Protocol J1P-MC-KFAJ(a)

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

NCT04433585

Approval Date: 19August2020

Title Page

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

Protocol Number: J1P-MC-KFAJ

Amendment Number: a

Compound: LY3471851

Study Phase: 2

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

Acronym: ISLAND-SLE

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Numbers

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
KFAJ Protocol	CCI [redacted]

Amendment [a]

This amendment occurred before any study participant was consented or dosed at any study site in Europe.

Overall Rationale for the Amendment:

The purpose of this protocol amendment is to correct typographical errors and clarify study procedures and statistical analysis plans in response to European regulatory agency feedback.

Table of Contents

1. Protocol Summary

1.1. Synopsis

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

Rationale: LY3471851 (also known as NKTR-358) is a polyethylene glycol (PEG)-conjugated recombinant human interleukin (IL)-2 (rhIL-2) with the capacity to promote the expansion and activation of regulatory T cells (Tregs) with relatively minimal effect on conventional T cells (Tcons). When compared to rhIL-2, PEGylation results in prolonged systemic exposure and improved binding to the high affinity IL-2 receptor most present on regulatory T cells (Tregs). In preliminary clinical studies, low-dose recombinant human IL-2 was shown to reverse IL-2 deficiency and the Treg deficit typically observed in patients with systemic lupus erythematosus (SLE) (von Spee-Mayer et al. 2016). Moreover, low-dose IL-2 therapy was associated with improvements in SELENA-SLEDAI and SLE Response Index (SRI-4 response) (He et al. 2016, He et al. 2020). Study J1P-MC-KFAJ (KFAJ) is a Phase 2 study to evaluate the efficacy and safety of LY3471851 in adult patients with SLE. Results of this study will be used to guide the dose selection for future studies and to further characterize the benefit/risk profile of LY3471851.

Objectives and Endpoints

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

	Week 24 achieve: • BILAG-based Composite Lupus Assessment (BICLA) response • SRI-4 response • Lupus Low Disease Activity State (LLDAS) Secondary objectives will be assessed using a composite estimand (as described above).
• To characterize the pharmacokinetics of LY3471851 in participants with SLE	LY3471851 plasma trough concentrations at Week 24

Abbreviations: BILAG = British Isles Lupus Assessment Group - 2004; Q2W = every 2 weeks; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI-4 = defined as a ≥4-point reduction in SLEDAI-2K score from baseline; SRI-4 = Systemic Lupus Erythematosus Responder Index-4.

Overall Design: Study J1P-MC-KFAJ (KFAJ) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study to evaluate the efficacy and safety of 3 dose levels of LY3471851 given via subcutaneous injection (SC) every 2 weeks (Q2W) versus placebo in adult study participants with at least moderately active SLE. The study duration is approximately 35 weeks over 3 required study periods:

- Screening period: beginning within 5 weeks before randomization
- Treatment period: 24 weeks, inclusive of the randomization visit to the last visit of this period, and
- Post-treatment follow-up period: minimally 6 weeks, with an additional 8 weeks for some participants.

An optional prescreening period precedes the required screening period.

Participants will maintain their usual standard-of-care medication regimen for SLE throughout the study. The maximum daily steroid dose allowed at entry will be prednisone 20 mg (or equivalent), which must be tapered to 10 mg daily (or equivalent) in time for the Week 12 assessments in order for the participant to be considered a responder.

Disclosure Statement: This is a parallel, 4-arm treatment study that is participant-blinded and investigator-blinded.

Number of Participants:

Approximately CCI [redacted] will be randomly assigned to study intervention.

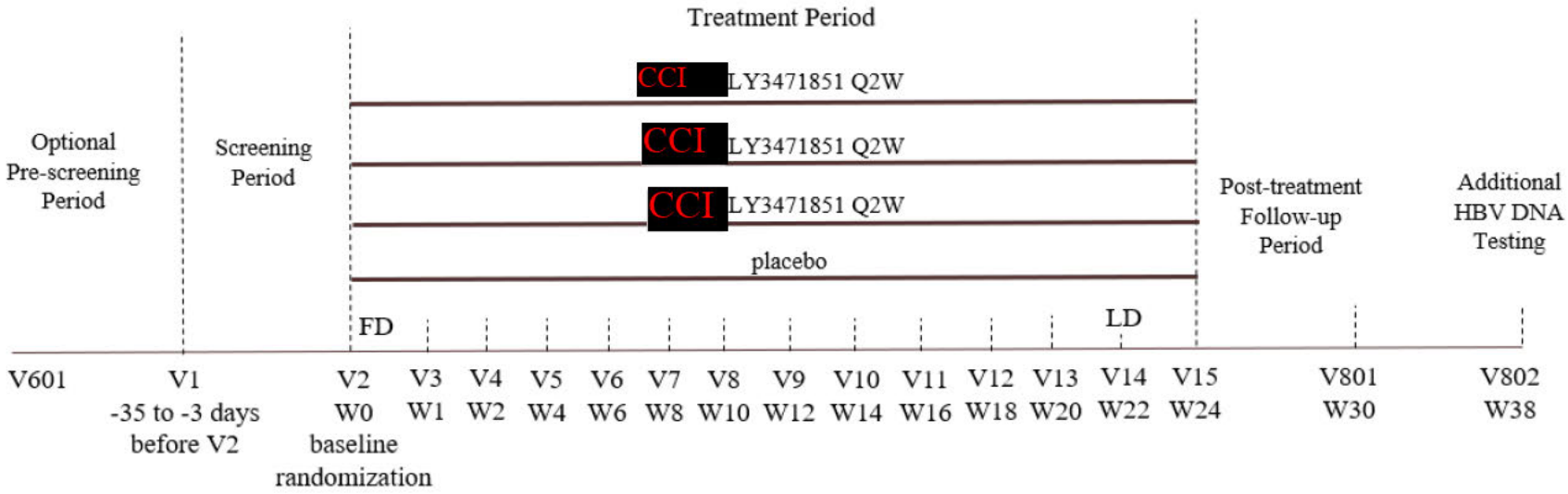
Intervention Groups and Duration:

Participants will be randomized in a 1:1:1:1 ratio CCI to receive one of the following study interventions:

- CCI LY3471851 Q2W
- CCI LY3471851 Q2W
- CCI LY3471851 Q2W, or
- placebo Q2W.

Data Monitoring Committee: No

1.2. Schema



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

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

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

1.3. Schedule of Activities (SoA)

Prescreening and screening periods of Study J1P-MC-KFAJ 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 from randomization		–5	
Study day		—	
Visit interval tolerance (days)		–35 to –3	
Fasting visit			No fasting in this period.
Informed consent (for prescreening only)	X		Central prescreening of ANA, CCI [redacted] is permitted after signing the prescreening ICF and can be performed before the participant signs the main KFAJ ICF (Section 4.1).
Informed consent (for Study KFAJ)		X	The KFAJ ICF must be signed before any required protocol-specific tests or required procedures are performed.
Inclusion and exclusion criteria, review and confirm		X	Participant eligibility must be reviewed and confirmed by an eligibility review committee prior to randomization.
Demographics	X	X	Collect at Visit 1 only if not already collected at Visit 601.
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: 1) any prior antimalarial or immunosuppressant therapy for SLE in the past 10 years (approved or investigational) that have now been discontinued, 2) any prior biologics or medications for immunologic disease in the past 24 weeks that have now been discontinued, and 3) any prior corticosteroids in the past 24 weeks that have now been discontinued.
Concomitant medications		X	
Adverse events (AEs)		X	AE collection begins when KFAJ ICF is signed (Section 8.3.1). CCI [redacted]
Substance use (alcohol, caffeine, tobacco use)		X	

Prescreening and screening periods of Study J1P-MC-KFAJ 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 from randomization		–5	
Study day		—	
Visit interval tolerance (days)		–35 to –3	
Fasting visit			No fasting in this period.
Physical Evaluation			
Vital signs		X	Blood pressure, body temperature, pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Physical examination		X	The complete physical exam will exclude pelvic, rectal, and breast exams and will include assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes (Section 8.2.2). The SLE symptom physical assessment is captured in the electronic tablet.
12-lead ECG (local)		X	
Chest x-ray (posterior-anterior view) (local)		X	Interpreted and reported by radiologist or pulmonologist. Not performed at screening if performed within 3 months before screening and if qualifying radiographs or equivalent imaging study and/or formal report are available for investigator's review. Lateral view may also be taken.
CCI [redacted]			
Clinician-Administered Questionnaires (Electronic)			
SLEDAI-2K		X	Collected via an electronic tablet device.
CCI [redacted]		[redacted]	[redacted]
Clinician-Administered Questionnaires (Paper)			
C-SSRS Screening/Baseline		X	Adapted for assessment of ideation and behavior categories only.
Self-harm Supplement Form		X	
Self-Harm Follow-Up Form		X	Required if triggered by the Self-Harm Supplement Form per instructions.

Prescreening and screening periods of Study J1P-MC-KFAJ 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 from randomization		–5	
Study day		—	
Visit interval tolerance (days)		–35 to –3	
Fasting visit			No fasting in this period.
Laboratory Tests and Sample Collections			
Hematology		X	
Clinical chemistry		X	
Urine total protein, urine creatinine, and urine protein/urine creatinine ratio (calculation)		X	
Urinalysis		X	
Estimated glomerular filtration rate (eGFR)		X	Calculated using the Modification of Diet in Renal Disease (MDRD) method.
Serum pregnancy		X	Only for women of childbearing potential (Section 8.2.5.1 and Appendix 10.4) and women with a history of tubal ligation. Central laboratory.
Follicle-stimulating hormone (FSH)		X	Required only to confirm "postmenopausal status" (Section 8.2.5.1 and Section 10.4.1).
Tuberculosis (TB) test		X	Participants who had a tuberculin skin test (TST) will return from 48 to 72 hours after placement to have their test results read (Section 8.2.6). Samples may be sent to central or local laboratory based on the type of test. A local laboratory must be qualified by local regulations.
HIV screening tests		X	
Hepatitis C virus (HCV) screening tests		X	HCV RNA will be measured to confirm positive hepatitis C virus antibody (Section 8.2.8).
Hepatitis B virus (HBV) screening tests		X	Includes testing for HBsAg and anti-HBc.
HBV DNA		X	Only for participants who are positive for anti-HBc at screening (Section 8.2.7).
Total immunoglobulins (IgG)		X	

Prescreening and screening periods of Study J1P-MC-KFAJ

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 from randomization		–5	
Study day		—	
Visit interval tolerance (days)		–35 to –3	
Fasting visit			No fasting in this period.
CCI [redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

Abbreviations: CCI [redacted]; C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; RNA = ribonucleic acid; CCI [redacted]; SF = short form; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; V = visit.

Treatment period of Study J1P-MC-KFAJ For early terminations that occur before the last visit in treatment period, see the activities listed for ETV in this table.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ETV	Comment
Weeks from Randomization	—	1	2	4	6	8	10	12	14	16	18	20	22	24	—	
Study day	1	8	15	29	43	57	71	85	99	113	127	141	155	169	—	
Visit interval tolerance (days)	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	—	
Fasting visit	X							X						X		
Inclusion and exclusion criteria, review and confirm	X															Participant eligibility must be reviewed and confirmed by an eligibility review committee prior to randomization.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	CCI [redacted]
Physical Evaluation																
Height	X															Without shoes.
Weight	X			X		X		X		X		X		X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Injection site assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Performed by independent injection site assessor before participant is seen by blinded site staff (Section 6.3, Section 8.2.11).

Treatment period of Study J1P-MC-KFAJ For early terminations that occur before the last visit in treatment period, see the activities listed for ETV in this table.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ETV	Comment
Weeks from Randomization	—	1	2	4	6	8	10	12	14	16	18	20	22	24	—	
Study day	1	8	15	29	43	57	71	85	99	113	127	141	155	169	—	
Visit interval tolerance (days)	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	—	
Fasting visit	X							X						X		
Symptom-directed physical examination				X		X		X		X		X		X	X	See Section 8.2.2. The SLE symptom physical assessment is captured in the electronic tablet.
12-lead ECG (local)								X						X	X	
Patient-Reported Outcomes (Electronic)																
CCI																
QIDS-SR16	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Administer before any clinical assessments.

Treatment period of Study J1P-MC-KFAJ For early terminations that occur before the last visit in treatment period, see the activities listed for ETV in this table.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ETV	Comment
Weeks from Randomization	—	1	2	4	6	8	10	12	14	16	18	20	22	24	—	
Study day	1	8	15	29	43	57	71	85	99	113	127	141	155	169	—	
Visit interval tolerance (days)	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	—	
Fasting visit	X							X						X		
CCI																
Clinician-Administered Questionnaires (Electronic)																
BILAG 2004	X			X		X		X		X		X		X	X	Collected via an electronic tablet device.
CCI																
Physician's Global Assessment (PGA) of Disease Activity – VAS	X			X		X		X		X		X		X	X	Collected via an electronic tablet device.
SLEDAI Flare Index	X			X		X		X		X		X		X	X	Collected via an electronic tablet device.
SLEDAI-2K	X			X		X		X		X		X		X	X	Collected via an electronic tablet device.
CCI																
Clinician-Administered Questionnaires (Paper)																
C-SSRS Since Last Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Adapted for the assessment of ideation and behavior categories only.

Treatment period of Study J1P-MC-KFAJ For early terminations that occur before the last visit in treatment period, see the activities listed for ETV in this table.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ETV	Comment
Weeks from Randomization	—	1	2	4	6	8	10	12	14	16	18	20	22	24	—	
Study day	1	8	15	29	43	57	71	85	99	113	127	141	155	169	—	
Visit interval tolerance (days)	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	—	
Fasting visit	X							X						X		
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Self-Harm Follow-Up Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.
Laboratory Tests and Sample Collections																
Hematology	X	X	X	X	X	X	X	X		X		X		X	X	
Clinical chemistry	X	X	X	X	X	X	X	X		X		X		X	X	
Lipid panel	X							X						X	X	For the fasting lipid panel, participants should not eat or drink anything but water for 12 hours before the visit. Fasting is not required at an ETV. If a participant attends these visits in a nonfasting state, the sample should still be collected. This will not be considered a protocol violation.
Urinalysis	X			X		X		X		X		X		X	X	
Urine total protein, urine creatinine, and urine protein/urine creatinine ratio (calculation)	X			X		X		X		X		X		X	X	

Treatment period of Study J1P-MC-KFAJ

For early terminations that occur before the last visit in treatment period, see the activities listed for ETV in this table.

Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ETV	Comment
Weeks from Randomization	—	1	2	4	6	8	10	12	14	16	18	20	22	24	—	
Study day	1	8	15	29	43	57	71	85	99	113	127	141	155	169	—	
Visit interval tolerance (days)	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	—	
Fasting visit	X							X						X		
Urine pregnancy (local)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	Only for women of childbearing potential (Section 8.2.5.1 and Appendix 10.4) and women with a history of tubal ligation.
HBV DNA								X						X	X	Only for participants who are positive for anti-HBc at screening (Section 8.2.7).

CCI

[redacted]

Treatment period of Study J1P-MC-KFAJ

For early terminations that occur before the last visit in treatment period, see the activities listed for ETV in this table.

Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ETV	Comment
Weeks from Randomization	—	1	2	4	6	8	10	12	14	16	18	20	22	24	—	
Study day	1	8	15	29	43	57	71	85	99	113	127	141	155	169	—	
Visit interval tolerance (days)	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	—	

[redacted]

CCI

Randomization and Dosing																
Randomization	X															
Dosing	X		X	X	X	X	X	X	X	X	X	X	X			No dosing at V3 or V15

Abbreviations: ACR = American College of Rheumatology; CCI [redacted] BILAG = British Isles Lupus Assessment Group; CCI [redacted] C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV = early termination visit; CCI [redacted] ;HBV = hepatitis B virus; IL = interleukin; CCI [redacted] QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology–Self Report; CCI [redacted] SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; CCI [redacted] V = visit; VAS = visual analog scale.

Post-treatment follow-up period of Study J1P-MC-KFAJ Visit 802 is only for randomized participants who were positive for anti-HBc at screening. All other participants will complete the study at V801.			
Visit number	V801	V802	Comment
Weeks from randomization	30 or ETV + 6 to 8 weeks (to ensure 8 weeks from last dose)	38 or ETV + 14 to 16 weeks (to ensure 16 weeks from last dose)	Visit 801 occurs at Week 30, 8 weeks after the last dosing visit at Week 22 for patients who complete the study. If required, Visit 802 occurs at Week 38, 16 weeks after the last dosing visit at Week 22 for patients who complete the study. For patients who terminate early, the interval between ETV and the post-treatment follow-up visit(s) should be adequate to ensure that 8 weeks have elapsed since last dose for Visit 801 and 16 weeks have elapsed since last dose for Visit 802.
Study day	211	267	
Visit interval tolerance (days)	±7	±7	
Fasting visit			No fasting in this period.
Concomitant medications	X	X	
Adverse events (AEs)	X	X	CCI [redacted]
Physical Evaluation			
Weight	X		
Vital signs	X	X	Blood pressure, body temperature, and pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Injection site assessment	X		Performed by independent injection site assessor before participant is seen by blinded site staff (Section 6.3, Section 8.2.11).
Symptom-directed physical examination	X	X	See Section 8.2.2.
Clinician-Administered Questionnaires (Paper)			
C-SSRS Since Last Visit	X	X	Adapted for the assessment of ideation and behavior categories only.
Self-Harm Supplement Form	X	X	
Self-Harm Follow-Up Form	X	X	Required if triggered by Self-Harm Supplement Form, per instructions.

Post-treatment follow-up period of Study J1P-MC-KFAJ Visit 802 is only for randomized participants who were positive for anti-HBc at screening. All other participants will complete the study at V801.			
Visit number	V801	V802	Comment
Weeks from randomization	30 or ETV + 6 to 8 weeks (to ensure 8 weeks from last dose)	38 or ETV + 14 to 16 weeks (to ensure 16 weeks from last dose)	Visit 801 occurs at Week 30, 8 weeks after the last dosing visit at Week 22 for patients who complete the study. If required, Visit 802 occurs at Week 38, 16 weeks after the last dosing visit at Week 22 for patients who complete the study. For patients who terminate early, the interval between ETV and the post-treatment follow-up visit(s) should be adequate to ensure that 8 weeks have elapsed since last dose for Visit 801 and 16 weeks have elapsed since last dose for Visit 802.
Study day	211	267	
Visit interval tolerance (days)	±7	±7	
Fasting visit			No fasting in this period.
Laboratory Tests and Sample Collections			
Hematology	X	X	
Clinical chemistry	X	X	
Urinalysis	X		
Urine pregnancy (local)	X	X	Only for women of childbearing potential (Section 8.2.5.1 and Appendix 10.4) and women with a history of tubal ligation.
CCI [redacted]			

Abbreviations: CCI [redacted] C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; V = visit.

2. Introduction

2.1. Study Rationale

LY3471851 (also known as NKTR-358) is a polyethylene glycol (PEG)-conjugated recombinant human interleukin (IL)-2 (rhIL-2) with the capacity to promote the expansion and activation of regulatory T cells (Tregs) with relatively minimal effect on conventional T cells (Tcons). When compared to rhIL-2, PEGylation results in prolonged systemic exposure and improved binding to the high affinity IL-2 receptor most present on regulatory T cells (Tregs). In preliminary clinical studies, low-dose recombinant human IL-2 was shown to reverse IL-2 deficiency and the Treg deficit typically observed in patients with systemic lupus erythematosus (SLE) (von Spee-Mayer et al. 2016). Moreover, low-dose IL-2 therapy was associated with improvements in SELENA-SLEDAI and SLE Response Index (SRI-4 response) (He et al. 2016, He et al. 2020).

Study J1P-MC-KFAJ (KFAJ) is a Phase 2 study to evaluate the efficacy and safety of LY3471851 in adult patients with SLE. Results of this study will be used to guide the dose selection for future studies and to further characterize the benefit/risk profile of LY3471851.

2.2. Background

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 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. 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 (SDI) (Cooper et al. 2007).

The standard-of-care for SLE varies widely and currently includes the use of corticosteroids, nonsteroidal anti-inflammatory drugs (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). 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). Patients with SLE need better treatment options.

The dysfunction in Treg cell biology has been proposed as a key defect in SLE, leading to the breakdown of immune self-tolerance (Ohl and Tenbrock 2015). The goal of LY3471851 therapy is to increase Treg number and function, with a minimal effect on Tcons and natural killer (NK) cells.

2.3. Benefit/Risk Assessment

The Investigator's Brochure (IB) designates local injection site reactions (ISR) as an identified risk of LY3471851, based on reports of primarily low-grade injection site reactions in the Phase 1 studies. Reports of cytokine release syndrome (CRS) and clinical symptom complex attributed to elevated cytokine levels were of Grade 1 severity. Eosinophilia without evidence of target organ damage was observed in some participants in the Phase 1 study in SLE. The safety findings from Phase 1 studies showed no evidence of adverse events characteristic of capillary leak syndrome, increased risk of infection, worsening or new onset autoimmune disease, cardiac disorders (cardiac rhythm disturbances, angina, or myocardial infarction), pulmonary disorders, central nervous system effects, or severe anemia/thrombocytopenia known to be associated with high-dose IL-2 (aldesleukin).

To minimize study participant risk in Study KFAJ, enrolled participants will receive study drug doses in the clinic to enable appropriate pre-dose safety assessments and post-dose monitoring. The routine safety assessments include physical examinations, clinical safety laboratory tests (including hematology and chemistry), suicidality/self-harm and depression evaluations, and collection of vital signs and spontaneously reported adverse events. The study design includes a post-treatment follow-up period with at least one study visit for safety assessments.

CCI [redacted]

In addition, based on observations of treatment-related biliary hyperplasia noted in nonclinical studies, as described in the IB, investigators should be aware of the possible occurrence of treatment-related hepatobiliary changes that could possibly include cholestasis. The protocol includes hepatic-related laboratory testing to support intensive monitoring for symptoms and physical signs suggestive of liver or biliary toxicity, including jaundice, scleral icterus, and pruritis. See also Section 8.2.9.

Ongoing study-level monitoring of safety data will be performed, as described in Section 8.2.

CCI [redacted]

The efficacy of LY3471851 in SLE has not been established. Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

In summary, in the context of the cumulative knowledge for LY3471851, the benefit/risk balance for this study is assessed to be acceptable for testing in Phase 2.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3471851 may be found in the IB.

3. Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
• To determine whether treatment with LY3471851 Q2W is superior to placebo in reducing the signs and symptoms of SLE as measured by SLEDAI-4	The study will compare LY3471851 with placebo in participants with SLE. The primary comparison of interest is the difference in proportion of participants who achieve SLEDAI-4 response at Week 24. The primary comparison will be assessed using a composite estimand where the intercurrent events of premature discontinuation and use of prohibited medication are part of the response definition.
Secondary	
• To determine whether treatment with LY3471851 Q2W is superior to placebo in reducing other measures of signs and symptoms of SLE	The study will compare LY3471851 with placebo in participants with SLE. Secondary comparisons of interest are the difference in proportion of participants who at Week 24 achieve: • BILAG-based Composite Lupus Assessment (BICLA) response • SRI-4 response • Lupus Low Disease Activity State (LLDAS) Secondary objectives will be assessed using a composite estimand (as described above).
• To characterize the pharmacokinetics of LY3471851 in participants with SLE	LY3471851 plasma trough concentrations at Week 24
[redacted]	

Abbreviations: BILAG = British Isles Lupus Assessment Group - 2004; CCI [redacted] Q2W = every 2 weeks; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI-4 = defined as a ≥4-point reduction in SLEDAI-2K score from baseline; CCI [redacted] SRI-4 = Systemic Lupus Erythematosus Responder Index-4.

4. Study Design

4.1. Overall Design

Study KFAJ is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study to evaluate the efficacy and safety of LY3471851 in adult study participants with at least moderately active SLE. The study has 3 required study periods and an optional prescreening period. A schematic of the study design is presented in Section 1.2.

Optional prescreening period

Study participants must have positive antinuclear, CCI [redacted] at Visit 1 to be eligible for randomization at Visit 2. The optional prescreening visit (Visit 601) is intended for those investigators who opt for central laboratory assessment of the prospective participant's antinuclear antibodies (ANA), CCI [redacted] status before full screening activities are initiated.

If opted for, the prescreening determination of ANA, CCI [redacted] status will be described in an appropriate informed consent form (ICF). Informed consent for the prescreening activities will be obtained, a participant identification number will be assigned, and samples for specified laboratory tests will be obtained. The optional prescreening visit can be repeated 2 times (no more) per participant, with a minimum of 4 weeks between visits. Repeated visits in the prescreening visit will not require re-consenting or assignment of a new participant identification number.

> Note: If the optional prescreening is opted for, central laboratory testing for ANA, CCI [redacted] is still required as part of the screening procedures conducted at Visit 1. Participants with negative results at Visit 1 will not be eligible for enrollment, despite positive values in prescreening.

Screening period

The required screening period begins with Visit 1, which occurs within 5 weeks before the planned randomization visit. If the participant had an optional prescreening visit, an assessment of ANA, CCI [redacted] will be repeated at Visit 1 for confirmation of study eligibility. The main Study KFAJ ICF will be signed before Visit 1 procedures are performed. 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.

Participants found to be eligible according to all of the study entry criteria will be randomly assigned in a 1:1:1:1 ratio to receive one of the following study interventions:

- CCI [redacted] LY3471851 every 2 weeks (Q2W)
- CCI [redacted] LY3471851 Q2W
- CCI [redacted] LY3471851 Q2W, or
- placebo Q2W.

CCI [redacted] Study interventions will be administered via subcutaneous injection (SC).

Double-blind treatment period

Randomized participants will begin the double-blind, placebo-controlled, 24-week treatment period at Visit 2. Participants will receive the first dose of the assigned study intervention at that visit and will continue to receive doses through the last scheduled dosing visit specified in the Schedule of Activities (SoA, Section 1.3). Participants will maintain their usual standard-of-care medication regimen for SLE and for other diseases throughout the study, unless these medication regimens are specifically excluded by the study entry criteria. Safety and efficacy assessments and laboratory sample collections will be performed as specified in the SoA.

Follow-up period

All participants will have a post-treatment follow-up visit (Visit 801) for safety assessments. Randomized participants who were positive for hepatitis B core antigen (anti-HBc) at screening will have one additional post-treatment follow-up visit (Visit 802).

Early discontinuation

Participants who permanently discontinue the study drug early or withdraw from the study (Section 7) will undergo early termination procedures, including an early termination visit (ETV) and the post-treatment follow-up visits specified in the SOA.

4.2. Scientific Rationale for Study Design

SLEDAI-4 response as the primary endpoint

The primary endpoint is the proportion of participants who achieve a SLEDAI-4 response at Week 24 (Section 8.1.1). The selection of SLEDAI-4 for the primary endpoint measure was based on analyses from 2 recent SLE Phase 3 studies involving more than 2200 patients in a similar patient population (Isenberg et al. 2016; Merrill et al. 2016). The purpose of those analyses was to characterize the clinical signs and symptoms most responsible for achieving responder status with Systemic Lupus Erythematosus Responder Index-5 (SRI-5), and then to use this information to design a more efficient study with clinically relevant endpoints (Kalunian et al. 2018). The primary endpoint of those 2 recent studies required a 5-point reduction in SLEDAI with no worsening in British Isles Lupus Assessment Group (BILAG) score or Physician's Global Assessment of Disease Activity (PGA). The analyses found that fewer than 1% of the study participants failed on SRI-5 due to BILAG or PGA worsening after achieving a ≥5-point reduction in SLEDAI. Also, in the belimumab phase 3 SLE trials (as reported in Arthritis Advisory Committee meeting briefing document 2010), the proportion of patients with a ≥4-point reduction in SLEDAI that failed to achieve a Systemic Lupus Erythematosus Responder Index-4 (SRI-4) due to worsening of the BILAG or PGA ranged from 0.3% to 2.2% (Kalunian et al. 2018). These data provide a rationale to focus on SLEDAI as the primary driver of clinical response. A 4-point reduction in SLEDAI is considered clinically meaningful and serves as the basis for the primary endpoint of SLEDAI-4 (Gladman et al. 2000).

Appropriateness of study population

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 patients who are representative of the general population of patients with at least moderately active SLE as defined by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) ≥6 during screening and ≥4 for clinical features at randomization before administration of study drug. This SLEDAI cutoff has been used in other Phase 2 studies of SLE (van Vollenhoven et al. 2018; Wallace et al. 2018).

Choice of control and number of treatment groups

A double-blind, placebo-controlled design limits bias for both participant assessments and investigator assessments and enables a clearer interpretation of the effects of active drug. The selection of placebo as a comparator for this study is warranted because there are few approved therapies for SLE and because study participants will be permitted to receive concomitant standard-of-care therapies. The multiple active dose levels will allow for an evaluation of safety and efficacy across a broad dose range and so provide information to guide dose selection for future studies.

Duration of treatment period and post-treatment follow-up

Evaluation of measures of efficacy at the Week 24 time point is consistent with the duration of treatment at the primary endpoint for proof-of-concept studies of other interventions for SLE (Furie et al. 2017; van Vollenhoven et al. 2018; Wallace et al. 2018).

In longer studies, SLE efficacy outcomes at Week 24 are similar to those observed at Week 52, which is the time point typically used for registration studies (Furie et al. 2011; Navarra et al. 2011; Isenberg et al. 2016; Merrill et al. 2016). Clinically meaningful effects were observed earlier than 24 weeks in open-label SLE studies of low-dose IL-2 formulations (He et al. 2016 [rhIL-2^{Ser125}]; Rosenzwajg et al. 2019 [aldesleukin and ILT-101]), which are hypothesized to work through a mechanism of action similar to that of LY3471851.

A post-treatment study visit will occur at Week 30, which is 8 weeks after the last dose of investigational product and corresponds to approximately 5 half-lives.

Optional prescreening period

An optional prescreening period 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.

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 these 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

Dose selection

The doses were selected based on evaluation of clinical safety, pharmacokinetic (PK), and pharmacodynamic (PD) data from a single-ascending dose study in healthy volunteers (SAD, Study 16-358-01), a multiple-ascending dose study in SLE patients (MAD, Study 17-358-02), and on nonclinical toxicology data.

The available clinical safety data, CCI [redacted] supports continued development over a longer time course in Phase 2, given the safety monitoring planned for individual participants and the planned safety data reviews (Section 8.2).

The lowest dose CCI [redacted] is predicted to achieve exposures that are within the range of exposures achieved with the CCI [redacted] doses previously administered in the SAD and MAD studies. These doses were associated with pharmacological effects. For example, up to a CCI [redacted] from baseline was observed in the percentage of CD25^{bright} Tregs, with a similar fold change in absolute numbers of CD25^{bright} Tregs reported.

The highest dose CCI [redacted] is predicted to achieve exposures that are similar to a dose of CCI [redacted] the highest dose tested in the MAD study. This dose was associated with pharmacological effects; increases in CD25^{bright} Tregs and total Tregs were observed at this dose. An approximate CCI [redacted] increase from baseline was observed in the absolute numbers of CD25^{bright} Tregs reported, which did not return to baseline between doses. The numbers of NK cells were highly variable across patients, with an increase in the absolute numbers of NK cells observed CCI [redacted] CCI [redacted]

An intermediate dose CCI [redacted] will also be evaluated. This dose is predicted to achieve exposures that are similar to a dose CCI [redacted] tested in both the SAD and the MAD studies. In the MAD study, the CCI [redacted] dose was associated with increases in CD25^{bright} Tregs and total Tregs; an approximate CCI [redacted] increase from baseline was observed in the absolute numbers of CD25^{bright} Tregs reported after each of the three doses, which did not return to baseline between doses. There was minimal effect on absolute numbers of NK cells at this dose level.

CCI [redacted]

4.4. End-of-Study Definition

A participant is considered to have completed the study if he or she has completed all required periods of the study, including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

The “end of the study” is defined as the date of the last visit or last scheduled procedure shown in the SoA for the last participant in the study globally.

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. 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, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Participant characteristics

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

Note: Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 10.4.

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 met at least 4 of the 11 Revised Criteria for Classification of Systemic Lupus Erythematosus according to the 1997 Update of the 1982 ACR (Tan et al. 1982; Hochberg 1997) before randomization.

[5] Have a positive ANA (titer ≥1:80) and/or a positive CCI [redacted] 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, CCI [redacted] during the screening period, see Section 5.4.1.

[6] Have a SLEDAI-2K score ≥6 at screening (Visit 1) and clinical SLEDAI-2K score ≥4 at randomization (Visit 2).

[7] Have active arthritis and/or active rash as defined by the SLEDAI-2K at screening and at randomization.

5.2. Exclusion Criteria

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

Corticosteroid use

[8] 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).

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

[10] Have received parenteral (that is, intravenous or intramuscular) corticosteroids within 12 weeks before randomization (Visit 2) or are expected to require parenteral corticosteroids during the study.

Other prior or concomitant therapy

[11] Have started treatment with or adjusted the dosage of NSAIDs intended for treatment of signs and symptoms of SLE within 2 weeks before randomization (Visit 2).

[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, 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 12 weeks before randomization (Visit 2).

[15] Have received an oral Janus kinase (JAK) inhibitor, including but not limited to baricitinib, tofacitinib, and upacitinib, within 12 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 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) 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 12 weeks of screening (Visit 1), or intend to receive a live vaccine during the study, or plan to receive such vaccine within 8 weeks of completing treatment in this study.

[21] Have received a Bacillus Calmette-Guerin (BCG) vaccination or treatment within 12 months 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 of completing treatment in this study.

[22] Have participated within the last 30 days in a clinical study involving an investigational product. 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 Study KFAJ.

[23] Have received treatment with aldesleukin or other IL-2–related treatment.

Current or historical infections

[24] 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 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.

[25] Have had, within 12 weeks before randomization (Visit 2), any of the following types of infection:

- Serious (requiring hospitalization, and/or intravenous or equivalent oral antibiotic treatment),
- Opportunistic (as defined in Winthrop at 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 and/or genital herpes may be considered for enrollment if discussed with the sponsor's designated medical monitor and if other eligibility criteria are met.

[26] Have human immunodeficiency virus (HIV) infection.

[27] Have a current infection with hepatitis B virus (HBV DNA) (that is, positive for hepatitis B surface antigen [HBsAg] and/or PCR positive for HBV DNA).

[28] Have a current infection with hepatitis C virus (that is, positive for HCV RNA).

[29] Have current or past history of active tuberculosis (TB) (see Section 8.2.6).

[30] Have or have had latent TB infection (LTBI) that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization and/or the United States Centers for Disease Control and Prevention, unless such treatment is underway (see Section 8.2.6).

Other current or historical medical conditions

[31] 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.

[32] Have active severe central nervous system lupus including aseptic meningitis, cerebral vasculitis, demyelinating syndrome, myelopathy, acute confusional state, psychosis, acute inflammatory demyelinating polyradiculoneuropathy, cranial neuropathy, plexopathy, status epilepticus, or cerebellar ataxia within 24 weeks before randomization (Visit 2).

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

[34] 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, or psoriatic arthritis in the 12 weeks before randomization (Visit 2).

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

[35] 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.

[36] 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.

[37] 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.

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

[39] Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (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 4 weeks prior to randomization (Visit 2).

[40] Have a history of lymphoproliferative disease; or have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly (other than primarily because of SLE); or have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years.

Exceptions:

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

[41] 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 Lilly or its designee, would pose an unacceptable risk to the participant.

[42] 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 post-treatment hypersensitivity reactions, including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis.

Diagnostic assessments or abnormal laboratory values

[43] Have any of the following specific abnormalities on screening laboratory tests:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times upper limit of normal (ULN)
- total bilirubin level (TBL) ≥1.5 times ULN
- hemoglobin <8.5 g/dL (<85.0 g/L)
- total white blood cell count (WBC) <2500 cells/µL (<2.50 × 10^3/µL or <2.50 GI/L)
- eosinophilia (absolute eosinophil count >3000 cells/µL (>3.0 × 10^3/µL or >3.0 GI/L)
- neutropenia – absolute neutrophil count (ANC) <1000 cells/µL (<1.00 × 10^3/µL or <1.00 GI/L)
- lymphopenia – absolute lymphocyte count (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)
- estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease [MDRD]) <50 mL/min/1.73 m^2 (FDA 2010).

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

[44] Have known hypogammaglobulinemia or a screening immunoglobulin G (IgG) level <565 mg/dL (<5.65 g/L).

[45] Have other abnormal laboratory values at screening that, in the opinion of the investigator, indicate unacceptable risk for the participant's safety in the study.

[46] Have screening electrocardiogram (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

[47] Have previously been randomized in this study or have received LY3471851 in any previous study.

[48] 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

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

[50] 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.

[51] Have a history of chronic alcohol abuse, intravenous (IV) drug abuse, or other illicit drug abuse within 1 year before screening.

Note: Marijuana is considered an illicit drug for the purposes of this study, regardless of local laws. Cannabidiol (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.

[52] 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.

[53] Are women who intend to become pregnant or breastfeed at any time in the study.

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

[55] 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.

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

Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (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 once during the screening period to determine a participant's eligibility for randomization:

- tests for ANA,CCI [redacted]
- tests related to lupus nephritis, and
- clinical chemistry, hematology, calculation of estimated glomerular filtration rate.

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 **one 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 **one 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 chest x-ray (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 a study participant according to the study protocol.

6.1. Study Interventions Administered

Study interventions

This study involves 3 dose levels of LY3471851 and placebo, as shown.

Treatment Name	LY3471851	Placebo
Dosage Formulation	CCI	0.9% sodium chloride
Dosage Levels		not applicable
Routes of Administration	subcutaneous injection	subcutaneous injection
Dosing Instructions	Dosing every 2 weeks	Dosing every 2 weeks

LY3471851 drug product will be provided as a sterile solution in a vial for SC injection. The drug product vials will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the investigation product (IPs). Dosing solutions will be prepared at each clinical study site by an unblinded pharmacist (or other unblinded qualified individual) and loaded into syringes for SC dosing (see Section 6.3 on blinding). When the dosing solutions are prepared according to the provided instructions, it will not be possible to distinguish LY3471851 from placebo.

Monitoring after dose administration

All participants should be monitored for 30 minutes or longer after dosing, according to investigator practice or local standard of care.

Packaging and labeling

LY3471851 will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice (cGMP). Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

6.2. Preparation/Handling/Storage/Accountability

The Pharmacy Manual provides instructions for the preparation, handling and storage of LY3471851 drug product and placebo, and site responsibility and accountability for the administered products.

Investigators should consult the information provided in the Pharmacy Manual or the label for specific preparation and administration information, including warnings, precautions, contraindications, adverse reactions, and dose modifications.

Preparation

The IPs must be prepared by an unblinded pharmacist (or other unblinded qualified individual) who is not involved in any other study-related procedures.

Handling and storage

Follow the storage and handling instructions for the IP as noted in the IP packaging. The handling and storage information for the administered product is located in the Pharmacy Manual.

Site responsibilities and accountability

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

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. 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 site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is 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 are provided in the Pharmacy Manual.

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 IP dispensing and collection, and
- returning all unused medication to Lilly or its designee at the end of the study.

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

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 treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

Unblinded pharmacist

Investigators and all individuals involved in administering the blinded treatment or performing assessments will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved party (unblinded pharmacist or other unblinded qualified individual) will be responsible for the preparation and dispensation of all study intervention. Blinded site personnel will administer the study intervention to the participant.

Independent assessor for injection site reactions

At every visit following the first dose and prior to any blinded study activity, an independent Injection Site Reaction (ISR) assessor who is not involved with other study procedures will evaluate each participant for the presence of ISRs. If the participant presents with symptoms of an ISR (see Section 8.2.11), the ISR assessor will examine the impacted areas and record the information in the electronic case report form (eCRF).

Whether an ISR is present or not, the ISR assessor will use a bandage (or similar material) to cover the anatomical area where the participant received his or her last dose. The purpose of covering this area is to minimize bias when blinded study personnel conduct other study assessments, given the known frequency of ISRs with the molecule.

Emergency unblinding

Emergency unblinding for adverse events 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.

If a participant's study treatment assignment is unblinded to blinded site personnel performing assessments, including the investigator, or to the participant, the participant must be discontinued from study drug, unless the investigator obtains specific approval from the sponsor's medical monitor for the participant to continue (Section 7.1.1).

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. 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.

In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor's clinical research physician for the participant to continue in the study.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee at the study site, under medical supervision. The date and time of each dose administered in the clinic will be

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

6.5. Concomitant Therapy

Participants will be instructed to consult the investigator or other appropriate study site personnel before taking any new medications or 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 enrollment 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 concomitant therapies of special interest, dosage information will also be collected as well as reason for use and route and dates of administration.

Allowed concomitant therapy

Participants will maintain their usual medication regimen for SLE and for any other diseases throughout the study unless specifically excluded in the protocol (Section 5.2). Doses must be stable prior to randomization, as stated in the exclusion criteria. 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,
- a single corticosteroid.

Dose adjustment for NSAIDs, antimalarials, and immunosuppressants

Doses of NSAIDs intended for treatment of signs and symptoms of SLE, antimalarials, and immunosuppressants should not be adjusted during the study's double-blind treatment period. Participants who require initiation or increase in dosage of NSAIDs for treatment of signs and symptoms of SLE, or of antimalarials, or of immunosuppressants after randomization may remain in the study and continue receiving study drug.

Dose adjustment for corticosteroids

See Section 6.5.1.

6.5.1. Corticosteroid Management Program

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

- Participants are restricted to prednisone ≤20 mg per day (or equivalent) at randomization (Visit 2), having been on stable doses for at least 2 weeks prior to randomization.
- Following randomization, the dose of prednisone (or equivalent) should not be increased above the participant's background level.
- Participants on >10 mg per day are required to taper their dose to ≤10 mg per day by Week 12 to be considered **responders**.
- The corticosteroid doses should not be changed after Week 18.
- Participants with intolerable or exacerbating disease are allowed access to standard-of-care therapy, including increasing the dose of prednisone (or equivalent). Such participants are allowed to remain in the study and continue receiving study drug, but they will be considered **nonresponders** for the efficacy analyses from the time of the medication change onward.

Guidance on corticosteroid tapering

The following guidance on corticosteroid tapering is provided for participants taking >10 mg prednisone (or equivalent) at baseline.

- Steroid tapering should begin no sooner than 4 weeks after randomization.
- Tapering should include a stepwise reduction in 2.5 mg/d to 5 mg/d increments, with each step reduction occurring at 2-week intervals. Thus, the stepwise reduction will occur in intervals that are consistent with the visit schedule.
- Participants who do not tolerate a reduction can increase the dose up to, but not exceeding, the dose at randomization.

Under this schedule, a participant on the highest allowed dose of 20 mg per day at randomization would taper his or her steroid dose in 2.5 mg per day increments at 2-week intervals to achieve the target of ≤10 mg per day in time for the assessments at Week 12.

Participants who are taking ≤10 mg prednisone (or equivalent) at baseline may have their dose tapered at the discretion of the investigator. However, the corticosteroid doses should not be changed after Week 18.

These recommendations recognize that there is variability in how corticosteroids are administered. The intent is to allow investigators flexibility in how corticosteroids are tapered for individual participants, provided that the participants reach the goal of ≤10 mg per day in time for the assessments at Week 12.

Concomitant therapy after permanent discontinuation of study drug

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

6.6. Dose Modification

Modification of the dose of the study intervention is not permitted in this study.

6.7. Intervention after the End of the Study

LY3471851 will not be available to participants following completion of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

In rare instances, it may be necessary for a participant to permanently discontinue study drug.

These sections describe reasons for a participant's

- permanent or temporary discontinuation of study drug (Section 7.1), or
- discontinuation (withdrawal) from the study (Section 7.2).

Discontinuation of specific sites or the trial as a whole ("stopping rules") are handled as part of regulatory, ethical, and trial oversight considerations in Appendix 10.1, Section 10.1.9.

7.1. Discontinuation of Study Intervention

Study drug may be permanently discontinued or temporarily withheld during the study.

Participants who permanently discontinue study drug early will undergo early termination procedures, which include

- an early termination visit (ETV)

  AND,

- post-treatment follow-up visits, as shown in the SOA.

7.1.1. Criteria for Permanent Discontinuation of Study Drug

Data collection and safety follow-up when study drug is permanently discontinued

If study drug is permanently discontinued, the participant will remain in the study to have an ETV and post-treatment follow-up visits, as shown in the SoA (Section 1.3).

See the SoA for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed. Safety follow-up is as outlined in the SoA (Section 1.3), Section 8.2 ("Safety Assessments), CCI [redacted] of the protocol.

The presence or absence of a clinically significant ISR will not unblind participants and is therefore not a protocol deviation.

Criteria for permanent discontinuation of study drug

Possible reasons for permanent discontinuation of study drug include, but are not limited to, the following:

Participant decision

- The participant requests to discontinue the study drug.

Pregnancy

- The participant becomes pregnant during the study (see Section 8.2.5.1).

Safety considerations

- The participant develops any of the following conditions during the study:
  - malignancy (except for successfully treated basal or squamous cell skin carcinoma)
  - HIV/acquired immune deficiency syndrome (AIDS) infection
  - active TB infection or untreated LTBI (Section 7.1.2; Section 8.2.6)
  - HCV RNA positive (Section 8.2.8)
  - HBV DNA positive and clinical assessment consistent with HBV reactivation

    Note: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification (Section 7.1.2; Section 8.2.7). 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 drug. Timing of discontinuation from study drug 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.
- The participant answered yes" to Question 4 or Question 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.

  Note: A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.
- The investigator, after consultation with the sponsor's designated medical monitor, determines that a systemic hypersensitivity reaction has occurred and is related to study drug administration.
- The participant has any of the following results on 2 consecutive samples taken at least 48 hours, but no more than 1 week, apart.
  - Total WBC <1000 cells/µL
  - ANC <500 cells/µL
  - ALC <200 cells/µL
  - Hemoglobin <6.5 g/dL
- The participant develops CRS. In consultation with the Lilly medical monitor, if an adverse event is deemed possibly or probably due to CRS based on the details and severity of clinical signs and symptoms, time course of symptom onset relative to study drug administration, and if possible, a cytokine panel from a blood sample obtained at the time of the event, the participant will be discontinued from study treatment, and will continue safety follow-up.
- The participant develops hypereosinophilia.
  - Participants with absolute eosinophil counts >1500 cells/µL and signs and/or symptoms of target organ involvement that is not consistent with lupus and/or with the

participant's lupus and medical history will be discontinued from study drug in consultation with the medical monitor. Participants will undergo appropriate medical evaluation, which should take into account the participant's known lupus and past medical history according to the participant's history and medical records, including previous imaging, biopsies and laboratory findings. Evaluation of target organ involvement will involve additional diagnostic tests as appropriate, including laboratory tests, imaging (for example, echocardiogram, CXR, computed tomography [CT] scan) and biopsies. New onset cardiac, pulmonary, and skin findings in the setting of peripheral eosinophilia will be considered as target organ involvement, unless attributable to other causes.

- Asymptomatic participants with an absolute eosinophil count >5000 cells/µL should have a repeat measurement to confirm the count. If the count is confirmed, the participant will be permanently discontinued from study drug and undergo appropriate medical evaluation.

- The participant has an adverse event or a SAE or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits the discontinuation of the study drug and appropriate measures being taken.

Hepatic event or liver test abnormality

- Participants who are discontinued from study drug because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic eCRF packet. Discontinuation of study drug because of abnormal liver tests should be considered by the investigator when a participant meets one of the following conditions after consultation with the sponsor's designated medical monitor (see Section 8.2.9).
  - ALT or AST >8 times ULN
  - ALT or AST >5 times ULN sustained for more than 2 weeks
  - ALT or AST >3 times ULN and TBL >2 times ULN or international normalized ratio (INR) >1.5
  - 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%)
  - alkaline phosphatase (ALP) >3 times ULN
  - ALP >2.5 times ULN and TBL >2 times ULN, or
  - ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Other reasons

- Unblinding: If an investigator, blinded site personnel who are performing assessments, or participant is unblinded to a participant's treatment assignment, the participant must be discontinued from the study drug and continue to post-treatment follow-up. In cases where there are ethical reasons to have the participant continue on study drug, the investigator must obtain specific approval from the sponsor's designated medical monitor for the participant to continue.

7.1.2. Criteria for Temporary Interruption (Withholding) of Study Drug

7.1.2.1. Infection-Related Criteria for Temporary Withholding of Study Drug

Temporary withholding of study drug is required for the development of any of the following infection-related criteria during the study:

- Serious or opportunistic infections, as defined in Exclusion Criteria (Section 5.2). Study drug is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment (exception for LTBI, noted below).
- Participants diagnosed with LTBI during the study are to be permanently discontinued from study drug unless the participant is a candidate for LTBI treatment, and is treated for LTBI as follows:
  - Study drug is temporarily withheld for at least the first 4 weeks of LTBI treatment.
  - After receiving at least 4 weeks of appropriate LTBI therapy (as per World Health Organization and/or the United States Centers for Disease Control guidelines), if there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance, study drug may be resumed.
  - The participant must complete appropriate LTBI therapy to remain eligible to receive study drug.
- 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 drug (Section 7.1).

7.1.2.2. Other Criteria for Temporary Withholding of Study Drug

In some circumstances, it may be advisable to temporarily interrupt study drug as a result of adverse events or abnormal laboratory values that have an unclear relationship to study drug. Except in an emergency, the investigator should consult with sponsor's designated medical monitor whenever possible before temporarily withholding study drug for reasons not specified in Section 7.1.2.1 above.

7.2. Participant Discontinuation/Withdrawal from the Study

Participant discontinuation (withdrawal from the study) is expected to be uncommon.

A participant will withdraw from the study in the following circumstances:

- at any time at his or her own request, or at the request of his or her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons

- if the participant enrolls in any other clinical study involving an investigational medicinal product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that 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.

Data collection and follow-up for participants who discontinue the study

At the time of discontinuing from the study, an ETV should be conducted, if possible, as shown in the SoA (Section 1.3). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study drug and from the study.

No follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

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.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor's clinical research physician agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor's clinical research physician to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational medicinal product. Safety follow-up is as outlined in the SoA (Section 1.3), Section 8.2 ("Safety Assessments), and Section 8.3 ("Adverse Events and Serious Adverse Events") of the protocol.

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 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 (Section 1.3). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1. Efficacy Assessments

Efficacy and patient-reported outcome assessments are described in Appendix 10.7. The primary and secondary efficacy endpoints are described in the following subsections.

The self-reported questionnaires will be administered in countries where the questionnaires have been translated into the native language of the region and linguistically validated. Any outcome measures that are participants' self-assessments should be completed before any clinical examinations are performed.

All patient-reported and clinician-reported efficacy assessments will be captured on an electronic tablet collected at site visits.

8.1.1. Primary Efficacy Outcome Measure: SLEDAI-4

The primary efficacy endpoint is the proportion of participants who achieve a SLEDAI-4 response at Week 24. A SLEDAI-4 response is defined as a ≥4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score from baseline. To be considered a SLEDAI-4 responder, participants must complete the 24-week treatment period and comply with concomitant medication rules (Section 9.4.1). Section 4.2 provides the rationale for the selection of SLEDAI-4 as the primary efficacy measure.

8.1.2. Secondary Efficacy Outcome Measures

8.1.2.1. British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA)

The BILAG-based Composite Lupus Assessment (BICLA) is a composite index used to assess disease activity in SLE. A BICLA response is defined as follows:

- Reduction of all baseline BILAG-2004 A to B or C or D; and baseline BILAG-2004 B to C or D; and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
- No worsening from baseline in SLEDAI-2K, where worsening is defined as any increase from baseline in SLEDAI-2K
- No worsening from baseline in participants' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA visual analogue scale (VAS)
- No permanent discontinuation of investigational product, and
- No use of restricted medications beyond the protocol-allowed threshold before assessment.

8.1.2.2. Systemic Lupus Erythematosus Responder Index-4 (SRI-4)

The SRI-4 is a composite index used to assess disease activity in SLE. The SLEDAI-2K component is used to capture clinically meaningful improvement in disease activity, while the BILAG and PGA of Disease Activity components ensure that the improvement in overall disease is not accompanied by disease worsening in other organ systems. A SRI-4 response is defined as follows:

- Reduction of ≥4 points from baseline in SLEDAI-2K score
- No new BILAG-2004 A or no more than 1 new BILAG -2004 B disease activity score, and
- No worsening (defined as an increase of ≥0.3 points [10 mm] from baseline) in PGA of Disease Activity.

Participants must complete 24 weeks of the study and comply with concomitant medication rules to be considered a responder for the SRI-4 analysis (Section 9.4.1).

8.1.2.3. Lupus Low Disease Activity State (LLDAS)

An LLDAS response is defined as a low level of disease activity attained with or without use of low-dose steroids and/or tolerated standard maintenance doses of standard-of-care immunosuppressant medications (Franklyn et al. 2016).

8.2. Safety Assessments

Visits and order of safety assessments

Safety assessments occur at visits specified in the SoA (Section 1.3). If multiple safety assessments are scheduled for the same visit, the preferred order of completion is

1) ECG and then vital signs,
2) other safety assessments, including physical examinations and nonleading (spontaneous) adverse event collection, followed by C-SSRS (Section 8.3.1.1), and finally
4) blood sample collection for clinical laboratory, CCI [redacted]

Data collection and reporting

The adverse event data collection and reporting requirements are described in Section 8.3 and Appendix 10.3. CCI [redacted]

Any clinically significant findings that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to Lilly or its designee as an adverse event via eCRF.

Safety monitoring

The principle investigator will monitor the safety data throughout the study and should discuss immediate safety concerns with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue the study drug.

The sponsor will monitor the safety data, including adverse events and SAE, discontinuations, vital signs, and clinical laboratory results by means of blinded reviews performed at least quarterly and by other appropriate methods. These methods include reviews by a functionally independent safety physician and/or clinical research scientist who regularly reviews SAE reports in real time and across studies, and who reviews applicable clinical safety and epidemiological publications from the literature. If this safety monitoring uncovers an issue that needs to be addressed by unblinding at the individual or group level, additional analyses of the safety data can be performed by the sponsor's independent internal safety review committee (Section 10.1.5).

Appropriateness of safety assessments

The safety assessments used in this study are routine elements of clinical health assessment and Phase 2 drug development.

8.2.1. Vital Signs

Vital signs (blood pressure, pulse rate, body temperature) will be measured as specified in the SoA (Section 1.3) and as 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 adverse event of 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

A complete physical examinations and symptom-directed physical examinations will be conducted at the visits specified in the SoA (Section 1.3). Symptom-directed physical examinations may also be conducted at other visits, as determined by the investigator, if a participant presents with complaints.

At screening and at approximately every third month thereafter, the specified physical examination, whether complete or symptom-directed, should include an assessment of TB risk factors and symptoms or signs of TB, including an assessment of peripheral lymph nodes (see Section 8.2.6).

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

- general appearance
- skin (other than the area covered by the bandage to assess ISRs)
- head, ears, eyes, nose, throat
- lymph nodes
- cardiovascular
- respiratory
- abdominal
- genitourinary (only as clinically indicated)

- extremities (tender/swollen joint counts to be documented separately), and
- neurologic.

Height (without shoes) and weight will also be measured and recorded as specified in the SoA (Section 1.3).

8.2.3. Electrocardiograms

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

Electrocardiograms 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.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the study site 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 and for immediate participant management, should any clinically relevant findings be identified.

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

The investigator or qualified designee must document his or her review of the ECG printed at collection. Any new clinically relevant finding will be reported as an AE.

8.2.4. Chest Radiography

A posterior–anterior (PA) CXR, interpreted and reported by a radiologist or pulmonologist, will be obtained as specified in the SoA (Section 1.3).

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 two conditions are met:
>
> - the CXR was performed within 3 months before initial screening, and
> - documentation of the CXR, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

For each participant, the CXR films or images or a radiology report must be available to the investigator for review before the participant is randomized. 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

Appendix 10.2 lists the clinical laboratory tests to be performed, and the SoA (Section 1.3) specifies the study visits at which samples are routinely collected for clinical laboratory tests. Samples for laboratory testing will be obtained in the event of anaphylaxis or generalized urticaria, as described in Section 8.3.6.1 and Appendix 10.2. Additional tests may be performed at any time during the study as deemed necessary by the investigator or as required by local regulations.

All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or adverse event or dose modification), then the results must be recorded in the eCRF.

Reviewing and recording test results

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents. 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 8 weeks 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 the 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.

Blinding of laboratory test results

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel (Appendix 10.2).

Sample retention

Unless otherwise specified [redacted] all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.5.1. Pregnancy Testing

Pregnancy testing is to be performed on women of childbearing potential (WOCBP) and women with a history of tubal ligation. Participants who are pregnant will be discontinued from the study (Section 7.1.1).

Visits and times

Serum pregnancy test will be done at screening only, and results will be confirmed by the central laboratory.

Urine pregnancy testing will be performed locally at visits specified in the SoA (Section 1.3). If the specified visit includes study drug administration, the urine pregnancy test must be "negative" within 24 hours before the study drug is administered.

Urine pregnancy testing may be performed at additional time points during the study treatment period and/or follow-up period, at the discretion of the investigator or if this is required by local regulations.

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

Optional follicle-stimulating hormone (FSH) testing

The participant's FSH level can be obtained during screening at the discretion of the investigator to assist in determining whether a woman meets the definition of "postmenopausal." The FSH level can also be optionally obtained during the study to determine the participant's postmenopausal status (see Section 1.3 and Appendix 10.4, Section 10.4.1).

8.2.6. Tuberculosis Testing and Monitoring

Tuberculosis 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 (Section 8.2.2), 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 tuberculin skin test (TST) using purified protein derivative (PPD) or positive *Mycobacterium tuberculosis* interferon gamma release assay (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. 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
  - 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.

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.

Diagnosed 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 World Health Organization and/or the United States Centers for Disease Control guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance. The participant may be rescreened 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.

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
- Physical examination that includes assessment for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes (Section 8.2.2).

8.2.7. Hepatitis B Testing and Monitoring

Initial testing for hepatitis B virus (HBV) infection includes hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (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 (Section 1.3), with temporary withholding or permanent discontinuation of study intervention if HBV DNA is positive, as described in Section 7.1.2 and Section 7.1.1, respectively.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected during the study, the study drug will be temporarily withheld or discontinued and participants should receive appropriate follow-up medical care as described in Section 7.1.1 and Section 7.1.2.

8.2.8. Hepatitis C Testing and Monitoring

Initial testing for HCV infection includes testing for antibodies to 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 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 drug will be discontinued (Section 7.1.1), and the participant should receive appropriate follow-up medical care.

8.2.9. Hepatic Safety Monitoring

Close hepatic monitoring

The laboratory tests listed in Appendix 10.5, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours, to confirm the abnormality and to determine whether it is increasing or decreasing, if these conditions occur:

If a participant with baseline...	has 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
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for the possible causes of the abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated medical monitor. At a minimum, this evaluation should include a 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 these conditions occur:

If a participant with baseline...	has the following elevations:
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN with hepatic signs/symptoms*, 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
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline with hepatic signs/symptoms*, or ALT or AST ≥3 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline

*** 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 a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time (PT-INR); viral hepatitis A, B,

C, and 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 sponsor's designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum 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/ gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (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 (hepatic safety eCRF) should be performed for participants who meet one or more of the following conditions:

- Elevation of serum ALT to ≥5 times ULN on two 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 two 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 two or more consecutive blood tests.
- Hepatic event considered to be a SAE.
- Discontinuation of study drug due to a hepatic event (Section 7.1.1).

Note that the interval between the two 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 intervention. Participants who have signs of suicidal ideation or behavior should be considered for discontinuation of study drug, following a risk assessment (see Section 7.1.1). See Section 8.3.1.1 for timing of adverse event collection relative to collection of the C-SSRS.

8.2.10.1. Columbia Suicide Self-Reported Scale (C-SSRS)

The Columbia Suicide-Severity Rating Scale (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 (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) 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. Depression Assessment with 16-Item Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR16) QIDS-SR16

The 16-Item Quick Inventory of Depressive Symptomatology–Self Report (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 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (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. Injection Site Assessment

Symptoms of a local injection site reaction may include erythema, induration, pain, pruritus, and edema. See Section 6.3 for activities relating to assessment of injection site reactions.

Solicited Events

Solicited data from injection site assessments will not be routinely classified as an adverse event.

Unsolicited Events

If a participant reports symptoms (that is, an unsolicited event, volunteered by participant) or if the investigator determines that a clinically relevant injection site reaction has occurred, the event will be captured as an adverse event. In such a case, a specific adverse event of Injection site reaction will be reported and the event followed up to completion, in addition to completing the injection site assessment questionnaire in the eCRF.

8.3. Adverse Events and Serious Adverse Events

Adverse events (AEs) 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 the definition of an AE or SAE and remain responsible for following up AEs 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).

Pregnancy after maternal or paternal exposure to IP does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported using the SAE process described in Appendix 10.3, Section 10.3.4, to collect data on the outcome for both mother and fetus. See also Section 8.3.5.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the time of the participant's signing of the main Study KFAJ ICF until the participant's last post-treatment follow-up visit.

Likewise, all SAEs will be collected from the signing the Study KFAJ ICF until the last post-treatment follow-up visit.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF are recorded by the site in the eCRF/electronic data entry tool, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF but prior to receiving study drug, the SAE needs to be reported ONLY if the SAE is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or the sponsor's designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAEs after the conclusion of study participation, that is, once the participants have discontinued and/or completed the study (the Participant Study Disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs CCI [redacted] will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a 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.

8.3.5. Pregnancy

For female participants and female partners of male participants, details will be collected for pregnancies occurring from after the start of study intervention and until 12 weeks after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the reporting procedures outlined in Appendix 10.4, Section 10.4.3.

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

CCI [redacted]

8.3.6.1. Systemic Hypersensitivity Reactions

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

to the sponsor in the eCRF. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

Sites should have appropriately trained medical staff and appropriate medical equipment available when the study participants are receiving study drug.

Blood sample collection for systemic allergic/hypersensitivity events, including CRS.

In the case of generalized urticaria or anaphylaxis, additional blood samples as described in Appendix 10.2 should be collected. Laboratory results are provided to the sponsor via the central laboratory.

8.3.6.2. Serious Infections and Opportunistic Infections

Completion of the Infection eCRF page is required for each infection reported as an AE or SAE. The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al. (2015) (Appendix 10.6).

8.3.7. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention. The sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational product so that the situation can be assessed. Note: Any AEs/SAEs that are associated with a product complaint will follow the processes outlined in Section 8.3.3 and Appendix 10.3.

Time period for detecting product complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used. If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

Prompt reporting of product complaints to the sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint. The Product Complaint Form will be sent to the sponsor by a method designated by the sponsor.

Follow-up of product complaints

Follow-up applies to all participants, including those who discontinue study intervention. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint. New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, an overdose of LY3471851 is considered any dose greater than the highest dose planned to be used in this study. The treatment for suspected overdose is supportive care.

In the event of an overdose, the investigator should:

1. Contact the sponsor's medical monitor immediately.
2. Closely monitor the participant for any AE or SAE and laboratory abnormalities until the study intervention can no longer be detected systemically (at least 12 weeks).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's medical monitor based on clinical evaluation of the participant.

8.5. Pharmacokinetics

Visits and times

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the plasma concentrations of LY3471851. The actual date and time (24-hour clock time) of dosing and sample collection must be recorded accurately on the appropriate forms.

Collection, handling, and analysis of samples

Instructions for the collection and handling of blood samples will be provided by the sponsor. Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of LY3471851 will be assayed using a validated PK assay. Analyses of samples collected from participants who received placebo are not planned.

Additional and unused samples

CCI [redacted]

In the case of systemic allergic/hypersensitivity reactions, additional blood samples will be obtained for PK analyses (Section 8.3.6.1).

Blinding

Drug concentration information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

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8.10. Medical Resource Utilization and Health Economics

This section is not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis for the primary endpoint is that there is no difference between LY3471851 and placebo in reducing the signs and symptoms of SLE as measured by the proportion of participants who achieve a SLEDAI-4 response at Week 24.

9.2. Sample Size Determination

CCI will be randomly assigned to study intervention. All randomized participants in the modified intent-to-treat (mITT) population will be considered evaluable.

Pairwise 2-sided tests of proportions with alpha = 0.05 will be performed on each LY3471851 dose versus placebo. With 70 participants per group, Study KFAJ has at least 80% power to detect a statistically-significant difference of 24% improvement over placebo in SLEDAI-4 response between LY3471851 and placebo at Week 24.

9.3. Populations for Analyses

The mITT population, which includes all randomized participants receiving at least 1 dose of study intervention, will be used in analyses of efficacy and patient-reported outcomes (PRO), unless otherwise noted in the SAP).

The following populations are defined for this study:

Population	Description
Entered	All participants who sign the informed consent form
Modified Intent-to-Treat (mITT)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received within each study period.
Pharmacokinetic (PK) Analysis	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and have PK data available.

9.4. Statistical Analyses

9.4.1. General Considerations

CCI Unless other indicated in the SAP, the analyses will be conducted as follows:

- Primary and secondary endpoint analyses will be tested at a 2-sided α level of 0.05 for frequentist analyses.
- The primary estimand that will be used to analyze primary and secondary endpoints is a composite response estimand where comparisons will not include data collected after

intercurrent events of changes to background therapies or discontinuation. Participants who discontinue treatment prior to 24 weeks or who are noncompliant with concomitant medication rules are defined as nonresponders. Endpoint definition effectively gives complete data which will be analyzed as described in Section 9.4.2 and Section 9.4.3.

- No adjustments for multiplicity will be performed.
- Efficacy and PRO analysis models may contain the independent variables such as treatment group, baseline disease activity, and geographic region.
- Missing data for dichotomous responder endpoints will be imputed using the nonresponder imputation (NRI) method.
- Participants will be considered nonresponders for the NRI analysis if
  - they do not meet all the clinical response criteria
  - they are noncompliant with concomitant medication rules (Section 6.5)
  - they permanently discontinue study intervention at any time before the end of the treatment period for any reason, or
  - they are randomized and do not have at least 1 postbaseline observation.
- Mixed-effects model for repeated measures (MMRM) is the main method for analyzing continuous efficacy endpoints.
- Additional imputation methods may be considered for all endpoint types.

Baseline will be defined as the last available value before the first dose of study intervention for both efficacy and safety analyses. In most cases, this value will be what is recorded at the randomization visit (Visit 2). Change from baseline will be calculated as the visit value of interest minus the baseline value. For the post-treatment Follow-up Period, the baseline is defined as the last nonmissing assessment on or prior to entering the post-treatment Follow-up Period, that is, on or prior to the Week 24 visit, or the early termination visit (including ETV).

Any change to the data analysis methods described in the protocol will require an amendment only if the change affects 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 SAP and the clinical study report. CCI

The SAP will be finalized prior to unblinding. It 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 primary and secondary endpoints.

9.4.1.1. 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. A summary of important protocol deviations will be provided.

9.4.1.2. Participant Characteristics

Demographic data are collected and responded 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.

9.4.1.3. Concomitant Therapy

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

Participants who require initiation or increase in dosage of corticosteroids, antimalarials, or immunosuppressants after randomization will be analyzed as nonresponders from the day of initiation or increase in medication (see Section 6.5).

9.4.1.4. Treatment Compliance

No analyses are planned to assess treatment compliance, given that participants will receive study intervention directly from the investigator or designee at the study site, under medical supervision (Section 6.4).

9.4.2. Primary Endpoints

The primary endpoint is the SLEDAI-4 response rate at Week 24 for the LY3471851 treatment group compared to placebo. Participants who fail to complete the 24-week treatment period or violate the concomitant medication rules will be imputed to nonresponse for the purpose of the primary endpoint analysis. The objective of the primary endpoint is to determine whether LY3471851 is superior to placebo.

The primary endpoint will be analyzed using a logistic regression model with baseline disease activity, corticosteroid dose at baseline, and geographic region as model covariates.

Treatment difference and 95% CIs will be reported.

9.4.3. Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following at Week 24:

- the proportion of participants who achieve a BILAG-based Composite Lupus Assessment (BICLA) response
- the proportion of participants who achieve SRI-4 response, and

- the proportion of participants who achieve LLDAS.

Dichotomous secondary endpoints will be analyzed using the model specified for the primary analysis.

9.4.3.1. Pharmacokinetic Analysis

Plasma concentrations of LY3471851 will be listed by time point using descriptive statistics. CCI [redacted]

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9.4.5. Safety Analyses

Safety analyses will include AEs, SAEs, CCI [redacted] C-SSRS, QIDS-SR16, vital signs, ECGs, and laboratory analytes, using the Safety Population data descriptively summarized by treatment group. Categorical safety measures will be summarized with incidence rates. Continuous safety

measures will be summarized as mean change by visit. Exposure to study intervention will be calculated for each participant and summarized by treatment group.

Adverse events will be coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA) and summarized by system organ class, preferred term, severity, and relationship to the study intervention. A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline, with baseline defined as all pre-existing conditions recorded at Visit 1 and any AEs recorded before the first dose of study intervention (that is, during the interval between 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 the analysis. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

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, CCI [redacted] will be summarized. Treatment-emergent adverse events (all, by maximum severity), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA system organ class (SOC) 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.

CCI [redacted]

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 (Columbia Lighthouse Project WWW).

Follow-up emergent AEs, SAEs including deaths, and AEs that lead to study discontinuation will be summarized. All AEs, including pre-existing conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

9.4.6. Other Analyses

9.4.6.1. Subgroup Analyses

Subgroup analyses may be conducted for the primary endpoint SLEDAI-4 at Week 24 using the mITT population. Subgroups that may be evaluated include interferon gene signature status, gender, race, geographic region, CCI [redacted] previous therapies, and disease duration,

9.4.6.2. Supplemental Analyses

Supplemental analyses will be performed on the primary endpoint using a treatment policy estimand where comparisons will be made while on treatment, but without regard to changes to background therapies or premature discontinuation. When using a treatment policy estimand, data will be analyzed using a logistic random effects model with treatment, baseline, visit, and visit-by-treatment interaction. Additional analyses of secondary endpoints may be performed using the same treatment policy estimand. Analysis details are in the statistical analysis plan.

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[redacted]

9.6. Data Monitoring Committee (DMC)

Not applicable. An IAC will be used to conduct the interim analysis (see Section 9.5 and Appendix 10.1, Section Appendix 10.1.5).

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 (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and
- Applicable laws and regulations.

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

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

The investigator will be responsible for the following:

- Substantial amendments to the protocol require European Competent Authority approval before implementation.
- 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, and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 United States Code of Federal Regulations (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 subinvestigators 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 one year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the participant or his or 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 representatives 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 (HIPAA) 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. The statement must include the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICFs.

Participants who are rescreened are required to sign a new ICF (see Section 5.4).

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

A copy of the ICFs must be provided to the participant or the participant's legally authorized representative and must be 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 or 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 or her data to be used as described in the informed consent.

The participant must be informed that his or 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.

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 electronic lupus assessment system. 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 the safety reviews routinely performed by the blinded study team, an 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 (see also Section 10.1.9).

The IAC reviewing the safety data will be fully independent from the study team and will include, at a minimum, a Lilly medical physician, a statistician, and a representative from the Lilly Global Patient Safety organization. Details about IAC membership, purpose, responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

CCI [redacted]

10.1.6. Dissemination of Clinical Study Data

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.

CCI [redacted]

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 eCRF. 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, contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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 15 years after study completion 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 electronic data capture system (EDC) will be used in this study for the collection of eCRF 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 eCRF.

Additionally, some of the clinician-administered questionnaires data will be collected by the investigative site personnel, via a paper source document and will be transcribed by the investigative site personnel into the EDC system. See the SoA (Section 1.3) for scales administered via paper.

Additionally, electronic clinical outcome assessment (eCOA) data (patient-reported outcome and clinician-administered questionnaires) will be directly recorded by the participant and investigative site personnel, into an instrument (for example, tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data. See the SoA (Section 1.3) for scales administered electronically.

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 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's data warehouse.

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

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

10.1.9. Study and Site Start and Closure

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

The sponsor or designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the sponsor.

Closure of study sites

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 a reasonable cause exists 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, these:

- 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 of participants by the investigator, and

- Discontinuation of further study intervention development.

Study stopping rules

The IAC will convene to evaluate unblinded safety data if

- 5 or more participants experience TEAEs in the same SOC or 3 or more participants experience a TEAE of CRS, and
- these TEAEs are judged as either serious or severe, and
- these TEAEs are related to blinded study treatment.

Study enrollment and/or further dosing may be stopped, pending the decision of the IAC CCI [redacted] Section 10.1.5). If the study is not stopped, the IAC will meet periodically; details are provided in the IAC charter.

CCI [redacted]

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations 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 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 a specialty in rheumatology will participate as investigators in this clinical trial. Physicians and other qualified healthcare professionals with other specialties and experience in treatment of patients with SLE may also participate as investigators.

10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable responses that may not be observed until later in the development of LY3471851 or after LY3471851 becomes commercially available.

The following table lists the maximum retention period for sample types. The retention period begins after the last participant visit for the study.

The maximum retention times may be shorter, if specified in local regulations and/or if ERBs/IRBs impose shorter time limits.

Any samples remaining after the specified retention period will be destroyed.

The sample retention facility will be selected by the sponsor or its designee.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacokinetics	Sponsor or designee	2 years
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]

10.2. Appendix 2: Clinical Laboratory Tests

The clinical laboratory tests listed in the table below will be performed by a central laboratory or by a local laboratory as specified in the table.

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

Protocol-specific requirements for the inclusion or exclusion of participants are specified in Section 5 of the protocol.

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

Investigators must document their review of each laboratory safety report.

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

If tests are done to obtain laboratory results with an intent to resume the study drug after a temporary withholding, the samples must be assayed centrally.

Clinical Laboratory Tests

Hematology [a]	**Clinical Chemistry** [a]
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBCs)	Chloride
Mean cell volume	Bicarbonate
Mean cell hemoglobin	Total bilirubin (TBL)
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBCs)	Alkaline phosphatase (ALP)
Absolute count of	Alanine aminotransferase (ALT)
Neutrophils, segmented	Aspartate aminotransferase (AST)
Neutrophils, juvenile (bands)	Gamma-glutamyl transferase (GGT)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Creatine kinase (CK)
Basophils	Uric acid
Platelets	Total protein
Cell morphology (RBC and WBC)	Albumin
	Calcium
Urinalysis [a]	Phosphorus
Specific gravity	Glucose
pH	Amylase
Protein	Lipase
Glucose	Cholesterol (total)
Ketones	Triglycerides
Bilirubin	
Urobilinogen	
Blood	**Lipid Panel** [a]
Nitrite	High-density lipoprotein (HDL)
Urine leukocyte esterase	Low-density lipoprotein (LDL)
Microscopic examination of sediment	
Urine Chemistry [a]	**Hormones (female)**
Total protein	Pregnancy test (serum [a] and urine [b])
Creatinine	Follicle-stimulating hormone (FSH) [a, c]
Calculation [a]	
Urine protein/urine creatinine ratio	
Estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease [MDRD])	

table continues

	Serology:
	Tuberculosis (TB) testing:
Total immunoglobulins	QuantiFERON-TB Gold test [a] or T-SPOT.TB [e] or TST [e]
IgM [a,d]	HIV testing [a]
IgA [a,d]	HCV testing:
IgG [a]	Hepatitis C antibody [a]
	HCV RNA [a]
	HBV testing:
[redacted] CCI	Hepatitis B core antibody (anti-HBc) [a]
	Hepatitis B surface antigen (HBsAg) [a]
Long-Term Stored Samples: [a,d]	HBV DNA [a]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
[redacted] CCI	**Pharmacokinetic Samples:** [a,d]
CCI [redacted]	CCI [redacted]
[redacted]	[redacted]
Lymphocyte Subsets [a, d]	
T, B, NK and T-cell subsets	

Abbreviations: anti-RNP = anti-ribonucleoprotein; CCI [redacted] DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RBC = red blood cell; RNA = ribonucleic acid; TBNK = T-cells, B-cells, and natural killer (NK) cells; TST = tuberculin skin test; WBC = white blood cell.

a Assayed by Lilly-designated laboratory.

b Urine pregnancy test to be performed only on women of childbearing potential and women with history of tubal ligation. Local testing. Result must be negative before dosing at each dosing visit.

c Optional, performed to confirm postmenopausal status.

d Results will not be provided to the investigative sites.

e Local testing. Local laboratory must be qualified by local regulations.

Selected tests may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions. The samples should be collected as close as possible to the onset of the event.

Hypersensitivity Tests [a]	
CCI	
LY concentration (PK)	N-methylhistamine
	Complements
	Cytokine panel

Abbreviation: PK = pharmacokinetic.

a Assayed by Lilly-designated laboratory.

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

10.3.1. Definition of AE

AE Definition

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: 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 study intervention.

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 pre-existing condition, including either an increase in frequency and/or in 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; report such overdoses 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 an 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 pre-existing diseases or conditions 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).

A 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. The term does not refer to an event which hypothetically might have caused death if the event 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 pre-existing 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

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.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE 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 information in the eCRF.

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 AE/SAE eCRF page.

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 one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a 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 one 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 diseases, 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 and/or Product Information, for marketed products, in his/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 a 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 post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. 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 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 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.

10.4. 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 post-menopausal unless permanently sterile (see below). If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, consider additional evaluation.

Woman NOT of Childbearing Potential (not-WOCBP)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (for example, mullerian agenesis, androgen insensitivity), apply investigator discretion to determining study entry. Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female, defined as women meeting one of the following criteria:
  - At least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note
  - Spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced the amenorrhea); additionally, if less than or equal to 50 years of age, has a FSH of ≥40 mIU/mL
  - At least 40 years of age with an intact uterus, not on hormone therapy, with cessation of menses for at least 1 year, and without an alternative medical cause, AND a FSH of ≥40 mIU/mL
  - At least 55 years of age, not on hormone therapy, having at least 12 months of spontaneous amenorrhea
  - At least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

10.4.2. Contraception

Females

Women of childbearing potential

Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Otherwise, women of childbearing potential participating must agree to use 2 forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study. Contraception must continue following completion of study drug administration for 12 weeks.

- Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.
- Two forms of effective contraception, where at least one form is highly effective (such as combination oral contraceptives, implanted contraceptives or intrauterine devices), will be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Women not of child-bearing potential (not-WOCBP)

Women who are not-WOCBP may participate in the study if they meet all study entry criteria. For such women, there are no conception requirements.

Males

No male contraception is required except in compliance with specific local government study requirements.

10.4.3. Collection of Pregnancy Information

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 obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will 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 fetal status (presence or absence of anomalies) or indication for the procedure.

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 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 <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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 discontinue study intervention and be withdrawn from the study.

10.5. Appendix 5: Liver Safety: Hepatic Monitoring Tests

Samples for selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required during follow-up with participants in consultation with the clinical research physician of the sponsor or sponsor's designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Antinuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Sponsor-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.6. Appendix 6: Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

The following table lists 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 such infections. 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)
	Post-transplant 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)
	Strongyloidosis (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).

10.7. Appendix 7: Efficacy and Patient-Reported Outcomes Assessments

CCI [redacted] the outcome measures used in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

10.7.1. British Isles Lupus Assessment Group 2004 (BILAG-2004)

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

- 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.

CCI [redacted]

10.7.3. Physician's Global Assessment (PGA) of Disease Activity – Visual Analog Scale

The PGA of Disease Activity is the physician's assessment of the participant's overall disease activity because of SLE, as compared with all possible subjects with SLE. The PGA of Disease Activity is scored using a 100-mm visual analog scale, where 0 mm (measured from the left starting point of the line) indicates no disease activity, and 100 mm (measured from the left starting point of the line) indicates severe disease activity. The PGA of Disease Activity score is indicated by making a vertical tick mark on the line between 0 and 100 mm. There are benchmarks of 0 (0 mm), 1 (33 mm), 2 (67 mm), and 3 (100 mm) on the line corresponding to no, mild, moderate, and severe SLE disease activity, respectively.

10.7.4. 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. It includes 24 clinical and laboratory variables with

manifestations graded by the affected organ system as follows: Central nervous system (CNS) (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).

10.7.5. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Flare Index

The SLEDAI Flare Index uses the SLEDAI-2K score, disease activity scenarios, treatment changes, and Physician's Global Assessment (PGA) of Disease Activity to define mild/moderate and severe flares. The index takes into account the absolute change in total scores, new or worsening symptoms, and increases in medication use or hospitalization because of the disease activity.

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10.8. Appendix 8: Abbreviations

Term	Definition
CCI [redacted]	[redacted]
AE	adverse event
CCI [redacted]	[redacted]
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
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 subjects are aware of the treatment received.
CBD	cannabidiol
CFR	United States Code of Federal Regulations
CK	creatine kinase
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.
CPK	creatinine phosphokinase
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
COA	clinical outcome assessment
CRF	case report form
CRS	cytokine release syndrome
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography

CXR	chest x-ray
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EDC	electronic data capture system
enroll	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.
enrollment	The act or time point of randomization, or the condition of have been assigned to a treatment (randomized).
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board (see IRB)
ETV	early termination visit
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C 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 IRB)
IGRA	interferon gamma release assay
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
CCI [redacted]	[redacted]

investigational product (IP)	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 (IRB), also called Independent Ethics Committee (IEC) or Ethical Review Board (ERB)
ISR	injection site reaction
IWRS	interactive web-response system
LLDAS	Lupus Low Disease Activity State
LTBI	latent tuberculosis infection
MAD	multiple-ascending dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model of repeated measures
NK	natural killer
NONMEM	nonlinear mixed effects modeling
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
PA	posterior–anterior
participant	Equivalent to Clinical Data Interchange Standards Consortium (CDISC) term "subject," meaning an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control. In this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials.
PEG	polyethylene glycol
PGA	Physician's Global Assessment
PK/PD	pharmacokinetics/pharmacodynamics
CCI	[redacted]
PK	pharmacokinetic
PPD	purified protein derivative
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
Q2W	every 2 weeks
QIDS-SR16	16-Item Quick Inventory of Depressive Symptomatology–Self Report
QTc	corrected QT interval

CCI	[redacted]
RNA	ribonucleic acid
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
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.
SELENA-SLEDAI	Safety of Estrogens in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SoA	Schedule of Activities
SOC	system organ class
SRI-4	Systemic Lupus Erythematosus Responder Index-4
SRI-5	Systemic Lupus Erythematosus Responder Index-5
study drug	See “study intervention”
study intervention	Any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol
TB	tuberculosis
TBL	total bilirubin level
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.
TST	tuberculin skin test
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential (see Appendix 10.4.1.)

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