Protocol ISA J1V-MC-BT01(a)

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

NCT05123586

Approval Date: 22-Sep-2021

Title Page

Intervention-Specific Appendix for LY3361237 (J1V-MC-BT01)

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

Master Protocol Number: J1V-MC-IMMA

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

ISA Number: J1V-MC-BT01
ISA Amendment Number: A

Compound: LY3361237
Study Phase: 2

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

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

Regulatory Agency Identifier Number(s)
Master protocol IND: 155806
EudraCT:2021-001406-30

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

Medical monitor name and contact information will be provided separately.

ISA Amendment Summary of Changes Table

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

Amendment A

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

Overall Rationale for the Amendment:

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

Section # and Name	Description of Change	Brief Rationale
Cover page	Changed "Indication-Specific" to "Intervention-Specific" Appendix	For internal document consistency
1.3. Schedule of Activities	Clarified that antiphospholipid antibodies are a panel of tests	To implement EULAR/ACR 2019 classification criteria, per regulatory request
1.3. Schedule of Activities	In row for antiphospholipid antibody panel, removed assessment at Visit 2	Moved assessment to Visit 1 (in master IMMA protocol) to implement EULAR/ACR 2019 classification criteria, per regulatory request
4.1.1. Internal Assessment Committee	Added a section heading above the previously available text Added a sentence with a cross-reference to the rules the IAC will consider for stopping or modifying the study	Regulatory request
5.1. ISA-Specific Inclusion Criteria	Added Criterion [1001] specifying that "clinical SLEDAI-2K score ≥4 (not including any items related to laboratory values)" must be met "at randomization (Visit 2)"	Moved a Visit 2 requirement into the BT01 ISA, removing it from IMMA master protocol inclusion criterion
6.5.1. Corticosteriod Management	Removed a statement about participants with "intolerable or exacerbating disease" continuing to receive study intervention and be considered nonresponders. Such participants will be permanently discontinued from study intervention (see master protocol IMMA Section 7.1)	Regulatory request
Section 10.1.1. Clinical Laboratory Test Performed Starting at Visit 2	In "Serology," described antiphospholipid antibody tests as a "panel"	For editorial consistency with similar text in IMMA master protocol

Section # and Name	Description of Change	Brief Rationale
10.5. Attachment 5: Study Stopping Criteria	Added new attachment with criteria to be used by IAC to trigger stopping or modifying the study	Regulatory response
10.6. Attachment 6: Provisions for Changes in Study Conduct During Exceptional Circumstances	Changed the attachment number	Editorial change based on adding a new preceding attachment
10.7. Attachment 7: Abbreviations and Definitions	Changed the attachment number	Editorial change based on adding a new preceding attachment

Table of Contents

1. Protocol Summary

1.1. Synopsis

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

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

Rationale: Findings from this study are intended to assess the utility of LY3361237 for the treatment of SLE, improve understanding of the benefit/risk relationship for LY3361237, and inform the design of future studies.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of 450 mg LY3361237 Q2W versus placebo with respect to arthritis and/or rash remission in participants with SLE	• Proportion of participants with arthritis and/or rash at baseline who achieve remission of arthritis and/or rash as defined by SLEDAI-2K at Week 24
Secondary	
• To compare 450 mg LY3361237 Q2W versus placebo with respect to SLE clinical signs and symptoms treatment response • To characterize the pharmacokinetics (PK) of 450 mg LY3361237 Q2W in participants with SLE	• Proportion of participants who achieve SLEDAI-4 response at Week 24 • Proportion of participants who achieve SRI-4 response at Week 24 • Steady-state trough serum concentration of LY3361237 at Week 24

Abbreviations: 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:

The overall protocol design consists of 2 components:

1) Master protocol (IMMA), which defines the platform concept and overall structure, as well as the elements of study conduct common across all investigations, including screening activities *and*

2) This ISA, J1V-MC-BT01, which defines the intervention-specific investigational requirements, including the clinical research objectives and endpoints and intervention-specific background information.

The design of this ISA is that of a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2-arm Phase 2 clinical trial to investigate the efficacy and safety of 450 mg LY3361237 Q2W plus SOC as a treatment for patients with SLE.

Disclosure Statement: This appendix to the master IMMA protocol is a parallel-group treatment study with 2 arms where participants and investigators are blinded to treatment assignment.

Number of Participants:

Approximately 90 participants will be randomly assigned in a 1:1 ratio to either LY3361237 or placebo.

Intervention Groups and Duration:

These are the intervention groups:

- 450 mg LY3361237 once Q2W plus SOC
- placebo plus SOC, given at matching intervals

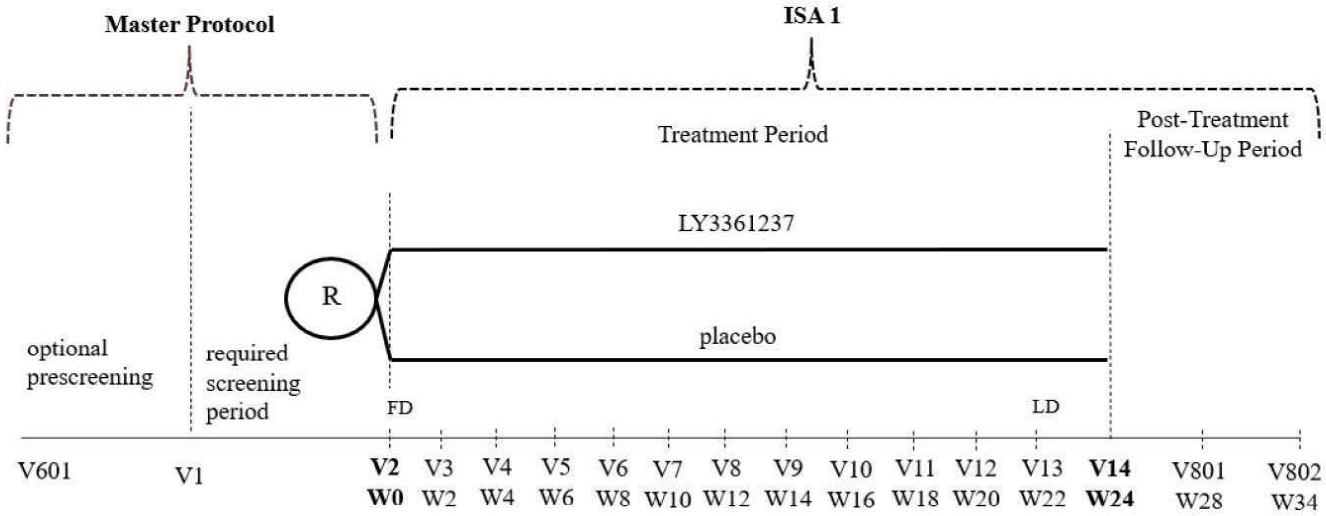
The doses are administered by SC injection.

For each group, the total duration of the treatment period is 24 weeks.

Data Monitoring Committee: Yes (Internal Assessment Committee)

1.2. Schema

Figure ISA1-1 illustrates the schema for this ISA.



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

Figure ISA1-1. Schema of a multicenter, randomized, double-blind Phase 2 clinical investigation comparing 450 mg of LY3361237 given via subcutaneous injection every 2 weeks versus placebo in adults with at least moderately active systemic lupus erythematosus (J1V-MC-BT01).

1.3. Schedule of Activities (SoA)

These tables describe activities conducted at the randomization visit (Visit 2) and at subsequent treatment and posttreatment visits.

Treatment Period of Study J1V-MC-BT01 For early permanent discontinuation occurring before the last visit in treatment period, see the activities in the ETV column.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ETV	UV	Comment
Weeks after randomization	—	2	4	6	8	10	12	14	16	18	20	22	24	—	—	
Study day	1	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	—	—	
Fasting visit	X												X			
Option for remote visit		X		X		X		X		X		X				The specified visits may occur remotely via mobile health care and/or telemedicine. Within 3 days after the remote visit, the participant will go to the site for dosing.
ICF for ISA	X															The ICF for this ISA must be signed before any ISA-specific test/procedures are performed. May be signed at Visit 1 or Visit 2.
Confirm study entry criteria	X															
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	
Physical evaluation																
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	Includes pulse rate, blood pressure, respiratory rate, and body temperature. Measured after participant has been sitting at least 5 minutes. See Section 8.2.1 of the master IMMA protocol.

Treatment Period of Study J1V-MC-BT01 For early permanent discontinuation occurring before the last visit in treatment period, see the activities in the ETV column.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ETV	UV	Comment
Weeks after randomization	—	2	4	6	8	10	12	14	16	18	20	22	24	—	—	
Study day	1	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	—	—	
Fasting visit	X												X			
Option for remote visit		X		X		X		X		X		X				The specified visits may occur remotely via mobile health care and/or telemedicine. Within 3 days after the remote visit, the participant will go to the site for dosing.
Symptom-directed physical examination	X		X		X		X		X		X		X	X	X	The SLE symptom physical assessment is captured in the electronic tablet; see Section 8.2.2 of the master IMMA protocol. At Week 12 and Week 24, assess for TB risk factors, and for signs and symptoms of active TB, including check of peripheral lymph nodes; see Section 8.2.6 of the master IMMA protocol.
12-lead ECG (local)							X						X			See Section 8.2.3 of the master IMMA protocol.
Patient-reported outcomes (electronic)																
QIDS-SR16	X		X		X		X		X		X		X	X		Administer before any clinical assessments. See Sections 8 and 8.2.10.2 of the master IMMA protocol.
Clinician-administered assessments (electronic)																
BILAG 2004	X		X		X		X		X		X		X	X		Collected via an electronic tablet device.

Treatment Period of Study J1V-MC-BT01 For early permanent discontinuation occurring before the last visit in treatment period, see the activities in the ETV column.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ETV	UV	Comment
Weeks after randomization	—	2	4	6	8	10	12	14	16	18	20	22	24	—	—	
Study day	1	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	—	—	
Fasting visit	X												X			
Option for remote visit		X		X		X		X		X		X				The specified visits may occur remotely via mobile health care and/or telemedicine. Within 3 days after the remote visit, the participant will go to the site for dosing.
CLASI	X		X		X		X		X		X		X	X		Collected via an electronic tablet device.
Physician's Global Assessment of Disease Activity	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.
SLICC/ACR Damage Index	X												X	X		Collected via an electronic tablet device.
28 tender and swollen joint counts	X		X		X		X		X		X		X	X		Collected via an electronic tablet device.
Clinician-administered assessments (paper)																
C-SSRS Since Last Assessment	X		X		X		X		X		X		X	X	X	Adapted for the assessment of ideation and behavior categories only.
Laboratory tests and sample collections																
Hematology	X		X		X		X		X		X		X	X	X	
Clinical chemistry	X		X		X		X		X		X		X	X	X	

Treatment Period of Study J1V-MC-BT01 For early permanent discontinuation occurring before the last visit in treatment period, see the activities in the ETV column.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ETV	UV	Comment
Weeks after randomization	—	2	4	6	8	10	12	14	16	18	20	22	24	—	—	
Study day	1	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	—	—	
Fasting visit	X												X			
Option for remote visit		X		X		X		X		X		X				The specified visits may occur remotely via mobile health care and/or telemedicine. Within 3 days after the remote visit, the participant will go to the site for dosing.
Lipid panel	X												X	X		Participants should not eat or drink anything but water for 12 hours before the test. Fasting is not required at an ETV. If a participant is nonfasting at time of collection, the sample should still be collected. This will not be considered a protocol violation.
Urinalysis	X		X		X		X		X		X		X	X	X	
Urine pregnancy (local)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Only for women of childbearing potential (WOCBP) and females with a history of tubal ligation. Result must be "negative" within 24 hours before dosing, when testing is conducted at dosing visits. See Section 8.2.5.1 and Appendix 10.4 of the master IMMA protocol; and see Attachment 10.1 of this ISA.

Treatment Period of Study J1V-MC-BT01 For early permanent discontinuation occurring before the last visit in treatment period, see the activities in the ETV column.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ETV	UV	Comment
Weeks after randomization	—	2	4	6	8	10	12	14	16	18	20	22	24	—	—	
Study day	1	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	—	—	
Fasting visit	X												X			
Option for remote visit		X		X		X		X		X		X				The specified visits may occur remotely via mobile health care and/or telemedicine. Within 3 days after the remote visit, the participant will go to the site for dosing.
HBV DNA							X						X	X		Performed only for participants who test positive for anti-HBc at screening. See Section 8.2.7 of the master IMMA protocol.
Urinary protein/creatinine ratio (UPCR)	X		X		X		X		X		X		X	X	X	
Urinary albumin/creatinine ratio (UACR)	X						X						X	X		
Estimated glomerular filtration rate (eGFR)	X						X						X	X		Calculated using Modification of Diet in Renal Disease (MDRD) method.
Receptor occupancy	X		X		X		X		X		X		X	X		
CCI																

Treatment Period of Study J1V-MC-BT01 For early permanent discontinuation occurring before the last visit in treatment period, see the activities in the ETV column.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ETV	UV	Comment
Weeks after randomization	—	2	4	6	8	10	12	14	16	18	20	22	24	—	—	
Study day	1	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	—	—	
Fasting visit	X												X			
Option for remote visit		X		X		X		X		X		X				The specified visits may occur remotely via mobile health care and/or telemedicine. Within 3 days after the remote visit, the participant will go to the site for dosing.
Immunogenicity (ADA) samples	X		X				X						X	X		Collect samples before dosing, if dosing is scheduled. Collect additional samples after a systemic hypersensitivity reaction. See Section 8.9 and Attachment 10.1 Section 10.1.2.
Anti-dsDNA	X		X		X		X		X		X		X	X		
Anti-Smith antibodies (anti-Sm)	X						X						X	X		
Antiphospholipid antibody panel							X						X	X		
Anti-RNP antibody	X						X						X	X		
Anti-SSA/Ro antibody	X						X						X	X		
Anti-SSB/La antibody	X						X						X	X		
Complement (C3 and C4)	X		X		X		X		X		X		X	X		
Total immunoglobulin G (IgG)	X						X						X	X		
Total immunoglobulin A (IgA)	X						X						X	X		
Total immunoglobulin M (IgM)	X						X						X	X		
Lymphocyte subsets	X						X						X	X		

Treatment Period of Study J1V-MC-BT01 For early permanent discontinuation occurring before the last visit in treatment period, see the activities in the ETV column.																
Visit number	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ETV	UV	Comment
Weeks after randomization	—	2	4	6	8	10	12	14	16	18	20	22	24	—	—	
Study day	1	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	—	—	
Fasting visit	X												X			
Option for remote visit		X		X		X		X		X		X				The specified visits may occur remotely via mobile health care and/or telemedicine. Within 3 days after the remote visit, the participant will go to the site for dosing.
Stored samples																
Genetic sample	X															Sample can be obtained at or after the specified visit. See Section 8.7.
Exploratory biomarker samples (Group 1)	X		X		X		X						X	X		
Exploratory biomarker sample (Group 2)	X		X				X						X	X		
Exploratory biomarker sample (Group 3)	X		X		X		X		X		X		X	X		
Randomization and dosing																
Randomization	X															
Administer study drug	X	X	X	X	X	X	X	X	X	X	X	X				
Register the visit in IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: ADA = anti-drug antibody; anti-dsDNA = anti-double stranded DNA; anti-HBc = antibody to hepatitis B core antigen; anti-RNP = anti-ribonucleoprotein; anti-SSA/Ro = anti–Sjögren's syndrome-related antigen A (also called anti-Ro); anti-SSB/La = anti–Sjögren's syndrome type B antigen (SSB), also known as La protein; BILAG 2004 = British Isles Lupus Assessment Group 2004; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS = Columbia – Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV = early termination visit; HBV = hepatitis B virus; ICF = informed consent form; ISA = intervention-specific appendix; IWRS = interactive web-response system; QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology-Self Report; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; TB = tuberculosis; UV = unscheduled visit; V = visit.

Posttreatment Follow-Up Period of Study J1V-MC-BT01 V802 is the last planned study visit for all participants. For participants who permanently discontinue the study during the treatment period, the posttreatment follow-up visits should be timed as follows: V801: ETV plus approximately 6 weeks since last dose V802: ETV plus approximately 12 weeks since last dose			
Visit number	V801	V802	Comment
Weeks after randomization	28	34	
Study day	197	239	
Visit interval tolerance (days)	±5	±5	
Fasting visit			No fasting in this period.
Option for remote visit	X	X	The specified visits may occur remotely via mobile health care and/or telemedicine.
Concomitant medications	X	X	
Adverse events (AEs)	X	X	
Physical evaluation			
Weight	X		
Vital signs	X	X	Includes pulse rate, blood pressure, respiratory rate, and body temperature. Measured after participant has been sitting at least 5 minutes. See the master IMMA protocol Section 8.2.1.
Symptom-directed physical examination	X	X	The SLE symptom physical assessment is captured in the electronic tablet. See Section 8.2.2 of the master IMMA protocol. At Visit 802, assess for risk factors, and for signs and symptoms of TB, including check of peripheral lymph nodes. See the master IMMA protocol Section 8.2.6.
12-lead ECG (local)	X		See the master IMMA protocol Section 8.2.3.
Patient-reported outcomes (electronic)			
QIDS-SR16		X	Administer before any clinical assessments. See Sections 8 and 8.2.10.2 of the master IMMA protocol.
Clinician-administered assessments (paper)			
C-SSRS Since Last Assessment	X	X	Adapted for the assessment of ideation and behavior categories only.
Laboratory tests and sample collections			
Hematology	X	X	
Clinical chemistry	X	X	
Urinalysis	X	X	
Urine pregnancy (local)	X	X	Only for women of childbearing potential (WOCBP) and females with a history of tubal ligation. See the master IMMA protocol Section 8.2.5.1 and Appendix 10.4; and see Attachment 10.1 of this ISA.

Posttreatment Follow-Up Period of Study J1V-MC-BT01 V802 is the last planned study visit for all participants. For participants who permanently discontinue the study during the treatment period, the posttreatment follow-up visits should be timed as follows: V801: ETV plus approximately 6 weeks since last dose V802: ETV plus approximately 12 weeks since last dose			
Visit number	V801	V802	Comment
Weeks after randomization	28	34	
Study day	197	239	
Visit interval tolerance (days)	±5	±5	
Fasting visit			No fasting in this period.
Option for remote visit	X	X	The specified visits may occur remotely via mobile health care and/or telemedicine.
HBV DNA		X	Performed only for participants who test positive for anti-HBc at screening. See the master IMMA protocol Section 8.2.7.
Urinary protein/creatinine ratio (UPCR)	X		
Urinary albumin/creatinine ratio (UACR)	X		
Estimated glomerular filtration rate (eGFR)	X		Calculated using Modification of Diet in Renal Disease (MDRD) method.
CCI			
Immunogenicity (ADA) samples		X	Collect additional samples after a systemic hypersensitivity reaction. See Section 8.9 and Attachment 10.1, Section 10.1.2.
Total immunoglobulin G (IgG)	X		
Total immunoglobulin A (IgA)	X		
Total immunoglobulin M (IgM)	X		
Randomization and dosing			No dosing in this period.
Register the visit in IWRS	X	X	

Abbreviations: ADA = anti-drug antibody; anti-HBc = antibody to hepatitis B core antigen; C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV = early termination visit; HBV = hepatitis B virus; IWRS = interactive web-response system; QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology-Self Report; SLE = systemic lupus erythematosus; V = visit.

2. Introduction

2.1. Study Rationale

This ISA (J1V-MC-BT01) is a Phase 2 study to evaluate the efficacy and safety of LY3361237 in adult patients with at least moderately active SLE. This study will be used to further characterize the safety, tolerability, efficacy, and PK/PD profile of LY3361237 in this study population. Findings from this study may inform the design of future studies and improve understanding of the benefit/risk relationship for LY3361237 as a treatment for SLE.

2.2. Background

LY3361237 is a human Ig G4-variant monoclonal antibody that binds and agonizes the inhibitory checkpoint receptor BTLA (CD272). BTLA is an Ig superfamily member and part of a family of checkpoint receptors that negatively regulate immune cell activation. BTLA is primarily expressed on B cells, T cells, and dendritic cells with highest expression on B cells and plasmacytoid dendritic cells, followed by $CD4^+$ T cells, with lowest expression on myeloid dendritic cells, gamma-delta ($\gamma\delta$), and $CD8^+$ T cells (Murphy and Murphy 2010). The natural ligand for BTLA is the tumor necrosis factor receptor superfamily member HVEM (TNFRSF14) (Gonzalez et al. 2005).

The binding of HVEM to BTLA leads to tyrosine phosphorylation of 2 conserved ITIMs on the cytoplasmic domain of BTLA (Sedy et al. 2005). The ITIM phosphorylation leads to recruitment of protein tyrosine phosphatases initiating inhibitory signaling. This inhibitory process is accomplished by dephosphorylating and downregulating positive cell receptor signaling (for example, T cell receptor or B cell receptor signal transduction cascades), and subsequent suppression of immune cell activation (Vendel et al. 2009).

Binding of LY3361237 to BTLA induces tyrosine phosphorylation of its cytoplasmic ITIM domains mimicking the activity observed with the natural ligand, HVEM. LY3361237 has been tested using in vitro bioassays and in vivo mouse models of autoimmune disease. It has been demonstrated to reduce lymphocyte activation and inflammatory cytokine production, resulting in resolution of inflammation in preclinical mouse models.

In a completed first-in-human SAD study (I9S-MC-BTAA), LY3361237 was well tolerated. No deaths or other SAEs were reported. No clinically important trends were reported in clinical laboratory data or vital signs data.

In addition, a randomized, placebo-controlled MAD study (I9S-MC-BTAB) of LY3361237 in participants with SLE has completed dosing in all cohorts. The available findings from this study support the initiation of this Phase 2 study.

For more information, see the IB for LY3361237.

2.3. Benefit/Risk Assessment

Risks

Potential risks associated with LY3361237 include:

- infection
- ISRs, and
- immediate hypersensitivity reactions, including urticaria, angioedema, and anaphylaxis.

Participants should be closely monitored for signs, symptoms, and/or laboratory values suggestive of these events, and appropriate medical evaluation and care should be provided. The management of immediate hypersensitivity reactions should be dictated by the signs and symptoms of the disease.

At the dose of LY3361237 planned for this study, these and other potential risks are considered to be monitorable and manageable using physical assessments, laboratory tests, and other assessments planned for this study.

Ongoing monitoring of safety data will be performed, as described in the master IMMA protocol (Section 8.2).

Potential benefits

The efficacy of LY3361237 in SLE has not yet been established. Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

Overall benefit/risk summary

In summary, taking into account the measures included to minimize risk to the study participants, the benefit/risk balance is assessed to be acceptable for testing LY3361237 in a Phase 2 study involving participants with SLE.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3361237 may be found in the IB.

3. Objectives, Endpoints and Estimands

This table describes objectives and endpoints for the evaluation of LY3361237 versus placebo.

Objectives	Endpoints
Primary	
• To compare the efficacy of 450 mg LY3361237 Q2W versus placebo with respect to arthritis and/or rash remission in participants with SLE	• Proportion of participants with arthritis and/or rash at baseline who achieve remission of arthritis and/or rash as defined by SLEDAI-2K at Week 24
Secondary	
• To compare 450 mg LY3361237 Q2W versus placebo with respect to SLE clinical signs and symptoms treatment response • To characterize the pharmacokinetics (PK) of 450 mg LY3361237 Q2W in participants with SLE	• Proportion of participants who achieve SLEDAI-4 response at Week 24 • Proportion of participants who achieve SRI-4 response at Week 24 • Steady-state trough serum concentration of LY3361237 at Week 24
Exploratory Objectives The following are exploratory objectives for the evaluation of LY3361237. • To compare the efficacy of 450 mg LY3361237 Q2W versus placebo for the following measures: ○ corticosteroid sparing effect ○ individual organ system SLE disease manifestations using ▪ SLEDAI-2K components, ▪ Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), and ▪ joint counts. ○ measures of SLEDAI-2K low-disease activity ▪ Lupus Low Disease Activity State (LLDAS) ○ BILAG-based Composite Lupus Assessment (BICLA) ○ Physician's Global Assessment of Disease Activity ○ Time to and incidence of any flare and first severe flare ○ Serologic markers of SLE ○ Interferon gene signature ○ SLICC/ACR Damage Index • To describe the observed safety of LY3361237 • To assess the potential development of anti-LY3361237 antibodies (ADA) • Characterize the exposure-response of 450 mg LY3361237 Q2W as related to biomarkers, receptor occupancy, efficacy, and safety endpoints • Explore the effect of 450 mg LY3361237 Q2W on exploratory biomarkers of SLE disease activity	

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

Abbreviations: ACR = American College of Rheumatology; ADA = anti-drug antibodies; BILAG = British Isles Lupus Assessment Group; 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; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; SRI-4 = Systemic Lupus Erythematosus Responder Index-4.

3.1. Primary Estimand

The primary clinical question of interest is this: What is the difference in the proportion of participants, with rash and/or arthritis present at baseline, who achieve remission of arthritis and/or rash as defined by the SLEDAI-2K after 24 weeks of intervention in participants with moderate to severe SLE who completed treatment and did not violate concomitant medication rules?

The estimand is described by the following attributes:

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

Endpoint: responder defined as achieving the 3 following criteria:

- Achievement of remission of arthritis and/or rash at Week 24 as measured by SLEDAI-2K and defined in Section 8.1.1.
- Did not permanently discontinue study intervention prior to Week 24.
- Did not violate any concomitant medication rules (Section 6.5) prior to Week 24.

Treatment condition: as randomized. Further details on study interventions and concomitant medications can be found in Section 6.

Intercurrent Event Strategies: The intercurrent events of interest "intervention discontinuation for any reason" and "any concomitant medication violation" will be handled through the endpoint definition (composite variable strategy) and will be considered nonresponders. All remaining intercurrent events are handled using the treatment policy.

Population-level summary: difference in proportions of remission of arthritis and/or rash as defined by SLEDAI-2K at Week 24 between treatment groups (LY3361237 versus placebo).

Rationale for estimand: This estimand assumes that if a participant discontinued treatment, the burden of treatment outweighed its benefits. It also assumes that if a participant violated the concomitant medication rules, the participant was not receiving sufficient benefit from treatment. Therefore, being a responder requires a positive response as well as completing treatment and not violating concomitant medication rules.

3.2. Secondary Estimands

SLEDAI-4

The clinical question of interest for a secondary objective regarding reduction in other SLE clinical signs and symptoms is this: What is the difference in the percentage of participants achieving SLEDAI-4 after 24 weeks of intervention in participants with moderate to severe SLE who completed treatment and did not violate concomitant medication rules?

The estimand is described by the following attributes:

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

Endpoint: responder defined as achieving the 3 following criteria:

- Achievement of SLEDAI-4 response as defined in Section 8.1.2.1.
- Did not permanently discontinue study treatment prior to Week 24.
- Did not violate any concomitant medication rules (Section 6.5) prior to Week 24.

Treatment condition: as randomized. Further details on study interventions and concomitant medications can be found in Section 6.

Intercurrent Event Strategies: The same strategies will be used as specified for the primary estimand.

Population-level summary: difference in proportion of participants achieving SLEDAI-4 response at Week 24 between intervention conditions.

Rationale for estimand: The same rationale is used as specified for the primary estimand.

SRI-4

The clinical question of interest for another secondary objective regarding reduction in other SLE clinical signs and symptoms is this: What is the difference in the percentage of participants achieving SRI-4 after 24 weeks of intervention in participants with moderate to severe SLE who completed treatment and did not violate concomitant medication rules?

The estimand is described by the following attributes:

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

Endpoint: responder defined as achieving the 3 following criteria:

- Achievement of SRI-4 response as defined in Section 8.1.2.2.
- Did not permanently discontinue study treatment prior to Week 24.
- Did not violate any concomitant medication rules (Section 6.5) prior to Week 24.

Treatment condition: as randomized. Further details on study interventions and concomitant medications can be found in Section 6.

Intercurrent Event Strategies: The same strategies will be used as specified for the primary estimand.

Population-level summary: difference in proportions of participants achieving SRI-4 response at Week 24 between intervention conditions.

Rationale for estimand: The same rationale is used as specified for the primary estimand.

Exploratory estimand(s)

Exploratory estimands will be described in the SAP.

4. Study Design

4.1. Overall Design

This ISA (BT01) is a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2-arm Phase 2 study to evaluate the efficacy and safety of LY3361237 plus SOC in adult study participants with at least moderately active SLE. This ISA has a required treatment period and a required posttreatment follow-up period. The master IMMA protocol describes an optional prescreening period and a required screening period. A schematic of the overall study design is presented in Section 1.2.

Optional prescreening period

The optional prescreening period is described in the master IMMA protocol (Section 4.1).

Screening period

The screening period is described in the master IMMA protocol (Section 4.1).

The ISA-specific ICF will be signed before any Visit 2 study procedures are performed.

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

- 450 mg LY3361237 Q2W plus SOC, and
- placebo Q2W plus SOC.

Participants will be stratified at randomization as specified in Section 6.3. Study interventions will be administered via SC injection.

Double-blind treatment period

Randomized participants will begin the double-blind, placebo-controlled, 24-week treatment period at Visit 2. Participants will receive the first dose of the assigned study intervention at that visit and will continue to receive doses through the last scheduled dosing visit specified in the SoA (Section 1.3). Participants will maintain their usual SOC medication regimen for SLE and for other diseases throughout the study, unless these medication regimens are specifically excluded (see Sections 5.2 and 6.5 of the master IMMA protocol) or unless changes are explicitly required by this protocol (for example, dose adjustment for corticosteroids [see Section 6.5.1]). Safety and efficacy assessments and laboratory sample collections will be performed as specified in the SoA (Section 1.3) and as described in the master IMMA protocol.

Follow-up period

All participants will have posttreatment follow-up visits (Visit 801 and Visit 802) for sample collections, including ADA and PK, and for safety assessments.

Early discontinuation of study intervention

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

4.1.1. Internal Assessment Committee

An IAC composed of qualified persons who are independent from the ISA study team may review the study data in an unblinded fashion.

Only the IAC is authorized to evaluate these unblinded analyses. The IAC may make recommendations to stop or alter the conduct of the ISA to ensure participant safety, if warranted. Criteria triggering the IAC to evaluate stopping or modifying the study are provided in Attachment 10.5.

Sites participating in this ISA will receive information about interim analysis results if the results have potential to impact the safety of study participants.

4.2. Scientific Rationale for Study Design

Remission of arthritis and/or rash as defined by SLEDAI-2K

The selection of the primary endpoint was based on analyses from 2 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 SRI-5 and then to use this information to design a more efficient trial 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 the BILAG score or Physician's Global Assessment (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. These data provide rationale to focus on SLEDAI as the primary driver of clinical response, and eliminate BILAG and PGA worsening as they have minimal impact on the endpoint.

A focus on arthritis and rash derived from an analysis to distinguish signal from noise in SLEDAI (Kalunian et al. 2018). This analysis employed a large Phase 3 dataset to assess prevalence of specific SLEDAI disease manifestations at baseline as an indicator of whether a specific manifestation is rare or prevalent. The fundamental assumption was that prevalent manifestations drive SLEDAI response, while rare manifestations contribute to noise.

The SLEDAI is a weighted disease activity index that measures presence or absence of disease in 9 organ systems. In the 2 SLE studies discussed above, disease activity in the mucocutaneous, musculoskeletal, or immunologic organ systems was present in over 70% of patients at baseline, with over 98% of patients having mucocutaneous and/or musculoskeletal disease at baseline. In contrast, in the other 6 organ systems these diseases were present in ≤15% of patients. These data provided the rationale to focus on mucocutaneous and musculoskeletal disease as the primary driver of clinical response.

The 9 SLEDAI organ systems are composed of specific disease symptoms. The musculoskeletal organ system consists of arthritis and myositis. Arthritis was the most prevalent symptom at baseline (>80% of patients) while myositis was rare (~1% of patients). The mucocutaneous organ system includes rash, alopecia, and mucosal ulcer. Rash was the most common symptom in this organ system (~70% of patients), followed by alopecia (~55%) and mucosal ulcer (~30%).

These data, in consultation with SLE experts, provide the rationale to focus on remission of arthritis and rash as the primary endpoint in this clinical trial.

Duration of treatment period

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 some longer studies, SLE efficacy outcomes at Week 24 have been 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).

Duration of posttreatment follow-up

A final posttreatment study visit will occur at Week 34, which is 12 weeks after the last dose of study intervention.

Corticosteroid taper

To minimize the potential confounding effect of corticosteroids, participants taking ≥10 mg of prednisone or prednisone equivalent at randomization are required to reduce their daily steroid dose to <10 mg, as described in Section 6.5.1.

4.3. Justification for Dose

This ISA (BT01) tests 1 dose level (450 mg), based primarily on available data from the LY3361237 Phase 1 studies:

- SAD Study BTAA in healthy participants (highest doses of 400 mg IV), and
- MAD Study BTAB in participants with SLE (SC doses of 50, 150, and 450 mg Q2W for 10 weeks).

The dose decision for this ISA (BT01) uses the safety, CCI data through the highest dose cohort in the SAD study and preliminary data for Cohorts 1, 2, and 3 (50, 150, and 450 mg dose levels) in the MAD study. A dose of 450 mg Q2W given SC during the treatment period of this ISA will maximize the likelihood of detecting an efficacy signal, CCI

CCI

CCI

4.4. End of Study Definition

A participant is considered to have completed J1V-MC-BT01 if the participant has completed all phases of the study, including the last scheduled procedure shown in the SoA of this ISA (Section 1.3). The end of J1V-MC-BT01 is defined as the date of the last scheduled procedure of the last participant assigned to treatment in J1V-MC-BT01.

5. Study Population

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before receiving a dose of study intervention. Participant eligibility will be reviewed and confirmed by an eligibility review committee prior to randomization.

See Section 5.1 (below) for ISA-specific inclusion criteria.

All other study inclusion and exclusion criteria relevant to this ISA are described in the master IMMA protocol (Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria).

5.1. ISA-Specific Inclusion Criteria

[1000] Have active arthritis and/or active rash as defined by the SLEDAI-2K at screening (Visit 1) and at randomization (Visit 2).

[1001] Have clinical SLEDAI-2K score ≥4 (not including any items related to laboratory values) at randomization (Visit 2).

6. Study Intervention

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

6.1. Study Interventions Administered

Study intervention

This study involves LY3361237 and placebo.

Treatment Name	LY3361237	Placebo
Dosage Formulation	Each vial delivers 300 mg LY3361237 at 75 mg/mL	0.9% sodium chloride
Dosage Levels	450 mg	not applicable
Routes of Administration	SC injection	SC injection
Dosing Instructions	Dosing Q2W	Dosing Q2W

Abbreviations: Q2W = every 2 weeks; SC = subcutaneous.

LY3361237 drug product will be provided as a sterile solution in a vial for SC injection. The drug product vial(s) will be supplied in carton(s) with the appropriate quantity specific to the planned dispensing schedule of the study intervention. The sponsor will centrally provide LY3361237 and placebo vials in a carton to be assigned via IWRS.

Detailed instructions for the preparation and handling of LY3361237 and placebo will be provided by the sponsor. The drug product will be administered using 3 injections, with a volume of no more than 2.0 mL per injection (maximum total volume 6.0 mL).

Preparation by unblinded pharmacist

Dosing solutions will be prepared by an unblinded pharmacist (or other unblinded qualified individual) and loaded into syringes for SC dosing (see Section 6.3 on blinding).

Monitoring after dose administration

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

Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the injection procedures, and for at least 1 hour afterwards.

Participant education

Site personnel should educate participants and/or caregivers about the symptoms and signs of hypersensitivity events and provide instructions on appropriate actions to take if these events occur.

6.2. Preparation/Handling/Storage/Accountability

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

Preparation

The study interventions 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 study interventions as noted in the packaging. The Pharmacy Manual also provides:

- handling and storage information for study interventions, and
- guidance and information for the final disposition of unused study interventions.

Site and sponsor responsibilities

See the master IMMA protocol (Section 6.2) for additional information site and sponsor responsibilities for preparation, handling, storage, and accountability of the study interventions.

6.3. Measures to Minimize Bias: Randomization and Blinding

Method of treatment assignment

Assignment to treatment groups within this ISA will be determined by a computer-generated random sequence using the IWRS. The sponsor will centrally provide LY3361237 and placebo vials in a carton to be assigned via IWRS.

Participants will be assigned to the LY3361237 group or to the placebo group in a 1:1 ratio within this ISA.

Stratification at randomization

The randomization will be stratified based on the following factors:

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

Blinding

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. Participants will remain blinded to their assigned study intervention as well.

Unblinded pharmacist or other qualified individual

To maintain the blind, an otherwise uninvolved party (unblinded pharmacist or other unblinded qualified individual) will be responsible for the preparation and dispensing of all study intervention.

When LY3361237 is prepared for use according to the instructions, it will not be possible for the participants and blinded site personnel to distinguish LY3361237 from placebo.

Blinded site personnel or blinded designee will administer the study intervention to the participant.

Other measures

Other measure to minimize bias are described in Section 6.3 of the master IMMA protocol.

6.4. Study Intervention Compliance

Measures to assure or assess compliance are described in the master IMMA protocol (Section 6.4).

Additional measures for this ISA

Participants will receive study intervention directly from the investigator or designee.

The date and time of each dose administered will be recorded in the source documents and recorded in the eCRF.

6.5. Concomitant Therapy

See the master IMMA protocol (Section 6.5) for information about

- recording of concomitant therapy
- allowed concomitant therapy, and
- dose adjustments for antimalarials and immunosuppressants.

6.5.1. Corticosteroid Management

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

- Enrolled participants are restricted to prednisone ≤20 mg per day (or equivalent) at randomization (Visit 2), having been on stable doses for at least 2 weeks prior to randomization.
- Following randomization, the dose of prednisone (or equivalent) should not be increased above the participant's background level.
- CCI [redacted]
- Participants with intolerable or exacerbating disease are allowed access to SOC therapy, including increasing the dose of prednisone (or equivalent). Such participants are allowed to remain in the study but will be permanently discontinued from study intervention (see the master IMMA protocol [Section 7.1]).

6.5.1.1. Guidance on Corticosteroid Tapering

These recommendations recognize there is variability in how corticosteroids are administered. The intent is to allow investigators flexibility in how corticosteroids are tapered for individual

participants, as long as the participants reach the goal of <10 mg per day in time for the assessments at Week 12.

Participants taking ≥10 mg prednisone (or equivalent) at baseline

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

- Steroid tapering should begin approximately 4 weeks after randomization.
- Tapering should include a stepwise reduction at 2-week intervals, with the daily dose being reduced by from 1 to 5 mg at the discretion of the investigator in each 2-week interval. Thus, the stepwise reductions will occur in intervals 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 at randomization (20 mg per day) would be able to have his or her steroid dose tapered 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 taking <10 mg prednisone (or equivalent) at baseline

Participants who are taking <10 mg prednisone (or equivalent) at baseline may have their dose decreased at the discretion of the investigator based on clinical symptoms.

6.6. Dose Modification

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

6.7. Intervention after the End of the Study

The study intervention will not be available to participants after they complete the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See the master IMMA protocol (Section 7).

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the ISA SoA (Section 1.3).

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

Any outcome measures that are participants' self-assessments should be completed before any clinical examinations are performed.

8.1. Efficacy Assessments

Attachment 10.3 of this ISA provides descriptions of efficacy assessments, scales, and indexes.

8.1.1. Primary Efficacy Outcome Measure: Remission of Arthritis and/or Rash as Defined by SLEDAI-2K

Remission of arthritis and/or rash is defined by the following, using SLEDAI-2K definitions: if only arthritis is present at baseline, then the primary endpoint is met if arthritis is absent at Week 24; if only rash is present at baseline, then the primary endpoint is met if rash is absent at Week 24; if both arthritis and rash are present at baseline, then the primary endpoint is met if either arthritis, or rash, or both arthritis and rash are absent at Week 24.

8.1.2. Secondary Efficacy Outcome Measures

8.1.2.1. Secondary Efficacy Outcome Measure: SLEDAI-4

A SLEDAI-4 response is defined as a ≥4-point reduction in SLEDAI-2K score from baseline.

8.1.2.2. Secondary Efficacy Outcome Measure: 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 2004 and Physician's Global Assessment 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 Physician's Global Assessment of Disease Activity.

8.1.3. Exploratory Efficacy Outcomes Measures

8.1.3.1. BILAG-based Composite Lupus Assessment (BICLA)

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

- Reduction of all baseline BILAG-2004 A **to** B or C or D; and baseline BILAG-2004 B **to** C or D; and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
- No worsening from baseline in SLEDAI-2K, where worsening is defined as any increase from baseline in SLEDAI-2K, and
- No worsening from baseline in participants' lupus disease activity, where worsening is defined by an increase ≥0.30 points on Physician's Global Assessment of Disease Activity.

8.1.3.2. 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 SOC immunosuppressant medications (Franklyn et al. 2016).

8.2. Safety Assessments

Planned time points for safety assessments are provided in the ISA SoA (Section 1.3).

See the master IMMA protocol (Section 8.2) for safety assessments and safety monitoring activities required for all ISAs.

Procedures specified in the following subsections and in Attachment 10.1 of this ISA must be followed in addition to those described in the master IMMA protocol.

8.2.1. 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.

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

Sample collection at time of systemic hypersensitivity events

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

8.2.2. 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). See also the master IMMA protocol (Appendix 10.5).

8.2.3. Injection Site Reactions

Symptoms and signs of a local ISR may include erythema, induration, pain, pruritus, and edema.

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

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

See the master IMMA protocol (Section 8.3) for definitions and reporting requirements, including timing and mechanism for reporting.

8.3.1. Adverse Events of Special Interest (AESIs)

See Section 8.2 of this ISA for additional samples and data collections when certain AEs occur.

8.4. Treatment of Overdose

For the purposes of this study, an overdose of LY3361237 is considered any dose higher than the dose assigned through randomization. The treatment for overdose is supportive care. See the IB for LY3361237.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately,
- Closely monitor the participant for any AE, SAE, or laboratory abnormalities for at least 10 weeks. See Section 8.3 of the master IMMA protocol for the timing and mechanism of reporting AEs or SAEs.
- Obtain CCI [redacted] study intervention if requested by the medical monitor, as determined on a case-by-case basis, and
- Document the quantity of the excess dose as well as the duration of the overdose.

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

8.5. Pharmacokinetics

Sampling visits and times

See the SoA of this ISA (Section 1.3) for the visits and times of PK sample collection.

The actual date and time (24-hour clock time) of dosing and sample collection must be recorded accurately on the appropriate forms.

Sample purpose

Venous blood samples are collected to determine the serum concentrations of LY3361237.

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. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for storage of samples is described in Attachment 10.4.

8.6. Pharmacodynamics

Sampling visits and times

See the SoA of this ISA (Section 1.3) for the visits for RO sample collection.

Sample purpose

CCI [redacted]

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 using a validated assay.

8.7. Genetics

Sampling visits and times

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA of this ISA (Section 1.3), where local regulations and IRB/IEC allow.

Sample use

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and

excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Samples may be used for research related to LY3361237 and its mechanism of action, the drug target, genetic variants thought to play a role in SLE, on the disease process and pathways associated with the disease or related diseases. The samples may also be used to develop tests or diagnostic tools or assays related to SLE or to LY3361237. The samples may also be used to investigate variable exposure or response to LY3361237. The assessment of variable response may include evaluation of AEs or differences in efficacy.

Molecular technologies are expected to improve during storage period and therefore cannot be specifically named. However, existing genetic research approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this protocol. The samples may be analyzed as part of single or multi-study assessment of genetic factors involved in the response to LY3361237 or to study interventions of this class to improve understanding of the disease or related conditions, and additional analyses may be conducted if necessary to further understand the clinical data of this study.

Confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel. The sponsor will store the blood and/or DNA samples in a secure storage space with adequate measures to protect confidentiality.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Attachment 10.4.

8.8. Biomarkers

Sampling visits and times

Serum, plasma (EDTA), whole-blood RNA, and whole-blood epigenetic samples for nonpharmacogenetic biomarker research will be collected at the visits specified in the SoA of this ISA (Section 1.3), where local regulations allow.

Sample use

Samples may be used for research on the drug target, disease process, variable response to LY3361237, pathways associated with SLE, mechanism of action of LY3361237, and/or research methods or in validating diagnostic tools or assays related to SLE or to LY3361237.

Confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Attachment 10.4.

8.9. Immunogenicity Assessments

Sampling visits and times

See the SoA of this ISA (Section 1.3) for the visits and times of collection of samples used to determine antibody production against LY3361237. The actual date and time (24-hour clock time) of dosing and sample collection must be recorded accurately on the appropriate forms.

To aid interpretation of these results, a predose blood sample for CCI will be collected at the same time points.

Sample collection, handling, and use

Instructions for the collection and handling of samples will be provided by the sponsor.

Immunogenicity will be assessed and characterized by a validated assay designed to detect ADAs in the presence of LY3361237 at a laboratory approved by the sponsor.

Sample retention and use

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Attachment 10.4. Samples may also be used for development and control of an immunogenicity assay.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data are not collected in this ISA.

9. Statistical Considerations

The SAP for this ISA will be finalized prior to the first unblinding. This ISA's SAP (SAP BT01) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

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

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

The null hypothesis corresponding to the secondary estimand is as follows:

- LY3361237 is not different from placebo with respect to the achievement of SRI-4 at Week 24.
- LY3361237 is not different from placebo with respect to the achievement of SLEDAI-4 at Week 24.

9.1.1. Multiplicity Adjustment

No adjustments for multiplicity will be performed.

9.2. Analyses Sets

The analyses sets are defined in Section 9.2 of the master IMMA protocol.

9.3. Statistical Analyses

The following subsections are to be read as supplement to the statistical considerations specified in Section 9 of the master IMMA protocol.

9.3.1. General Considerations

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

See the master IMMA protocol (Section 9.3.1) for platform trial considerations, such as borrowing of placebo data.

Considerations specific to this ISA include the following:

- Primary and secondary endpoint analyses will be tested at a CCI [redacted]
- The primary and secondary estimand that will be used to analyze the primary and secondary endpoints is a composite response where comparisons will not include data collected after intercurrent events including any concomitant medication violation or treatment discontinuation. Participants who discontinue 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 Sections 9.3.2 and 9.3.3.

- If an ISA, aside from BT01, has reached a planned analysis, then placebo borrowing across ISAs may be performed.

Changes to the data analysis methods

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

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

The primary efficacy endpoint is the proportion of participants with rash and/or arthritis at baseline who achieve remission of arthritis and/or rash, as defined by the SLEDAI-2K at Week 24. Remission is achieved if one of the following occurs:

- If only arthritis is present at baseline, then the primary endpoint is met if arthritis is absent at Week 24.
- If only rash is present at baseline, then the primary endpoint is met if rash is absent at Week 24.
- If both arthritis and rash are present at baseline, then the primary endpoint is met if either arthritis, or rash, or both arthritis and rash are absent at Week 24.

Participants who fail to complete the 24-week treatment period or violate the concomitant medications rules will be treated as nonresponders for the purpose of the primary endpoint analysis. The objective of the primary endpoint is to determine whether LY3361237 is superior to placebo.

The primary endpoint will be analyzed CCI [redacted]. See Section 6.3 for stratification at randomization.

The CCI [redacted] will be reported. CCI [redacted].

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

Secondary efficacy endpoints include the proportion of participants who achieve SRI-4 response and SLEDAI-4 response at Week 24. Participants who fail to complete the 24-week treatment period or violate the concomitant medications rules will be treated as nonresponders for the purpose of these 2 secondary endpoints analyses. The SRI-4 response at treatment completion will be analyzed using the model specified for the primary analysis. The SLEDAI-4 response at treatment completion will be analyzed using the model specified for the primary analysis.

Other secondary endpoints include pharmacokinetics endpoints. The analyses for pharmacokinetic endpoints are specified in Section 9.3.3.1.

9.3.3.1. Pharmacokinetics/Pharmacodynamics

CCI [redacted]

9.3.4. Exploratory Endpoints

Exploratory endpoints to compare the efficacy of 450 mg LY3361237 Q2W to placebo include, but are not limited to,

- corticosteroid sparing effect
- individual organ system SLE disease manifestations which includes
  - SLEDAI-2K components
  - CLASI, and
  - joint counts
- measures of SLEDAI-2K low-disease activity, which includes LLDAS
- BICLA
- Physician's Global Assessment of Disease Activity
- time to any flare
- time to first severe flare
- incidence of any flare
- serologic markers of SLE
- interferon gene signature, and
- SLICC/ACR Damage Index.

Exploratory endpoints related to biomarkers, target engagement, efficacy, and safety include the characterization of exposure-response. Exploratory exposure-response analyses may use graphical or model-based approaches as appropriate.

Exploratory analyses of corticosteroid sparing effect, individual organ system SLE disease manifestations, LLDAS, BICLA, Physician's Global Assessment of Disease Activity, time to any flare, time to first severe flare, incidence of flare, SLICC/ACR Damage Index, exposure-response, and exploratory biomarkers of SLE disease activity may be performed. In most cases, estimands for these exploratory objectives will use the hypothetical strategy for continuous endpoints and composite strategy for dichotomous endpoints. Exploratory analyses will be further described in the SAP that is finalized before ISA data is unblinded.

For analyses of immunogenicity data, see Section 9.3.6.6 of the master IMMA protocol.

9.3.5. Safety Analyses

See Section 9.3.5 of the master IMMA protocol regarding safety analyses.

For this ISA, safety analyses will compare LY3361237 to placebo with no placebo borrowing.

9.3.6. Other Analyses

9.3.6.1. Participant Disposition

See Section 9.3.6.1 of the master IMMA protocol.

9.3.6.2. Participant Characteristics

In addition to the participant characteristics detailed in Section 9.3.6.2 of the master IMMA protocol, SLICC will also be summarized.

9.3.6.3. Concomitant Therapy

See Section 9.3.6.3 of the master IMMA protocol.

9.3.6.4. Treatment Compliance

Treatment compliance with study intervention will be summarized by treatment group. A participant will be considered significantly noncompliant if he or she fails to receive the study intervention within the required treatment window as defined in the SoA. Overall compliance with therapy is defined to be missing no more than 20% of the expected doses and not missing 2 consecutive doses.

9.3.6.5. Patient-Reported Outcomes

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

9.3.6.6. Subgroups

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

9.3.6.7. Sensitivity Analyses

No sensitivity analyses are planned for this ISA.

9.4. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

9.5. Sample Size Determination

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

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

10. Attachments to the ISA

10.1. Attachment 1: Clinical Laboratory Tests

Use of central or local laboratories

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

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

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

Laboratory tests for inclusion/exclusion of potential study participants

Protocol-specific laboratory requirements for inclusion or exclusion of potential study participants are included in Section 5 of the master IMMA protocol. See also Section 5 of this ISA.

Pregnancy testing

Pregnancy testing is described in the master IMMA protocol, in the SoA of this ISA (Section 1.3), and in the tables below.

Allowance for additional testing

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

Investigator responsibilities

Investigators must document their review of the laboratory safety results.

Provision of laboratory results

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

10.1.1. Clinical Laboratory Tests Performed Starting at Visit 2

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

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

	Notes
Lipid Panel	Assayed by Lilly-designated laboratory.
High-density lipoprotein (HDL)	
Low-density lipoprotein (LDL-C)	If triglycerides >400 mg/dL, then LDL will be assayed.
Very-low-density lipoprotein (VLDL-C)	Calculated.

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

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

	Notes
Hormones (females)	
Urine pregnancy (local)	Evaluated locally. If the urine pregnancy test is inconclusive at any visit, an additional serum pregnancy test should be collected.

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

	Notes
Serology	Assayed by Lilly-designated laboratory.
Hepatitis B virus (HBV) DNA	
Anti-dsDNA	
Anti-Smith antibodies (anti-Sm)	
Anti-RNP antibody	
Anti-SSA/Ro antibody	
Anti-SSB/La antibody	
Antiphospholipid antibody panel Anticardiolipin antibody IgG Anticardiolipin antibody IgM Anticardiolipin antibody IgA Lupus anticoagulant Anti-beta-2 glycoprotein 1 IgG Anti-beta-2 glycoprotein 1 IgM Anti-beta 2 glycoprotein 1 IgA	
Complement (C3 and C4)	

	Notes
Pharmacokinetics (PK) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3361237 concentration	

	Notes
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
anti-LY3361237 antibodies	

	Notes
Additional Testing	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Receptor occupancy (RO)	

	Notes
Immunoglobulins	Assayed by Lilly-designated laboratory.
IgG	
IgM	
IgA	

	Notes
Lymphocyte Subsets	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
T, B, and NK cells	
B cell panel (CD19, CD20, CD27, CD38, CD69, CD24, CD138, CD10, IgD)	

	Notes
Genetics Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

	Notes
Exploratory Biomarker Storage Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Group 1:	
Serum	
Plasma (EDTA)	
Whole Blood (epigenetics)	
Group 2:	
RNA	
Serum	
Group 3:	
Serum	

Abbreviations: anti-dsDNA = anti-double stranded DNA; anti-RNP = anti-ribonucleoprotein; anti-SSA/Ro = anti-Sjögren's syndrome-related antigen A (also called anti-Ro); anti-SSB/La = anti-Sjögren's syndrome type B antigen (SSB), also known as La protein; DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; NK = natural killer; RNA = ribonucleic acid.

10.1.2. Laboratory Tests to be Obtained at Time of a Systemic Hypersensitivity Event

Selected tests may be obtained in the presence of generalized urticaria or if anaphylaxis is suspected.

After the participant has been stabilized, the samples should be collected as close as possible to the onset of the event (within 1 to 2 hours after the event). If necessary, samples may be obtained as late as 12 hours after the event. Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

Record the date and time at which the samples are collected.

	Notes
Hypersensitivity Tests	Assayed by Lilly-designated laboratory.
Tryptase and *N*-methylhistamine (NMH)	If a tryptase sample is obtained more than 2 hours after the event (that is, within 2-12 hours) or is not obtained because more than 12 hours have lapsed since the event, obtain urine for NMH testing. Note that for tryptase serum samples obtained within 2-12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
Anti-LY3361237 antibodies (ADA) for immunogenicity	ADA testing should include drug specific IgE or the basophil activation test (BAT). (The BAT is an *in vitro* cell based assay that only requires a serum sample; it is a surrogate assay for drug-specific IgE but is not specific for IgE.) These tests are not routinely available and need to be developed for individual molecules based on their evolving safety profile. Samples are collected, and testing conducted once the assay is available, as appropriate.
LY3361237 concentration (pharmacokinetics)	
Complements	C3, C3a, and C5a
Cytokine panel	IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

10.2. Attachment 2: Contraceptive Guidance

See the master IMMA protocol (Appendix 10.4, Section 10.4.1) for definitions of WOCBP, women not of childbearing potential, and postmenopausal state.

10.2.1. Contraception Guidance for Females Participating in this ISA

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Must…	**Must not…**

agree to either remain abstinent, or	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

stay in a same sex relationship without sexual relationships with males	

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Topic	**Condition**
Pregnancy testing	Have a negative serum result at screening followed by a negative urine result within 24 hours prior to treatment exposure (dosing).
Contraception	Must agree to use 2 forms of effective contraception, where at least 1 form must be highly effective (less than 1% failure rate).

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal, • post coital douche • lactational amenorrhea

10.2.2. Contraception Guidance for Males Participating in this ISA

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

10.3. Attachment 3: Efficacy Assessments

The following are efficacy assessments used in this ISA; see also Section 8.1.

10.3.1. British Isles Lupus Assessment Group 2004 (BILAG 2004)

See the master IMMA protocol (Appendix 10.8, Section 10.8.2) for the description of this scale.

10.3.2. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI is a validated scale used to assess cutaneous manifestations of SLE consisting of 2 scores. The first summarizes the activity of the disease, and the second is a measure of the damage done by the disease. Activity is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and nonscarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia.

10.3.3. Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity is the physician's assessment of the participant's overall disease activity because of SLE, as compared with all possible participants with SLE. The Physician's Global Assessment 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 the most severe disease activity possible for all participants with SLE (or death). The 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.

10.3.4. 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 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 (Buyon et al. 2005).

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

See the master IMMA protocol (Appendix 10.8, Section 10.8.1) for the description of this scale.

10.3.6. Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index

The SLICC/ACR Damage Index is scored on 41 items representing damage to 12 organ systems. The index records damage occurring in participants with SLE regardless of its cause and includes specific comorbidities associated with SLE that may be due to treatment-related toxicity (Gladman et al. 1996, 1997).

10.3.7. Tender/Swollen Joint Count (28 Joints)

See the master IMMA protocol (Appendix 10.8, Section 10.8.3) for the description of this scale.

10.4. Attachment 4: Sample Retention

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

The following table lists the maximum retention period for sample types.

The retention period begins after the last participant visit for this ISA.

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

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	Maximum Retention Period Starting After the Last Participant's Last Visit
Pharmacokinetics (PK)	Sponsor or designee	1 year
Genetics	Sponsor or designee	15 years
Exploratory biomarkers	Sponsor or designee	15 years
Immunogenicity	Sponsor or designee	15 years

10.5. Attachment 5: Study Stopping Criteria

The IAC may conduct unblinded safety data reviews, as described in Section 4.1.1.

The following criteria will trigger the IAC to evaluate whether to stop or modify the study:

- 3 or more participants experience TEAEs in the same system organ class, and
- these TEAEs are assessed as severe by the investigator, or meet at least 1 serious criterion, or both.

Pending evaluation of the IAC, enrollment in the ISA, further dosing, or both, may be stopped, or the dose or other study parameters may be modified.

10.6. Attachment 6: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this attachment

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include,

but are not limited to, evaluation of PROs via a tablet and/or web-based collection system.

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

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

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: urinalysis, UPCR, anti-dsDNA, complements (C3 and C4), PK, immunogenicity, genetics sample, and tests of exploratory biomarker samples. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Adjustments to visit windows

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

This table describes allowed adjustments to the type of visit (on-site or remote) and the allowed adjustments to visit interval tolerances (visit windows).

Treatment Period (SoA)		
Visit Number	**Type of Visit**	**Visit Interval Tolerance**
Visit 2	on-site only	same as shown in the SoA
Visit 3	in-clinic for injections; other procedures may be remote	same as shown in the SoA
Visit 4	on-site only	same as shown in the SoA
Visit 5	in-clinic for injections; other procedures may be remote	same as shown in the SoA
Visit 6	on-site only	same as shown in the SoA
Visit 7	in-clinic for injections; other procedures may be remote	same as shown in the SoA
Visit 8	on-site only	same as shown in the SoA
Visit 9	in-clinic for injections; other procedures may be remote	
Visit 10	on-site only	same as shown in the SoA
Visit 11	in-clinic for injections; other procedures may be remote	
Visit 12	on-site only	same as shown in the SoA

Treatment Period (SoA)		
Visit Number	**Type of Visit**	**Visit Interval Tolerance**
Visit 13	in-clinic for injections; other procedures may be remote	
Visit 14	on-site only	same as shown in the SoA
Early Termination and Posttreatment Follow-Up Period (SoA)		
Visit 801	on-site or remote	same as shown in the SoA
Visit 802	remote	same as shown in the SoA
ETV	on-site or remote	same as shown in the SoA

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

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.7. Attachment 7: Abbreviations and Definitions

Term	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
anti-dsDNA	anti-double stranded DNA
AST	aspartate aminotransferase
BICLA	BILAG-based Composite Lupus Assessment
BILAG 2004	British Isles Lupus Assessment Group 2004
blinding	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BTLA	B and T lymphocyte attenuator (CD272)
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
E_{max}	maximum effect
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.
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

ETV	early termination visit
EULAR	European League Against Rheumatism
GCP	good clinical practice
HVEM	herpes virus entry mediator
IAC	internal assessment committee
IB	Investigator's Brochure
ICF	informed consent form
IEC	independent ethics committee
Ig	immunoglobulin
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.
interim analysis	An analysis of clinical trial data by treatment group that is conducted before the primary outcome database lock.
IRB	institutional review board
ISA	intervention-specific appendix
ISR	injection site reaction
ITIM	immunoreceptor tyrosine-based inhibitory motif
IWRS	interactive web-response system
LLDAS	lupus low dose activity state
MAD	multiple-ascending dose
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
participant	equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PC	product complaint
PD	pharmacodynamics
PK	pharmacokinetics
PRO	patient-reported outcomes

Q2W	every 2 weeks
QIDS-SR16	16-Item Quick Inventory of Depressive Symptomatology-Self Report
RNA	ribonucleic acid
RO	receptor occupancy
SAD	single-ascending dose
SAP	statistical analysis plan
SC	subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-4	defined as a ≥4-point reduction in SLEDAI-2K score from baseline
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus Erythematosus International Collaborating Clinics
SoA	Schedule of Activities
SOC	standard of care
SRI	Systemic Lupus Erythematosus Responder Index
SRI-4	a composite index used to assess disease activity in SLE; see Section 8.1.2.2
SRI-5	Systemic Lupus Erythematosus Responder Index-5
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.
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.
UPCR	urine protein/creatinine ratio
WOCBP	women of childbearing potential

11. References

Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med*. 2005;142:953–962. https://doi.org/10.7326/0003-4819-142-12_part_1-200506210-00004

Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis*. 2016;75(9):1615–1621. https://doi.org/10.1136/annrheumdis-2015-207726

Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an anti–interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthritis Rheumatol*. 2017;69(2):376–386. https://doi.org/10.1002/art.39962

Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2011;63(12):3918–3930. https://doi.org/10.1002/art.30613

Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum*. 1996;39:363-369. https://doi.org/10.1002/art.1780390303

Gladman D, Urowitz MB, Goldsmith C, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index in patients with systemic lupus erythematosus. *Arthritis Rheum*. 1997;40(5):809-813. https://doi.org/10.1002/art.1780400506

Gonzalez LC, Loyet KM, Calemine-Fenaux J, et al. A coreceptor interaction between the CD28 and TNF receptor family members B and T lymphocyte attenuator and herpesvirus entry mediator. *Proc Natl Acad Sci USA*. 2005;102(4):1116-1121. https://doi.org/10.1073/pnas.0409071102

Isenberg DA, Petri M, Kalunian K, et al. Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis*. 2016;75(2):323–331. https://doi.org/10.1136/annrheumdis-2015-207653

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

Merrill JT, van Vollenhoven RF, Buyon JP, et al. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis*. 2016;75(2):332–340. https://doi.org/10.1136/annrheumdis-2015-207654

Murphy TL, Murphy KM. Slow down and survive: enigmatic immunoregulation by BTLA and HVEM. *Annu Rev Immunol.* 2010;28:389-411. https://doi.org/10.1146/annurev-immunol-030409-101202

Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet.* 2011;377(9767):721–731. https://doi.org/10.1016/S0140-6736(10)61354-2

Sedy JR, Gavrieli M, Potter KG, et al. B and T lymphocyte attenuator regulates T cell activation through interaction with herpesvirus entry mediator. *Nature Immunol.* 2005;6(1):90-98. https://doi.org/10.1038/ni1144

van Vollenhoven RF, Hahn BH, Tsokos GC, et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet.* 2018;392(10155):1330–1339. https://doi.org/10.1016/S0140-6736(18)32167-6

Vendel AC, Calemine-Fenaux J, Izrael-Tomasevic A, et al. B and T lymphocyte attenuator regulates B cell receptor signaling by targeting Syk and BLNK. *J. Immunol.* 2009;182:1509-1517. https://doi.org/10.4049/jimmunol.182.3.1509

Wallace DJ, Furie RA, Tanaka Y, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet.* 2018;392(10143):222–231. https://doi.org/10.1016/S0140-6736(18)31363-1

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

Leo Document ID = aff765dd-2000-4563-b1cd-82d86e73b359

Approver: PPD

Approval Date & Time: 22-Sep-2021 13:01:33 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 22-Sep-2021 14:25:54 GMT

Signature meaning: Approved