of corticosteroid use during the study is supported by data from the tabalumab Phase 3 SLE trials, where fewer than 20% of participants in the placebo groups required an increase in prednisone over the first 24 weeks, and fewer than 10% required an increase in prednisone in the first 8 weeks (Kalunian et al. 2018).

4.2.1. Participant Input into Design

The sponsor involved patients in the design of this study by engaging patients in simulations and other face-to-face or virtual collaborative events for related SLE trials. The insights gained from those events were used to ensure that this study design is supportive of the well-being of the study participants and that the study procedures can be implemented effectively at the investigative sites.

4.3. Justification for Dose

Justifications for doses of investigational interventions are provided in the relevant ISA.

4.4. End of Study Definition

One investigational intervention is included in this platform trial at its inception. Overall, the platform trial is designed to enable the investigation of multiple interventions over a total period of approximately 7 years.

Consistent with local law and regulations, the competent authority and relevant ethics committees in each participating country will be notified about the completion or early termination of each ISA.

The end of the platform trial (IMMA) is the last scheduled procedure shown in the SoA for the last participant globally in the last intervention investigation (last ISA).

End-of-study definitions for investigations of particular interventions are provided in the ISAs.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before receiving a dose of study intervention.

Participant eligibility will be reviewed and confirmed by an eligibility review committee prior to randomization.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

For rescreening and retesting activities within the screening period, see Section 5.4.

5.1. Inclusion Criteria

Patients will be included in the study only if all of the following inclusion criteria are met:

Informed consent

[1] Are capable of giving signed informed consent as described in Appendix 10.1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF(s) and in this master protocol and in the relevant ISA, including compliance with the use of contraceptives.

Note: Contraceptive use should be consistent with local regulations regarding the methods of contraception for persons participating in clinical studies. For contraception requirements, see the relevant ISA.

Participant characteristics

[2] Are male or female patients from 18 to 65 years of age (inclusive) at the time of screening (Visit 1).

SLE-related inclusion criteria

[3] Have received a clinical diagnosis of SLE at least 24 weeks before the screening visit (Visit 1).

[4] Have documentation of having a total score of 10 or more points on EULAR/ACR 2019 classification criteria for SLE (Aringer et al. 2019) before randomization (Visit 2).

[5] Have a positive ANA (titer ≥1:80) and/or a positive anti-dsDNA and/or positive anti-Sm antibody test at screening (Visit 1) as assessed by the central laboratory.

Note: This criterion must be assessed on the samples collected at Visit 1, not the prescreening samples collected at Visit 601. For repeat testing for ANA, anti-dsDNA, and/or anti-Sm during the screening period, see Section 5.4.1.

[6] Have a SLEDAI-2K score ≥6 and clinical SLEDAI-2K score ≥4 (not including any items related to laboratory values) at screening (Visit 1).

[7] Must be receiving at least 1 background standard-of-care medication for SLE (that is, for example, an NSAID, antimalarial, oral immunosuppressant, or systemic corticosteroid medication, as specified in "Allowed Concomitant Therapy for SLE" in Section 6.5).

[8] Additional SLE-related inclusion criteria, if applicable, are defined in the relevant ISA.

5.2. Exclusion Criteria

Patients will be excluded from the study if any one of the following criteria is met:

Corticosteroid use

[9] Are currently receiving oral corticosteroids at doses >20 mg per day of prednisone (or equivalent) or have adjusted the dosage of corticosteroids within 2 weeks before randomization (Visit 2).

[10] Have received topical corticosteroids, other than stable use of Class VI (mild, such as desonide) or Class VII (least potent, such as hydrocortisone), within 8 weeks before randomization (Visit 2).

[11] Have received parenteral corticosteroids within 12 weeks before randomization (Visit 2) or are expected to require parenteral corticosteroids during the study.

Other prior or concomitant therapy

[12] Have started treatment with or adjusted the dosage of an antimalarial (such as hydroxychloroquine, chloroquine, or quinacrine) within 12 weeks before randomization (Visit 2); or have received more than a single antimalarial within 12 weeks before randomization (Visit 2).

[13] Have started treatment with or adjusted the dosage of an immunosuppressant (such as methotrexate, leflunomide, azathioprine, mycophenolate mofetil, or mizoribine) within 12 weeks before randomization (Visit 2); or have received more than a single immunosuppressant within 12 weeks before randomization (Visit 2).

[14] Have received an oral calcineurin inhibitor, such as cyclosporine, tacrolimus, sirolimus, or voclosporin, within 4 weeks before randomization (Visit 2).

[15] Have received an oral JAK inhibitor, including but not limited to baricitinib, tofacitinib, and upadacitinib, within 4 weeks before randomization (Visit 2).

[16] Have received cyclophosphamide (or any other cytotoxic agent) within 12 weeks before randomization (Visit 2).

[17] Have received biologic therapies in the specified number of weeks before screening:

[17a] rituximab, ocrelizumab (or other B cell-depleting agent), or ustekinumab within 24 weeks before randomization (Visit 2),

[17b] other biologic therapies including, but not limited to, anticytokine or receptor blocker (etanercept, infliximab, certolizumab, adalimumab, golimumab, tocilizumab, anakinra, ixekizumab, secukinumab, belimumab, abatacept, anifrolumab) within 12 weeks before randomization (Visit 2).

[18] Have received intravenous Ig within 24 weeks before randomization (Visit 2).

[19] Have received plasmapheresis within 12 weeks before randomization (Visit 2).

[20] Have received any live vaccine (that is, live attenuated) within less than 4 weeks of screening (Visit 1), or intend to receive a live vaccine during the study, or plan to receive such vaccine within 8 weeks or 5 half-lives (whichever is longer) of completing treatment in this study.

Note: The following are not considered live vaccines: RNA vaccines, vaccines with inactive viral elements, and/or nonreplicating viral vector vaccines.

[21] Have received a BCG vaccination or treatment within less than 4 weeks of screening (Visit 1) or intend to have vaccination with BCG during the course of the study, or plan to receive such vaccination within 8 weeks or 5 half-lives (whichever is longer) of completing treatment in this study.

[22] Have been dosed within the last 30 days in a clinical study involving an investigational product, including any prior ISAs of this master protocol. If the previous investigational product has a long half-life, at least 5 half-lives or 30 days (whichever is longer) should have passed before the randomization visit (Visit 2) of this master protocol.

Current or historical infections

[23] Have a current or recent acute, active infection. For at least 30 days prior to screening (Visit 1) and up to the time of randomization (Visit 2), participants must have no symptoms and/or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.

Note: Participants with an upper respiratory infection or a vaginal/oral candida infection being treated only symptomatically and not requiring systemic anti-infectives may be considered for enrollment if other eligibility criteria are met. Other uncomplicated local infections should be discussed with the sponsor's medical monitor.

[24] Have had any of the following types of infection within 3 months prior to the screening visit (Visit 1) or develops any of these infections before the randomization visit (Visit 2):

- Serious (requiring hospitalization, or intravenous or equivalent oral antibiotic treatment, or both)
- Opportunistic (as defined in Winthrop et al. 2015)

  Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
- Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- Recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis).

  Note: Participants with only recurrent, mild and uncomplicated orolabial herpes, or genital herpes, or both may be considered for enrollment if discussed with the sponsor's designated medical monitor and if other eligibility criteria are met.

[25] Have HIV infection.

[26] Have a current infection with HBV (that is, positive for HBsAg and/or PCR positive for HBV DNA).

[27] Have a current infection with HCV (that is, positive for HCV RNA) (see Section 8.2.8).

[28] Have active TB (see Section 8.2.6).

[29] Have or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and the United States CDC, unless such treatment is underway (see Section 8.2.6).

Other current or historical medical conditions

[30] Have severe active lupus nephritis defined clinically and/or by urine protein/creatinine ratio >300 mg/mmol (as an estimate of approximate proteinuria >3 g/day) or active urinary sediment with red blood cell cast(s), or histological evidence of lupus nephritis (Class III, IV, V, or VI according to the International Society of Nephrology classification criteria) within 12 weeks before randomization (Visit 2).

Note: For laboratory retesting related to lupus nephritis, see Section 5.4.1.

[31] Have active central nervous system lupus as defined by ACR nomenclature for neuropsychiatric lupus syndromes and as captured by SLEDAI-2K (seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, and cerebrovascular accident within 24 weeks before randomization (Visit 2).

[32] Have active fibromyalgia that, in the investigator's opinion, would make it difficult to appropriately assess SLE activity for the purposes of this study.

[33] Have been treated for or had an active occurrence of a systemic inflammatory condition other than SLE, such as, but not limited to, rheumatoid arthritis, juvenile chronic arthritis, spondyloarthropathy, Crohn's disease, ulcerative colitis, psoriasis, or psoriatic arthritis in the 12 weeks before randomization (Visit 2).

Note: Participants with secondary Sjögren's syndrome are not excluded.

[34] Have experienced a thrombotic event within 24 weeks before randomization, or are on anticoagulants and in the opinion of the investigator are not well-controlled regarding management of hypercoagulable risk.

[35] Have experienced any of the following within 12 months before screening: myocardial infarction, unstable ischemic heart disease, stroke, or New York Heart Association Stage IV heart failure.

[36] Have a history of clinically significant or uncontrolled cardiovascular disease (for example, hypertension, angina, congestive heart failure); endocrine disorder (for example, diabetes, thyroid dysfunction); or respiratory, hepatic, renal, gastrointestinal, hematologic, or neuropsychiatric disorder; or any other serious and/or unstable illness that in the opinion of the investigator, could constitute an unacceptable risk to the participant when taking an investigational product or could interfere with the interpretation of study data.

[37] Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

[38] Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **or**

have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS,

and the ideation or behavior occurred within the 4 weeks prior to randomization (Visit 2).

[39] Have a diagnosis or history of malignant disease within 5 years prior to randomization (Visit 2).

Exceptions:

- Participants with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease within 5 years prior to randomization may participate in the study if other study entry are met.
- Participants with basal cell or squamous epithelial carcinomas of the skin that have been completely resected with no evidence of metastatic disease for at least 3 years may participate in the study if other study entry criteria are met.

[40] Have had any major surgery within 12 weeks before randomization (Visit 2) or will require major surgery during the study that, in the opinion of the investigator in consultation with the sponsor's medical monitor or designee, would pose an unacceptable risk to the participant.

[41] Have a known allergy to the investigational intervention or any of its excipients, clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or history of severe posttreatment hypersensitivity reactions, including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis.

Diagnostic assessments or abnormal laboratory values

[42] Have any of the following specific abnormalities on screening laboratory tests (Visit 1):

- ALT or AST >2 times ULN
- TBL ≥1.5 times ULN
- hemoglobin <8.0 g/dL (<80.0 g/L)
- total WBC <2500 cells/μL (<2.50 × 10^3/μL or <2.50 GI/L)
- neutropenia – ANC <1000 cells/μL (<1.00 × 10^3/μL or <1.00 GI/L)
- lymphopenia – ALC <500 cells /μL (<0.50 × 10^3/μL or <0.50 GI/L)
- thrombocytopenia – platelets <50,000 cells/μL (<50 × 10^3/μL or <50 GI/L)
- eGFR (MDRD method) <45 mL/min/1.73 m^2 (FDA 2020).

Note: For repeat testing of screening laboratory tests, see Section 5.4.1.

[43] Have known hypogammaglobulinemia or a screening (Visit 1) IgG level <565 mg/dL (<5.65 g/L).

[44] Have other abnormal laboratory values at screening (Visit 1) which, in the opinion of the investigator, indicate unacceptable risk for the participant's safety in the study.

[45] Have screening ECG abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the participant's safety in the study.

Previous or concurrent clinical study experience

[46] Have previously been randomized in any study investigating an intervention used in this study.

Note: Patients who received only placebo in a non-IMMA study (that is, not one of the ISAs of this master protocol) may be considered for enrollment if other study entry criteria are met.

See criterion [22] for patients who received at least 1 dose of investigational intervention in an ISA of this master protocol.

[47] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other exclusions

[48] Are largely or wholly incapacitated, permitting little or no self-care, such as being bedridden or confined to wheelchair.

[49] Have donated more than a single unit of blood within 4 weeks before randomization (Visit 2) or intend to donate blood during the course of the study.

[50] Have evidence of current or history within 1 year of any substance use disorder of any severity as defined by the DSM-V (APA 2013) in the opinion of the investigator, excepting disorders of nicotine or caffeine use.

Note: Marijuana is considered an illicit drug for the purposes of this study, regardless of local laws. CBD products may be used during the study if they are derived exclusively from hemp. Participants who use hemp-based CBD products must be on a stable dose for at least 10 days prior to randomization, and participants must remain on that stable dose during the study.

[51] Are unable or unwilling to make themselves available for the required number of study visits or unwilling to follow the restrictions and procedures of the study.

[52] Are pregnant or are intending to become pregnant or to breastfeed at any time in the study.

[53] Are investigative site personnel directly affiliated with this study or are their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[54] Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study, which requires exclusion of their employees.

[55] Additional exclusion criteria, if applicable, are defined in the relevant ISA.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failure is defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1. Allowed Retesting of Screening Investigations

Repeating laboratory tests during the screening period does not constitute rescreening.

In particular, the following laboratory tests may be repeated **1 time** during the screening period to determine a participant's eligibility for randomization:

- tests for SLE, such as ANA, anti-dsDNA, and/or anti-Sm antibodies
- tests related to lupus nephritis, and
- clinical chemistry, hematology, and calculation of eGFR.

See Section 8.2.6 for retesting related to TB.

5.4.2. Rescreening of Individuals Who Failed Screening

Informed consent for rescreenings

Individuals who are to be rescreened must first sign a new ICF (Appendix 10.1, Section 10.1.3). Such individuals will be assigned a new participant number.

Rescreening after failure to meet study entry criteria

An individual who does not meet the criteria for participation in this study may be rescreened **1 time** if the reason for the screen failure has resolved and if the sponsor has approved the rescreening. The interval between the failure to meet study entry criteria and the start of rescreening should be at least 4 weeks.

Rescreening for administrative reasons

An individual may be rescreened **1 time** for an administrative reason, including, for example, but not limited to, falling out of the screening window because of scheduling conflicts. The sponsor does not need to approve rescreening for an administrative reason. The rescreening can start immediately after the administrative reason has resolved.

Procedures not required to be repeated during rescreening

Individuals in rescreening who have already completed the protocol-required screening CXR or TB tests are not required to repeat these procedures if they were performed within 90 days before the date of signing the rescreening ICF. However, these procedures can be repeated at the discretion of the investigator.

6. Study Intervention

Study intervention is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Interventions Administered

Study interventions, and, if applicable, investigational medical devices are described in the ISAs.

A placebo control group is included in the design of each ISA.

6.2. Preparation/Handling/Storage/Accountability

Study interventions will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Site responsibilities

The following are responsibilities of the investigator or his or her designee:

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention; the only exception is when study intervention is being self- or caregiver-administered. At the study site, all study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions will be provided by the sponsor.

The investigator or designee is also responsible for

- explaining the correct use of the study interventions
- verifying that instructions are followed properly
- maintaining accurate records of study intervention dispensing and collection, and
- returning all unused clinical trial material to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Sponsor responsibilities

The sponsor or its designee will supply study interventions in accordance with current Good Manufacturing Practice.

Clinical trial materials will be labeled according to the country's regulatory requirements.

The sponsor or its designee will provide instructions about clinical trial material supplies and about the preparation and handling of study interventions.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinding will be maintained throughout the conduct of the study as described in the separate Unblinding Plan.

Method of treatment assignment

Assignment to the ISAs and to the treatment groups within the ISAs will be determined by a computer-generated random sequence using an IWRS. The randomization ratios are specified in the individual ISAs. At the inception of this protocol, 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.

Emergency unblinding

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

The investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted in case of an emergency. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

Discontinuation after unblinding

A participant must be discontinued from study intervention if a participant's study treatment assignment is unblinded to blinded site personnel performing study assessments, including the investigator, or to the participant, unless there are ethical reasons for the participant to continue receiving study intervention. In such a case, the investigator must obtain specific approval from the sponsor's clinical research physician in order for the participant to continue receiving study intervention (see Section 7.1).

Additional measures to minimize bias

Additional measures to minimize bias may be described in the ISAs.

6.4. Study Intervention Compliance

Deviations from the prescribed dosage regimen should be recorded in the eCRF.

The investigator should verify that participants have the ability to understand and comply with study instructions. Before enrolling a participant, the investigator is responsible for discussing with the participant methods to attain high compliance with study procedures, including administration of study intervention.

If a participant is noncompliant with study procedures, administration of study intervention, or both, the investigator should assess the participant to determine the cause of the noncompliance and to educate or manage the participant as appropriate to improve compliance.

If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the participant may be permanently discontinued from study intervention or from the study (see Sections 7.1 and 7.2).

Additional measures

If there are additional measures to assure or assess compliance or adherence, they will be described in the ISAs.

6.5. Concomitant Therapy

Participants will be instructed to consult the investigator or other appropriate study site personnel before taking any new medications or nutritional supplements during the study. The sponsor's medical monitor should be contacted if there are any questions.

Recording of concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of study entry or receives during the study must be recorded along with

- reason for use
- route of administration, and
- dates of administration, including start and end dates.

For allowed concomitant therapies which are standard of care for SLE (as listed below), dosage information will also be collected as well as reason for use and route and dates of administration.

Allowed concomitant therapy for SLE

Participants should maintain their usual medication regimen for SLE and for any other diseases throughout the study unless specifically excluded by entry criteria (see Section 5 of this master protocol and, if applicable, in the relevant ISA) or unless changes are explicitly required (see following text on dose adjustment for corticosteroids). Doses of these usual medications must be stable prior to randomization, as stated in the study entry criteria, and should remain stable during the treatment period unless adjustments are explicitly allowed, as stated herein or in the relevant ISA.

Permitted concomitant background standard-of-care medications for SLE can include any combination of these:

- NSAIDs
- a single antimalarial (such as hydroxychloroquine, chloroquine, or quinacrine)
- a single oral immunosuppressant from the following list: methotrexate, azathioprine, mycophenolate mofetil, or mizoribine; and
- a single type of systemic corticosteroid.

Dose adjustments for antimalarials and immunosuppressants

Doses of antimalarials and immunosuppressants should not be adjusted during the study's treatment period.

If...	Then...	Nonresponder
a participant requires initiation or increase in the dosage of antimalarials and/or immunosuppressants.	the participant may remain in the study and continue receiving study intervention.	Data from such participants will be analyzed as nonresponder data.

Dose adjustment for corticosteroids

See Section 6.5 of the relevant ISA.

Concomitant therapy after permanent discontinuation of study intervention

Standard-of-care therapy can be resumed or modified after the participant is permanently discontinued from the study intervention.

6.6. Dose Modification

Dose modifications, if allowed, are described in the relevant ISA.

6.7. Intervention after the End of the Study

Interventions available after the end of the study, if applicable, are described in the ISAs.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The following sections describe reasons for

- temporary or permanent discontinuation of a participant's dosing (discontinuation of study intervention), and
- discontinuation (withdrawal) of a participant from the study.

For discontinuation of study sites, of ISAs, or of this master protocol as a whole, see Appendix 10.1, Section 10.1.9.

7.1. Discontinuation of Study Intervention

Continuing in the study after discontinuation of study intervention

A participant who prematurely discontinues dosing with study intervention is strongly encouraged to remain in the study for safety monitoring through the treatment period and posttreatment follow-up as per ISA requirements.

See this master protocol (Section 8) and the relevant ISA (Section 1.3 [SoA] and Section 8) for data to be collected at the time of discontinuation from the study intervention and for activities in the posttreatment follow-up period and for any further evaluations that need to be completed.

Possible reasons for discontinuation of study intervention

The following reasons for early **permanent** discontinuation of study intervention apply to any ISA conducted under this master protocol.

Note: For laboratory values that meet early permanent discontinuation thresholds, the study intervention should be discontinued unless, in the opinion of the investigator, the laboratory abnormality is due to intercurrent illness or another identified factor. After consultation with the sponsor's designated medical monitor, the participant may be able to continue receiving study intervention. Laboratory tests may be repeated within 1 week to confirm whether discontinuation criteria have been met. Furthermore, if study intervention is not discontinued because of intercurrent illness, the investigator must confirm that the laboratory value no longer meets early discontinuation thresholds after the resolution of the intercurrent illness or other identified factor.

- **Hepatic event or liver test abnormality**

  The study drug should be interrupted or discontinued if one or more of these conditions occur:

Elevation	Exception
ALT or AST >8 times ULN	
ALT or AST >5 times ULN for more than 2 weeks	
ALT or AST >3 times ULN and either TBL >2 times ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/discontinuation decisions rather than TBL >2 times ULN.

Elevation	Exception
ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3 times ULN, when the source of increased ALP is the liver	
ALP >2.5 times ULN and TBL >2 times ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/discontinuation decisions rather than TBL >2 times ULN.
ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA 2009 and other consensus guidelines, with minor modifications.	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited nondrug etiology is identified.

- **Abnormal hematology lab values:**
  - hemoglobin <7.0 g/dL (<70.0 g/L)
  - total white blood cell count (WBC) <1500 cells/µL (<1.50 × 10^3/µL or <1.50 GI/L)
  - absolute neutrophil count (ANC) <600 cells/µL (<0.60 × 10^3/µL or <0.60 GI/L)
  - absolute lymphocyte count (ALC) <250 cells/µL (<0.25 × 10^3/µL or <0.25 GI/L)
- **HBV or HCV**: The participant tests positive for HBV DNA (see Section 8.2.7) and clinical assessment is consistent with HBV reactivation, **or** tests positive for HCV RNA (Section 8.2.8).

  Note: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification (Section 7.1.1). The participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study intervention. The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.
- **Suicidal Ideation and Behavior:** The participant answered "yes" to Question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS, **or** answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS. The participant may be assessed by a psychiatrist or other appropriately trained professional to assist the investigator in deciding whether the participant should be discontinued from the study intervention.

- **Certain adverse events (AEs):**
  - The participant experiences a severe AE, an SAE, or a change in a laboratory value or an ECG finding (see Section 8.2.3) that, in the opinion of the investigator, merits the discontinuation of the study intervention and appropriate measures being taken. In this case, the sponsor's medical monitor is to be notified immediately, and the event is to be documented.
  - The participant has a systemic hypersensitivity reaction. The investigator should consult the sponsor-designated medical monitor, in determining that such an event has occurred and whether the participant should be permanently discontinued from the study intervention.
  - The participant develops a malignancy.

    Exception: Participants may be allowed to continue to receive study intervention if they develop no more than 2 successfully treated nonmelanoma skin cancers during the study.
  - The participant develops HIV or AIDS infection.
  - The participant develops active TB or untreated LTBI (Section 8.2.6).
  - Serious or opportunistic infections, as defined in Section 5.2.
- **Unblinding:** If an investigator, site personnel performing assessments, or participant is unblinded to the participant's randomly assigned intervention, the participant must be discontinued from the study intervention. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from Lilly or its designee for the participant to continue receiving the study intervention.
- **Pregnancy:** The participant becomes pregnant (Section 8.2.5.1).
- **Participant decision:** The participant requests to discontinue receiving the study intervention.
- **Participant noncompliance:** The investigator decides that the participant is noncompliant with study intervention administration or other study procedures; in this case, the participant may be discontinued from study intervention or from the study (Section 7.2).
- **Participant with intolerable or exacerbating disease:** A participant with increased disease activity should discontinue study intervention at the discretion of the investigator and receive standard-of-care treatment, which may include biologic therapies.

7.1.1. Temporary Discontinuation (Withholding) of Study Intervention

Infection-related criteria for temporary withholding

Temporary withholding of study intervention is required if the participant meets any of the following infection-related criteria during the study:

- A participant diagnosed with LTBI during the study is to be permanently discontinued from study intervention unless the participant is a candidate for LTBI treatment, and is treated for LTBI as follows:

  - Study intervention is temporarily held for at least the first 4 weeks of LTBI treatment.
  - After receiving at least 4 weeks of appropriate LTBI therapy (as per WHO or US Centers for Disease Control guidelines), if there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance, study intervention may be resumed.
  - The participant must complete appropriate LTBI therapy to remain eligible to receive study intervention.
- HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. The sponsor's designated medical monitor should be contacted regarding study status of the participant. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention (Section 7.1).

Other criteria for temporary withholding

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational intervention. Except in cases of emergency, it is recommended that the investigator consult with the sponsor-designated medical monitor before temporarily interrupting therapy.

7.2. Participant Discontinuation/Withdrawal from the Study

Data collection and follow-up for participants who discontinue (withdraw) from the study

In rare instances, it may be necessary for a participant to be discontinued early from the study. The participant will be permanently discontinued both from the study intervention and from the study at that time. At the time of discontinuing from the study, if possible, an ETV and any applicable posttreatment follow-up visits should be conducted, as shown in the SoA of the relevant ISA. See this master protocol (Section 8) and the relevant ISA (Section 1.3 [SoA] and Section 8) for data to be collected at the time of discontinuation from the study and for activities to be completed in the posttreatment follow-up period and for any further evaluations that may need to be completed.

Reasons for early discontinuation (withdrawal) from the study

Discontinuation (withdrawal) is expected to be uncommon.

A participant will be discontinued (withdrawn) from the study in the following circumstances:

- at any time at his/her own request, or at the request of his/her designee (for example, legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or
- if the participant, for any reason, requires treatment with a therapeutic agent that is not allowed by the protocol and has been demonstrated to be effective for treatment of the

study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Withdrawal of consent for disclosure

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA of this master IMMA protocol (Section 1.3) and in the SoA of the relevant ISA.

Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct. Since key efficacy data may be collected via an electronic tablet, adherence to the data collection modality specified in the SoA is also essential and is required for study conduct.

Unless otherwise specified in the relevant ISA, efficacy and safety assessments and sample collections should be completed prior to dosing at the dosing visits.

8.1. Efficacy Assessments

Efficacy assessments and endpoints are described in the relevant ISA.

See Appendix 10.8 for descriptions of assessments of disease activity used in the screening period (Visit 1) of this master protocol.

8.2. Safety Assessments

Visits and order of safety assessments

Safety assessments occur at visits specified in this master IMMA protocol SoA (Section 1.3) and in the SoA of the relevant ISA.

If multiple safety assessments are scheduled to occur at the same visit, the preferred order of completion is

1) QIDS-SR16, ECG, and then vital signs,
2) other safety assessments, including physical examinations, CXR, and nonleading (spontaneous) AE collection, followed by C-SSRS (Section 8.3.1.1), and finally
4) sample collection for clinical laboratory, PK, PD, pharmacogenetic, biomarker, and immunogenicity testing.

Data collection and reporting

The AE data collection and reporting requirements are described in Section 8.3 and Appendix 10.3.

For some interventions studied under this master protocol, there may be predefined AESIs. If so, the additional sample or data collections for AESIs will be specified in the ISAs.

Investigator safety monitoring

The principle investigator will monitor the safety data throughout the study. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Sponsor safety monitoring

The sponsor will monitor the safety data, including AEs and SAE, discontinuations, vital signs, and clinical laboratory results by means of periodic blinded reviews and by other appropriate

methods. The SAE reports will be reviewed in real time and across studies and will include review of applicable clinical safety and epidemiological publications from the literature. If this safety monitoring activity uncovers an issue that needs to be addressed by unblinding at the individual or group level, members of the IAC can conduct additional analyses of the safety data. The IAC is an advisory group for this study formed to protect the integrity of the study in unblinded safety data reviews. See Appendix 10.1, Section 10.1.5.

Appropriateness of safety assessments

The safety assessments used in this study are routine elements of clinical health assessment and drug development.

Safety assessments described in this master protocol and in ISAs

The following sections describe safety assessments applicable to all ISAs.

See the ISAs for any additional safety assessments which may be applicable to a particular ISA.

8.2.1. Vital Signs

Vital signs will be measured as specified in the SoA of this master protocol (Section 1.3) and in the SoA of the relevant ISA, and as well as whenever clinically indicated. Additional vital signs may be measured during the study visits if warranted, as determined by the investigator.

Blood pressure and pulse rate should be measured after the participant has been sitting for at least 5 minutes.

Unscheduled orthostatic vital signs should be assessed, if possible, during any dizziness or posture-induced symptoms. If the participant feels unable to stand, sitting or supine vital signs will be recorded.

8.2.2. Physical Examinations

Complete physical examinations and symptom-directed physical examinations will be conducted at the visits specified in the SoA of this master protocol (Section 1.3) and in the SoA of the relevant ISA. Symptom-directed physical examinations may also be conducted at other visits, as determined by the investigator, if a participant presents with complaints or as needed per local standard of care.

A complete physical examination should include the following regions and body systems:

- general appearance
- skin
- head, ears, eyes, nose, throat
- lymph nodes
- cardiovascular
- musculoskeletal
- respiratory
- abdominal
- genitourinary (only as clinically indicated)
- extremities (tender/swollen joint counts are documented separately), and

- neurologic.

The complete physical examination will exclude pelvic, rectal, and breast examinations, unless clinically indicated. The SLE symptom physical assessment is captured in the electronic tablet.

Height and weight

Height without shoes and weight will be measured and recorded as indicated in the SoAs.

8.2.3. Electrocardiograms

For each participant, 12-lead ECGs will be collected as specified in the SoA of this master protocol (Section 1.3) and in the SoA of the relevant ISA. The ECGs should be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and must remain supine but awake during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets the study entry criteria if applicable, and for immediate participant management if any clinically relevant findings should be identified.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT/QTc interval) after enrollment, the investigator or qualified designee, in conjunction with the sponsor's medical monitor, will determine whether the participant can continue to receive study intervention in the study and whether any change in participant management is needed.

The investigator's or qualified designee's review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding will be reported as an AE.

8.2.4. Chest Radiography

A PA CXR, interpreted and reported by a radiologist or pulmonologist, will be obtained as specified in the SoA of this master protocol (Section 1.3) and in the SoA of the relevant ISA, if applicable. The CXR films or images or a radiology report must be available to the investigator for review before the participant is randomized.

In addition to the PA CXR, a lateral CXR can also be obtained if, in the opinion of the investigator, a lateral view is indicated.

Note: Participants do not need to have a CXR at screening if, based on the judgment of the investigator, both of the following 2 conditions are met:

- the CXR was performed within 6 months before initial screening, and
- documentation of the CXR, read by a qualified radiologist or pulmonologist, is sufficient for pericardial and pleural effusion per EULAR/ACR 2019 classification criteria and for TB evaluation according to local standard of care.

Certain findings from CXR may be consistent with a condition that excludes a participant from the study; see Section 5.2.

Note: Results of a chest CT scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the sponsor's medical monitor.

8.2.5. Laboratory Tests

See Appendix 10.2 and the SoA (Section 1.3) for the clinical laboratory tests to be performed during the screening period of this master protocol. See the relevant ISA for clinical laboratory tests to be performed in treatment and posttreatment study periods.

All protocol-required laboratory assessments, as defined in the ISAs and in this master protocol, must be conducted in accordance with the SoAs, standard collection requirements, and applicable study laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

Reviewing and recording test results

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Repeat testing after clinically significant abnormal findings

All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within a time period equivalent to the maximum 5 half-lives of active interventions after the last dose of study intervention, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Laboratory tests after hypersensitivity events

See the relevant ISA.

Allowance for additional laboratory testing

Additional tests may be performed at any time during the study as deemed necessary by the investigator or as required by local regulations.

8.2.5.1. Pregnancy Testing

Pregnancy testing (serum or urine) is to be performed for WOCBP and females with a history of tubal ligation. Participants who are pregnant will be discontinued from the study intervention (see Section 7.1).

Visits and times

Pregnancy testing (serum or urine) will be performed as specified in Appendix 10.2, in the SoA of this master protocol (Section 1.3), and in the relevant ISA. If the specified study visit includes administration of study intervention, the urine pregnancy test must be "negative" within 24 hours before dosing.

If a urine pregnancy test is not available, a local serum pregnancy test is an acceptable alternative.

Additional pregnancy testing (serum or urine) may be performed at additional time points at the discretion of the investigator or if this is required by local regulations.

If the urine pregnancy test is inconclusive at any visit, an additional serum pregnancy test should be collected.

Optional FSH testing

The participant's FSH level can be obtained during screening at the discretion of the investigator to assist in determining whether the participant meets the definition of *postmenopausal*. The FSH level can also be optionally obtained during the study to determine the participant's postmenopausal status (see Appendix 10.4).

8.2.6. Tuberculosis Testing and Monitoring

TB testing

During screening, all participants are to be assessed for risk factors, symptoms, and signs of TB with all of the following:

- Thorough history to determine the lifetime risk factors for TB infection, for TB progression, and for symptoms and/or signs of active TB, and
- Signs of previous or active TB by means of
  - Thorough physical examination for signs of active TB, including measurement of body temperature (Section 8.2.1) and assessment of peripheral lymph nodes, and
  - PA CXR interpreted and reported by radiologist or pulmonologist (Section 8.2.4).

All participants with no history of LTBI or active TB, and no history of positive Mantoux TST using PPD or positive *Mycobacterium tuberculosis* IGRA must have one of the following:

- PPD TST
  - The TST is performed by injecting 0.1 mL of tuberculin PPD into the inner surface of the forearm. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. Measure induration at site of intradermal injection 48 to 72 hours after intradermal injection. The test must be read during this window of time. The reaction should be measured in millimeters of induration (palpable, raised, hardened area or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).

- An induration of 5 or more millimeters is considered positive in:
  - HIV-infected persons
  - A recent contact of a person with TB disease
  - Persons with fibrotic changes on chest radiograph consistent with prior TB
  - Persons with organ transplants, and
  - Persons who are immunosuppressed for other reasons (for example, taking the equivalent of >15 mg/day of prednisone for 1 month or longer, or taking TNF-α antagonists)
- An induration of 10 or more millimeters is considered positive in all other potential clinical trial participants.
- Two-step testing (repeat TST from 1 to 3 weeks after the first TST) is recommended for certain participant groups, based on investigator judgment, including:
  - persons receiving immunosuppressant treatment
  - persons with a history of temporally remote increased risk of TB infection, and
  - persons for whom the first test is negative, as per local public health and/or professional medical society recommendations.

- IGRA for *M tuberculosis*. Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.

  Note: If the investigator suspects false positive IGRA results in a participant with no increased risk of TB infection during lifetime, and no evidence of prior or current TB on physical examination and/or on CXR interpreted by radiologist and/or pulmonologist, as well as with investigator assessment by history and physical examination, and CXR report documented in CRF, the investigator may discuss retesting with the sponsor's designated medical monitor.

Retesting

One retest is allowed for participants with an "indeterminate" QuantiFERON®-TB Gold assay or "borderline" T-SPOT®.TB assay. Participants with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT.TB assays will be excluded.

Rescreening after diagnosis and treatment of LTBI

Participants diagnosed with LTBI are excluded (Section 5.2) unless they are candidates for LTBI treatment, are treated for LTBI, and the following criteria are met:

- After receiving at least 4 weeks of appropriate LTBI therapy (as per WHO or the United States CDC guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance. In this case, the participant may be rescreened (Section 5.4.2) and is not excluded due to LTBI.
- The participant must continue and complete appropriate LTBI therapy in order to remain eligible to continue to receive study intervention (Section 7.1).

Monitoring during the study

For all participants, monitoring for TB is to be continuous throughout the study. At a minimum, each participant is to have the following documented at least every 3 months:

- Thorough history to determine any risk factors for TB infection and for TB progression, symptoms or signs of active TB, and
- Thorough physical examination for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes.

8.2.7. Hepatitis B Testing and Monitoring

As specified in the SoA of this master protocol (Section 1.3), initial testing for HBV infection includes HBsAg and anti-HBc.

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
- If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required.
  - If the screening HBV DNA is positive, the participant is excluded.
  - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study, as specified in the SoA of the relevant ISA.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected ("positive") during the study, the study intervention will be temporarily withheld or permanently discontinued and participants should receive appropriate follow-up medical care as described in this master protocol Sections 7.1 and 7.1.1.

8.2.8. Hepatitis C Testing

As specified in the SoA of this master protocol (Section 1.3), initial testing for HCV infection includes testing for anti-HCV.

- If anti-HCV is positive, a serum test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded (see Section 5.2).

Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study intervention will be discontinued (Section 7.1), and the participant should receive appropriate follow-up medical care.

8.2.9. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN
ALP <1.5 times ULN	ALP ≥2 times ULN
TBL <1.5 times ULN	TBL ≥2 times ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline

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

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN with hepatic signs/symptoms [a] or ALT or AST ≥5 times ULN
ALP <1.5 times ULN	ALP ≥3 times ULN
TBL <1.5 times ULN	TBL ≥2 times ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline with hepatic signs/symptoms [a] or ALT or AST ≥3 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline

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

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for HDV, CMV, EBV, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, MRCP, ERCP, cardiac echocardiogram, or a liver biopsy.

8.2.9.1. Additional Hepatic Data Collection in Participants Who Have Abnormal Liver Tests During the Study

Additional hepatic safety data collection in hepatic safety CRFs should be performed for participants who meet 1 or more of the following 5 conditions:

- Elevation of serum ALT to ≥5 times ULN on 2 or more consecutive blood tests (if baseline ALT <1.5 times ULN)
    - In participants with baseline ALT ≥1.5 times ULN, the threshold is ALT ≥3 times baseline on 2 or more consecutive tests.
- Elevated TBL to ≥ 2 times ULN (if baseline TBL <1.5 times ULN) (except for cases of known Gilbert's syndrome)

- In participants with baseline TBL ≥1.5 times ULN, the threshold should be TBL ≥2 times baseline.

- Elevation of serum ALP to ≥2 times ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 times ULN)
  - In participants with baseline ALP ≥1.5 times ULN, the threshold is ALP ≥2 times baseline on 2 or more consecutive blood tests.
- Hepatic event considered to be an SAE
- Discontinuation of study drug due to a hepatic event (Section 7.1)

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

8.2.10. Suicidal Ideation and Behavior Risk Monitoring

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study intervention. Participants who have signs of suicidal ideation or behavior should be considered for discontinuation of study intervention, following a risk assessment (see Section 7.1). See Section 8.3.1.1 for timing of AE collection relative to collection of the C-SSRS.

At screening, suicidal ideation and behavior and depressive symptomatology will be assessed by use of the

- C-SSRS, and
- QIDS-SR16

See the SoA of the relevant ISA for assessments in the treatment and posttreatment follow-up periods.

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

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

8.2.10.2. 16-Item Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR16)

The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's DSM-V (APA 2013). A participant is asked to consider each statement as it relates to the way he or she has felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity.

The domains assessed by the instrument include 1) sad mood, 2) concentration, 3) self-criticism, 4) suicidal ideation, 5) interest, 6) energy/fatigue, 7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), 8) decrease/increase in appetite/weight, and 9) psychomotor agitation/retardation.

8.2.11. Additional Safety Data and Sample Collections

For some interventions, additional data or sample collections may be necessary when certain AE occur (for example, systemic hypersensitivity reactions, injection or infusion site reactions, serious infections, opportunistic infections). See the ISAs for such AEs and for any additional instructions, if applicable.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 10.3:

- AEs
- SAEs
- PCs

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and, if applicable, all AEs of special interest (AESIs, as defined in the ISAs) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event (AE)					
AE	Signing of the first ICF	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event (SAE)					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the first ICF	Start of intervention	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE [a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	End of time period equal to at least 5 terminal half-lives after last dose; consult the IB or the sponsor's medical monitor	Within 24 hours (see Section 10.4.3)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Product Complaints (PC)					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; IB = investigator's brochure; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

[a] These SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading (spontaneous) AE collection should occur before the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS collection but was not captured during the nonleading AE collection, sites should not change the AE form.

However, if an AE is serious or leads to discontinuation, the AE should be included on the AE form. Also, the process for reporting SAEs should be followed.

8.3.2. Adverse Events of Special Interest (AESIs)

See the relevant ISA.

8.4. Treatment of Overdose

See the relevant ISA.

8.5. Pharmacokinetics

See the relevant ISA.

8.6. Pharmacodynamics

See the relevant ISA.

8.7. Genetics

See the relevant ISA.

8.8. Biomarkers

See the relevant ISA.

8.9. Immunogenicity Assessments

See the relevant ISA.

8.10. Medical Resource Utilization and Health Economics

See the relevant ISA.

9. Statistical Considerations

The SAP for this master protocol (MP-SAP) will be finalized prior to the first unblinding. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. 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 endpoint. Intervention-specific details regarding hypotheses and statistical testing are in its respective ISA.

9.1.1. Multiplicity Adjustment

See Section 9.3.1.

9.2. Analyses Sets

This table describes analyses sets defined for all ISAs unless otherwise specified in the ISA:

Participant Analysis Set	Description	Used to Analyze Endpoints Related to...
Modified intent-to-treat (mITT)	All randomized participants receiving at least 1 dose of study intervention. Participants will be included in the analysis set according to their randomly assigned intervention.	• efficacy objectives • patient-reported outcomes, if applicable
Safety	All randomized participants receiving at least 1 dose of study intervention. Participants will be included in the analysis set according to the intervention they actually received.	• safety
Pharmacokinetics (PK)	All randomized participants receiving at least 1 dose of study intervention and have PK data available.	• PK

Additional intervention-specific analyses sets may be described in respective ISAs.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Unless otherwise indicated in ISA-specific analyses, the following general considerations apply to the analyses:

- CCI [redacted]
- No adjustments for multiplicity will be performed.

- Efficacy and PRO analysis models may contain the independent variables. These variables may include, but are not limited to, treatment group, ISA, baseline disease activity, and geographic region.
- Missing data for dichotomous responder endpoints will be imputed using the NRI method.
- Participants will be considered nonresponders if they
  - do not meet all the clinical response criteria
  - are noncompliant with concomitant medication rules (Section 6.5), or
  - permanently discontinue study intervention at any time before the end of the treatment period for any reason.
- CCI
- Additional imputation methods may be considered for all endpoint types. Additional imputations will be specified in the ISAs.

CCI

Other models may also be considered for the analyses if deemed appropriate for an ISA. Details regarding additional models will be specified in the ISAs.

Changes to the data analysis methods

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

9.3.2. Primary Endpoint(s)/Estimand(s)

9.3.2.1. Primary Analysis for Initial ISA (BT01)

The primary endpoint for the initial ISA (BT01) is the proportion of participants who achieve remission of arthritis and/or rash at 24 weeks compared to the placebo population. Participants who fail to complete the 24-week treatment period or who violate the concomitant medication rules will be imputed as nonresponders for purposes of the primary endpoint analysis.

The primary null hypothesis is that there is no difference between the intervention and placebo on remission of arthritis and/or rash response at 24 weeks. Analysis will be done using CCI [redacted] with effects specified in the initial ISA (BT01).

9.3.2.2. Primary Analysis for Subsequent ISAs

Subsequent interventions will be compared to all placebo data available at time of treatment completion for the intervention of interest. The primary endpoint for ISAs which enter the trial after the initial ISA (BT01) will be specified in the ISA and analyzed using either a Bayesian hierarchical random effects model, a mixed effects model, or other models deemed appropriate.

Model details will be provided in the master protocol SAP and intervention-specific independent effects, will be specified in the relevant SAPs.

9.3.3. Secondary Endpoint(s)/Estimand(s)

For the initial ISA (BT01) dichotomous secondary endpoints (for example, SRI-4 and SLEDAI-4) will be analyzed using a CCI with effects specified in the initial ISA (BT01). For subsequent ISAs which enter the trial after the initial ISA (BT01), dichotomous secondary endpoints will be specified in the ISA and analyzed using either a Bayesian hierarchical random effects model, a mixed effects model, or other models deemed appropriate. Intervention-specific effects will be specified in the respective ISAs.

9.3.4. Exploratory Endpoint(s)/Estimand(s)

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

9.3.5. Safety Analyses

Safety analyses will include evaluation of all reported AEs, AESIs, C-SSRS, QIDS-SR16, ECGs, vital signs, and laboratory analytes. Unless otherwise specified in the ISA, safety analyses will compare the intervention to all available placebo at time of analysis. Exposure to each intervention will be calculated for each participant and summarized by treatment arm. Categorical safety measures will be summarized by treatment for each ISA with incidence rates. The mean change of the continuous safety measures will be summarized for each ISA by visit. Exposure to study intervention will be calculated for each participant and summarized by treatment group for each ISA.

9.3.5.1. Adverse Events

AEs will be coded according to MedDRA and summarized by system organ class, preferred term, severity, and relationship to the study intervention. A 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, during Visits 1 and 2 and recorded with the time of onset before the first dose of study intervention). The treatment period will be used as the postbaseline period for analysis. For events that are sex-specific, the denominator and computation of the percentage will only include participants of the given sex.

The number and percentage of participants who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an AE, and AESIs will be summarized. TEAEs (all, by maximum severity), SAEs (including deaths), and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class and preferred term.

Treatment-related TEAEs (TEAEs related to study intervention) are defined as events that are indicated by the investigator on the eCRF to be related to treatment.

In addition to general safety parameters, safety information on specific topics of AESIs may also be presented. Potential AESIs will be identified by a standardized MedDRA query or a Lilly-defined MedDRA preferred term listing.

Follow-up emergent AEs, SAEs (including deaths), and AEs that lead to a participant's discontinuation from study intervention or discontinuation from study will be summarized. All AEs, including preexisting conditions, will be listed by participant, visit, preferred term, treatment group, severity (intensity), and relationship to the study intervention.

9.3.5.2. Columbia–Suicide Severity Rating Scale

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (C-SSRS WWW). Suicidal ideation and/or behavior and self-injurious behavior with no suicidal intent, on the basis of the C-SSRS, will be listed by participant.

9.3.6. Other Analyses

9.3.6.1. Participant Disposition

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete the study or discontinue, 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.

9.3.6.2. Participant Characteristics

Participant characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include original genetic sex, age, age category, weight, race, geographic region, country, anti-dsDNA status (positive; negative), and baseline disease activity, including baseline SLEDAI-2K, Physician's Global Assessment of Disease Activity, BILAG 2004, tender joint count, swollen joint count, CLASI, and other clinical measurements. Intervention-specific analyses are described in the respective ISAs.

Demographic data are collected and summarized to demonstrate that the study population represents the target patient population. A summary of baseline participant characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by treatment group using descriptive statistics. Other participant characteristics will be summarized by treatment group as deemed appropriate within each ISA.

9.3.6.3. 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 latest version of the WHO drug dictionary.

9.3.6.4. Treatment Compliance

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

9.3.6.5. Pharmacokinetics/Pharmacodynamics

Intervention-specific PK/PD analyses are described in the relevant ISAs, in a separate PK/PD analysis plan, or in both.

9.3.6.6. Immunogenicity

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

- participants with preexisting ADA, and
- participants with TE-ADA to the active study intervention.

TE-ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared 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 ISAs and ISA-SAPs.

9.3.6.7. Patient-Reported Outcomes

Intervention-specific analyses of PROs, if applicable, are described in the relevant ISAs.

9.3.6.8. Subgroups

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

9.3.6.9. Sensitivity Analyses

No sensitivity analyses are planned for the initial ISA. Sensitivity analyses in subsequent ISAs regarding borrowing may include methods described in Section 9.3.1.

Supplemental analyses may be performed on the primary endpoint for alternative approaches to nonresponder criteria, prohibited medication use, or other intercurrent events of interest. Details of sensitivity analyses and alternative models are specified in the ISA and/or MP-SAP.

9.4. CCI

CCI

CCI

CCI [redacted]

9.5. Sample Size Determination

At the inception of this master protocol, 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 9.3.1. If borrowing occurs at time of primary database lock for 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 respective ISAs.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines,
- Applicable ICH GCP Guidelines,
- Applicable laws and regulations.

The protocol, protocol amendments, ICFs, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB or IEC by the investigator and reviewed and approved by the IRB or IEC before the study is initiated.

Any amendments to the protocol will require IRB or IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each principal investigator will sign the separate protocol signature page and send a copy of the signed page to a Lilly representative.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center. The sponsor or its representatives must approve the ICFs, including any changes made by the ERB/IECs, before the ICFs are used at the investigative sites.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants who are rescreened are required to sign a new ICF (see Section 5.4.2).

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

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 randomization. In addition, the committee will help ensure that high quality data are entered into the EDC system for the 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.

Internal Assessment Committee (IAC)

In addition to safety reviews routinely performed by the sponsor as described in Section 8.2, the IAC 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 IAC will also be responsible for review of the available efficacy data.

The IAC 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, but will not include any Lilly study team members. Details about the IAC membership, purpose, responsibilities, and operation will be described in an IAC 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.

10.1.6. Dissemination of Clinical Study Data

Clinical study reports (CSRs)

A CSR will be provided for each ISA.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, CSR, blank or annotated CRFs, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data).

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This documentation might include laboratory and diagnostic test reports, medical records, and clinical notes.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Data monitoring and management

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (for example, CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the

sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical assessment data, according to the SoA, will be collected by authorized study personnel via a paper source document and will be transcribed by the authorized study personnel into the EDC system and will serve as the source documentation.

Additionally, eCOA data (participant-focused outcome instrument, and clinician assessments) will be directly recorded by the participant and investigator site personnel, into an instrument (for example, a tablet, according to the SoA). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data. Therefore, the data must be recorded contemporaneously.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive and/or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global PC management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

Study start

The study start date is the date on which the clinical trial will be open for recruitment of participants.

Study discontinuation and site closure

Either the master protocol as a whole or only a particular ISA may be discontinued at the discretion of the sponsor if the sponsor judges discontinuation to be necessary for medical, safety, regulatory, futility, lack of benefit/efficacy, or discontinuation of study intervention development, or other reasons consistent with applicable laws, regulations, and GCP.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Physicians with experience in clinical trials and experience in treating patients with SLE will participate as investigators in this clinical trial.

Other qualified health care professionals with experience in clinical trials and in treating patients with SLE may also participate as investigators.

10.1.12. Sample Retention

See the relevant ISA.

10.2. Appendix 2: Clinical Laboratory Tests

Use of central or local laboratories

Clinical laboratory tests will be performed by a central laboratory or by a local laboratory as detailed in the tables in this appendix.

If laboratory tests are performed to obtain results with an intent to resume administration of study intervention after a temporary interruption, the samples must be assayed centrally.

In circumstances where the sponsor approves local laboratory testing in lieu of the central laboratory testing specified in the tables, the local laboratory must be qualified in accordance with applicable local regulations.

Laboratory tests for inclusion/exclusion of potential study participants

Protocol-specific laboratory requirements for inclusion or exclusion of potential study participants are included in Section 5 of this master protocol. For any additional laboratory testing which may be required before a participant is randomized to a treatment group, see Section 5 of the relevant ISA.

Pregnancy testing

Pregnancy testing is described in the SoA (Section 1.3), in Section 8.2.5.1, and in the table below, as well as in the relevant ISA.

Allowance for additional laboratory testing

Additional tests may be performed at any time during the study as determined necessary by the investigator or as required by local regulations.

Investigator responsibilities

Investigators must document their review of the laboratory safety results.

Provision of laboratory results

Laboratory test results that could unblind the study will not be reported to investigative sites or to other blinded personnel.

10.2.1. Clinical Laboratory Tests Performed at Visit 1

	Notes
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (red blood cells [RBC])	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (white blood cells [WBC])	
Total absolute neutrophil count	
Absolute count of:	
Neutrophils, segmented	
Bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC and reticulocytes)	

	Notes
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Indirect bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Amylase	
Lipase	
Cholesterol	
Triglycerides	
Haptoglobin	
Lactate dehydrogenase (LDH)	

	Notes
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	

	Notes
Urine Chemistry	Assayed by Lilly-designated laboratory.
Protein	
Creatinine	
Albumin	

	Notes
Hormones (females)	Assayed by Lilly-designated laboratory.
Pregnancy test – serum	
Follicle-stimulating hormone (FSH)	

	Notes
Calculations	Calculated by Lilly-designated laboratory.
Urinary protein/creatinine ratio (UPCR)	
Urinary albumin/creatinine ratio (UACR)	
Estimated glomerular filtration rate (eGFR)	Modification of Diet in Renal Disease (MDRD) method.

	Notes
Serology	Assayed by Lilly-designated laboratory.
Tuberculosis (TB) testing:	
QuantiFERON®-TB Gold	Assayed by Lilly-designated laboratory.
T-SPOT®.TB	May be tested and evaluated locally. Local laboratory must be qualified by local regulations.
Tuberculin skin test (TST)	Tested and evaluated locally. Local staff must be qualified to administer and interpret the test.
Human immunodeficiency virus (HIV)	Assayed by Lilly-designated laboratory.
Hepatitis C virus (HCV) testing:	Assayed by Lilly-designated laboratory.
Hepatitis C antibody	
HCV RNA	
Hepatitis B virus (HBV) testing:	Assayed by Lilly-designated laboratory.
Hepatitis B core antibody (anti-HBc)	
Hepatitis B surface antigen (HBsAg)	
Hepatitis B virus (HBV) DNA	
CCI	

	Notes
Immunoglobulins	Assayed by Lilly-designated laboratory.
Immunoglobulin G (IgG)	

	Notes
Additional Testing	Assayed by Lilly-designated laboratory.
Thyroid-stimulating hormone (TSH)	

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Information for ISAs having devices: The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155. Both the investigator and the sponsor will comply with all local medical device reporting requirements. The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1 of the relevant ISA for the list of sponsor medical devices, if applicable.

10.3.1. Definition of AE

AE Definition

An AE is any untoward medical occurrence in a study participant and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

For investigational devices, when applicable: An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. For trials that include an investigational device: Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

- Deficiencies in labeling information, and
- Use errors for device or drug-device combination products due to ergonomic design elements of the product.

PCs related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and PC Recording

When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate eCRF page and PC information is reported on the PC form.

Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the eCRF page for AE/SAE and the PC form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB in his or her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone. Contacts for SAE reporting can be found in site training documents.

SAE Reporting via Paper CRF
Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting can be found in site training documents.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming a woman *not* of childbearing potential.

Any amount of spotting should be considered menarche. If fertility is unclear (for example, amenorrhea in athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

*Woman **not** of childbearing potential*

Females are considered women not of childbearing potential if

- they have a congenital anomaly such as Mullerian agenesis
- they are infertile due to surgical sterilization, or
- they are postmenopausal (see below).

Examples of surgical sterilization include hysterectomy and bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above (for example, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal state

A female in the postmenopausal state is defined as a female meeting at least 1 of the following criteria:

- at any age with at least 6 weeks postsurgical bilateral oophorectomy, with or without hysterectomy, confirmed by operative note
- at least 40 years of age and up to 55 years old, with an intact uterus and not on hormone therapy, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with an FSH >40 mIU/mL

  Note: For this definition to apply, the female should have no other pertinent medical condition such as anorexia nervosa and should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.
- 55 or older not on hormone therapy who has had at least 12 months of spontaneous amenorrhea, or
- at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

10.4.2. Contraception Guidance

See the ISA to which the participant has been assigned.

10.4.3. Collection of Pregnancy Information

10.4.3.1. Male Participants with Partners Who Become Pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After learning of a pregnancy in the female partner of a male study participant, the investigator will promptly obtain the necessary signed consent from the pregnant female partner directly, and within 24 hours after obtaining this consent, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.3.2. Female Participants Who Become Pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will permanently discontinue study intervention but may remain in the study, following the usual visit schedule, including the posttreatment follow-up period. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The

follow-up on the pregnancy outcome should continue independently of intervention or study discontinuation.

10.5. Appendix 5: Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

The following are examples of infections that may be considered opportunistic in the setting of biologic therapy (adapted from Winthrop et al. 2015). This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy. This list is not exhaustive. Infections will be categorized by Lilly as opportunistic according to "Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance" by Winthrop et al. (2015).

Examples of infections that may be considered opportunistic in the setting of biologic therapy.

Bacterial	
	Bartonellosis (disseminated disease only)
	Campylobacteriosis (invasive disease only)
	Legionellosis
	Listeriosis (invasive disease only)
	Nocardiosis
	Tuberculosis
	Non-tuberculous mycobacterial disease
	Salmonellosis (invasive disease only)
	Shigellosis (invasive disease only)
	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral	
	BK virus disease including polyomavirus-associated nephropathy
	Cytomegalovirus disease
	Hepatitis B virus reactivation
	Hepatitis C virus progression
	Herpes simplex (invasive disease only)
	Herpes zoster (any form)
	Posttransplant lymphoproliferative disorder (Epstein-Barr virus)
	Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus
Fungal	
	Aspergillosis (invasive disease only)
	Blastomycosis
	Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual)
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
	Paracoccidioides infections
	Penicilliosis
	Pneumocystosis
	Sporotrichosis
	Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Parasitic	
	Leishmaniasis (visceral only)
	Strongyloidiasis (hyperinfection syndrome or disseminated disease)
	Microsporidiosis
	Toxoplasmosis
	Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
	Cryptosporidiosis (chronic disease only)

Source: Adapted from Winthrop et al. (2015).

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

See Section 8.2.9 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[d]	Anti-actin antibody[b]

table continues

table continued

Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

a Not required if anti-actin antibody is tested.

b Not required if anti-smooth muscle antibody is tested.

c Assayed ONLY by investigator-designated local laboratory; no central testing available.

d Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

See Appendix 10.3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.8. Appendix 8: Efficacy Assessments

The following are assessments of disease activity used in the screening period (Visit 1) of this master protocol.

10.8.1. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

The SLEDAI-2K is a validated global disease activity instrument that focuses on disease manifestations across 9 organ systems (Gladman et al. 2002). It includes 24 clinical and laboratory variables with manifestations graded by the affected organ system as follows:

- Central nervous system (seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebral vascular accident)
- Vascular (vasculitis)
- Musculoskeletal (arthritis, myositis)
- Renal (urinary casts, hematuria, proteinuria, pyuria)
- Mucocutaneous (rash, alopecia, mucosal ulcers)
- Cardiovascular and Respiratory (pleurisy, pericarditis)
- Immunologic (low complement, increased DNA binding)
- Constitutional (fever), and
- Hematologic (thrombocytopenia, leukopenia).

10.8.2. British Isles Lupus Assessment Group 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.

BILAG category scores are provided below:

- 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.

10.8.3. Tender/Swollen Joint Count (28 Joints)

The 28 joints to be examined and assessed as tender or not tender for tender joint count and as swollen or not swollen for swollen joint count include 14 joints on each side of the participant's body:

- the 2 shoulders
- the 2 elbows
- the 2 wrists
- the 10 metacarpophalangeal joints
- the 2 interphalangeal joints of the thumb
- the 8 proximal interphalangeal joints, and
- the 2 knees.

10.9. Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local ERBs, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- a change in the method of study intervention administration,
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, evaluation of PROs via a tablet and/or web-based collection system.

Mobile health care: Health care visits may be performed by a mobile health care provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, vital signs, weight, physical examinations, ECGs, collection of blood and urine samples, and evaluation of PROs via a tablet and/or web-based collection system. There will not be procedures additional to what is specified in the SoA.

Other alternative locations: Procedures which could be done at an alternate location in very exceptional circumstances include, but are not limited to, ECGs and collections of blood and urine samples.

Data capture

In source documents and the CRF, the study site should capture the type of visit, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and PCs remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: ANA, anti-dsDNA, and anti-Sm antibody tests. The local laboratory must be qualified in accordance with applicable local regulations.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit (Visit 1) are valid for a maximum of 35 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 35 days from Visit 1, the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 35 days from Visit 1.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 35 days from screening Visit 1: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at screening Visit 1 to ensure participant eligibility at randomization Visit 2.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Screening (SoA)		
For this visit...	**Permitted Visit Types**	**Visit Interval Tolerance**
Screening (Visit 1)	on-site only	same as shown in SoA, but flexibility can be considered following consultation with, and with prior approval by, the sponsor

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immune deficiency syndrome
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
anti-dsDNA	anti-double stranded DNA
anti-HBc	antibody to hepatitis B core antigen
anti-HCV	antibodies to HCV
anti-Sm	anti-Smith antibodies
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guerin
BILAG 2004	British Isles Lupus Assessment Group 2004
blinding	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
CBD	cannabidiol
CDC	Centers for Disease Control and Prevention
CEC	clinical events committee
CFR	Code of Federal Regulations
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index

CMV	cytomegalovirus
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia – Suicide Severity Rating Scale
CT	computerized tomography
CTA	clinical trial agreement
CXR	chest x-ray
device deficiencies	equivalent to product complaint
DNA	deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders. 5th ed.
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eCOA	electronic Clinical Outcome Assessment
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
enroll/enrollment	Treatment assignment; the act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.

ERB	Ethics (or ethical) review board. An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human participants involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial participants.
ERCP	endoscopic retrograde cholangiopancreatography
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials, European clinical trials database
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
IAC	Internal Assessment Committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee; see "ERB"
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IGRA	interferon gamma release assay
IND	Investigational New Drug application

Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An analysis of clinical trial data by treatment group that is conducted before the primary outcome database lock. Also, an analysis comparing intervention groups at any time before the final reporting database is locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board; see "ERB"
ISA	intervention-specific appendix
ISA-SAP	statistical analysis plan for intervention-specific appendix
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
JAK	Janus kinase
LTBI	latent tuberculosis infection
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
MP-SAP	statistical analysis plan for the master protocol
MRCP	magnetic resonance cholangiopancreatography
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
PA	posterior–anterior

participant	Equivalent to Clinical Data Interchange Standards Consortium (CDISC) term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetics
PPD	purified protein derivative
PRO	patient-reported outcomes
PT-INR	prothrombin time, international normalized ratio
QIDS-SR16	16-Item Quick Inventory of Depressive Symptomatology - Self Report
QTc	corrected QT interval
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SoA	Schedule of Activities
TB	tuberculosis
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TE-ADA	treatment-emergent anti-drug antibody
TNF-α	tumor necrosis factor alpha
TST	tuberculin skin test
ULN	upper limit of normal

US	United States
WBC	white blood cell count
WHO	World Health Organization
WOCBP	women of childbearing potential

11. References

Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue. Measurement of fatigue in systemic lupus erythematosus: a systematic review. *Arthritis Rheum*. 2007;57(8):1348-1357. https://doi.org/10.1002/art.23113

Alexander BM, Ba S, Berger MS, et al.; GBM AGILE Network. Adaptive global innovative learning environment for glioblastoma: GBM AGILE. *Clin Cancer Res*. 2018;24(4):737-743. https://doi.org/10.1158/1078-0432.CCR-17-0764

[APA] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Publishing; 2013.

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71(9):1400-1412. https://doi.org/10.1002/art.40930

Barker AD, Sigman CC, Kelloff GJ, et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther*. 2009;86(1):97-100. https://doi.org/10.1038/clpt.2009.68

Bateman RJ, Benzinger TL, Berry S, et al.; DIAN-TU Pharma Consortium for the Dominantly Inherited Alzheimer Network. The DIAN-TU next generation Alzheimer's prevention trial: adaptive design and disease progression model. *Alzheimers Dement*. 2017;13(1):8-19. https://doi.org/10.1016/j.jalz.2016.07.005

[C-SSRS WWW] The Columbia Lighthouse Project. The Columbia Protocol for Research. Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide. Version 2.0. Accessed January 30, 2019. http://cssrs.columbia.edu/wp-content/uploads/ScoringandDataAnalysisGuide-for-Clinical-Trials-1.pdf

Cooper GS, Treadwell EL, St Clair EW, et al. Sociodemographic associations with early disease damage in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2007;57(6):993-999. https://doi.org/10.1002/art.22894

[FDA] Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing and labeling. Draft Guidance September 2020. Accessed March 23, 2021. https://www.fda.gov/media/78573/download

[FDA] Food and Drug Administration. Guidance for industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation; July 2009. Accessed March 23, 2021. https://www.fda.gov/media/116737/download

Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol*. 2002;29:288-291. PMID: 11838846.

Herbst RS, Gandara DR, Hirsch FR, et al. Lung master protocol (Lung-MAP)-a biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res*. 2015;21(7):1514-1524. https://doi.org/10.1158/1078-0432.CCR-13-3473

Kalunian K, Urowitz M, Isenberg D, et al. Clinical trial parameters that influence outcomes in lupus trials that use the systemic lupus erythematosus responder index. *Rheumatology (Oxford)*. 2018;57(1):125-133. https://doi.org/10.1093/rheumatology/kex368

Merrill JT, Manzi S, Aranow C, et al. Lupus community panel proposals for optimising clinical trials: 2018. *Lupus Sci Med*. 2018;5(1):e000258. https://doi.org/10.1136/lupus-2018-000258

Özel F, Argon G. The effects of fatigue and pain on daily life activities in systemic lupus erythematosus. *Agri*. 2015;27(4):181-189. https://doi.org/10.5505/agri.2015.38278

Rees F, Doherty M, Grainge MJ, et al. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology*. 2017;56:1945-1961. https://doi.org/10.1093/rheumatology/kex260

Ritchie CW, Molinuevo JL, Truyen L, et al. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. *Lancet Psychiatry*. 2016;3(2):179-186. https://doi.org/10.1016/S2215-0366(15)00454-X

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74(12):2107-2116. https://doi.org/10.1136/annrheumdis-2015-207841

Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med*. 2017;377(1):62-70. https://doi.org/10.1056/NEJMra1510062

Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis Care Res (Hoboken)*. 2014;66(4):608-616. https://doi.org/10.1002/acr.22173

Leo Document ID = 76e37930-98bd-4537-a25c-e36bb2014ad6

Approver: PPD

Approval Date & Time: 22-Sep-2021 13:01:06 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 22-Sep-2021 14:24:48 GMT

Signature meaning: Approved