Protocol: J1A-MC-KDAD(b)

Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants With Moderately to Severely Active Rheumatoid Arthritis

NCT04634253

Approval Date: 11-Dec-2020

Title Page

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Protocol Title: A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants with Moderately to Severely Active Rheumatoid Arthritis

Protocol Number: J1A-MC-KDAD

Amendment Number: (b)

Compound: LY3462817

Study Phase: Phase 2

Short Title: A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants with Moderately to Severely Active Rheumatoid Arthritis

Acronym: KDAD

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 150710

EudraCT number: 2020-002673-10

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

Approval Date: 11-Dec-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
KDAD Amendment (a)	21-Sep-2020
Original Protocol	05-Aug-2020

Amendment [b]

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

Overall Rationale for the Amendment:

The purpose of this protocol amendment is to clarify study procedures and statistical considerations in response to European regulatory agency feedback.

Section # and Name	Description of Change	Brief Rationale
Section 6.3. Measures to Minimize Bias: Randomization and Blinding Section 7.1.2. Criteria for Permanent Discontinuation of Study Intervention Section 8.2.6. Tuberculosis Testing and Monitoring	Removed medical monitoring wording	Clarification
Section 7.1.1. Criteria for Temporary Interruption (Withholding) of Study Intervention Section 7.1.1.1. Infection-related Criteria for Temporary Withholding of Study Intervention Section 7.2.1. Discontinuation of Inadvertently Enrolled Participants	Modified medical monitoring wording	Clarification
Section 9.2. Sample Size Determination	• DAS28-CRP change from baseline explained • MMRM analysis information added	Clarification
Section 9.4.1. General Considerations	Clarified adjustments for multiplicity	Clarification
Section 9.5. Interim Analyses	Provided additional clarification on interim analysis	Clarification

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants with Moderately to Severely Active Rheumatoid Arthritis

Short Title: A Phase 2 Study to Evaluate the Efficacy and Safety of LY3462817 in Participants with Moderately to Severely Active Rheumatoid Arthritis

Rationale:

Rheumatoid arthritis (RA) is a common, systemic autoimmune inflammatory disease, characterized by synovial inflammation leading to pain, swelling, stiffness, and progressive destruction and deformity of small and large joints. Current treatment of RA prioritizes timely initiation and modification of disease-modifying antirheumatic drug (DMARD) therapy to bring patients to a target of sustained low disease activity (LDA) or remission. Patients typically begin treatment with oral conventional synthetic DMARDs (csDMARDs); but if the treatment target is not achieved, they receive additional therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). However, 20 to 30% of patients with RA remain refractory to current therapies. There is a need for new, effective treatment options in these patients.

LY3462817 is a humanized immunoglobulin (Ig) G1 monoclonal antibody that binds to and is an agonist to human programmed cell death protein 1 (PD-1). LY3462817 binding to PD-1 is expected to stimulate the physiological immune inhibitory pathway to restore immune regulation; this constitutes a novel approach to treat patients with autoimmune or auto-inflammatory diseases.

This study aims to evaluate the efficacy of LY3462817 in adult participants with moderately to severely active RA who have had an inadequate response to either csDMARD or to bDMARDs/tsDMARDS.

Objectives and Endpoints

Objectives	Endpoints and Estimands
Comparison Groups: Placebo vs LY3462817 **[time frame for endpoint evaluation: 12 weeks from randomization, unless stated otherwise]**	
Primary	
To evaluate the efficacy of LY3462817 in adult participants with moderately to severely active RA	Change from baseline in DAS28-CRP. The primary comparison will be assessed using a hypothetical efficacy estimand strategy to address the intercurrent event of early discontinuation where the mean change from baseline will be evaluated using only data up until discontinuation as if all subjects remained on

	randomized treatment.
Secondary	
To describe the safety and tolerability of LY3462817 compared to placebo	• Safety assessments such as AEs, SAEs

To evaluate the effect of LY3462817 on measures of disease activity	• Proportion of participants achieving ACR20, ACR50, and ACR70
	• Change from baseline for physician-assessed individual components:
	  o 68 tender joint count
	  o 66 swollen joint count
	  o physician's global assessment of disease activity (VAS)
	• Change from baseline for mean SDAI
	• Change from baseline for mean CDAI

To describe the effect of LY3462817 on PROs	Change from baseline for:
	• Individual components of the ACR core set:
	  o patient's global assessment of disease activity (VAS),
	  o patient's global assessment of arthritis pain (VAS), and
	  o patient's assessment of physical function (HAQ-DI)
	• SF-36

To characterize the pharmacokinetics of LY3462817	Observed drug concentration

Abbreviations: ACR = American College of Rheumatology; ACR20 = 20% improvement in American College of Rheumatology criteria; ACR50 = 50% improvement in American College of Rheumatology criteria; ACR70 = 70% improvement in American College of Rheumatology criteria; AE = adverse event; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; HAQ-DI = Health Assessment Questionnaire-Disability Index; PRO = patient-reported outcome; RA = rheumatoid arthritis; SAE = serious adverse event; SDAI = Simplified Disease Activity Index; SF-36 = Study 36-Item Short Form Health Survey; VAS = visual analog scale.

Overall Design

This is a Phase 2, proof-of-concept, placebo-controlled, double-blind, randomized study in adult participants with moderately to severely active RA who have had an inadequate response to csDMARDs, or to bDMARDs/tsDMARDs. Participants will be administered LY3462817 or placebo intravenously (IV) once every 4 weeks (Q4W).

Screening Period (Visit 1, Days -42 to -1)

Participants will sign the informed consent document(s) at Visit 1, prior to completion of any procedures. Participants will be evaluated for study eligibility ≤42 days prior to the baseline visit (Visit 2).

Period 1: Double-blind Treatment (Visits 2 to 6; 12 weeks)

At the baseline visit (Visit 2), participants who fulfill the eligibility criteria will be randomized to receive LY3462817 700 mg, LY3462817 300 mg, or placebo in an allocation ratio of 2:1:1.

The double-blind treatment period will establish the clinical efficacy and safety of LY3462817. The study will be evaluated for the primary objective at the end of the double-blind treatment period.

Period 2 (Visits 6 to 10; 12 weeks)

In Period 2, participants assigned to LY3462817 at baseline, and achieving low disease activity (CDAI ≤10) at Week 14 will continue to receive LY3462817 to assess safety and tolerability data and evaluate clinical activity with additional dosing. All other participants at Week 14, regardless of baseline treatment assignment, will receive standard of care treatment at the investigator's discretion.

Post-treatment Safety Follow-up Period (Visits V801 and 802; 12 weeks)

Following Period 2, participants will be followed posttreatment for 12 weeks to assess safety, study drug exposure, and clinical disease activity.

Disclosure Statement: This is a parallel, 3-arm treatment study that is participant-blinded and investigator-blinded.

Number of Participants:

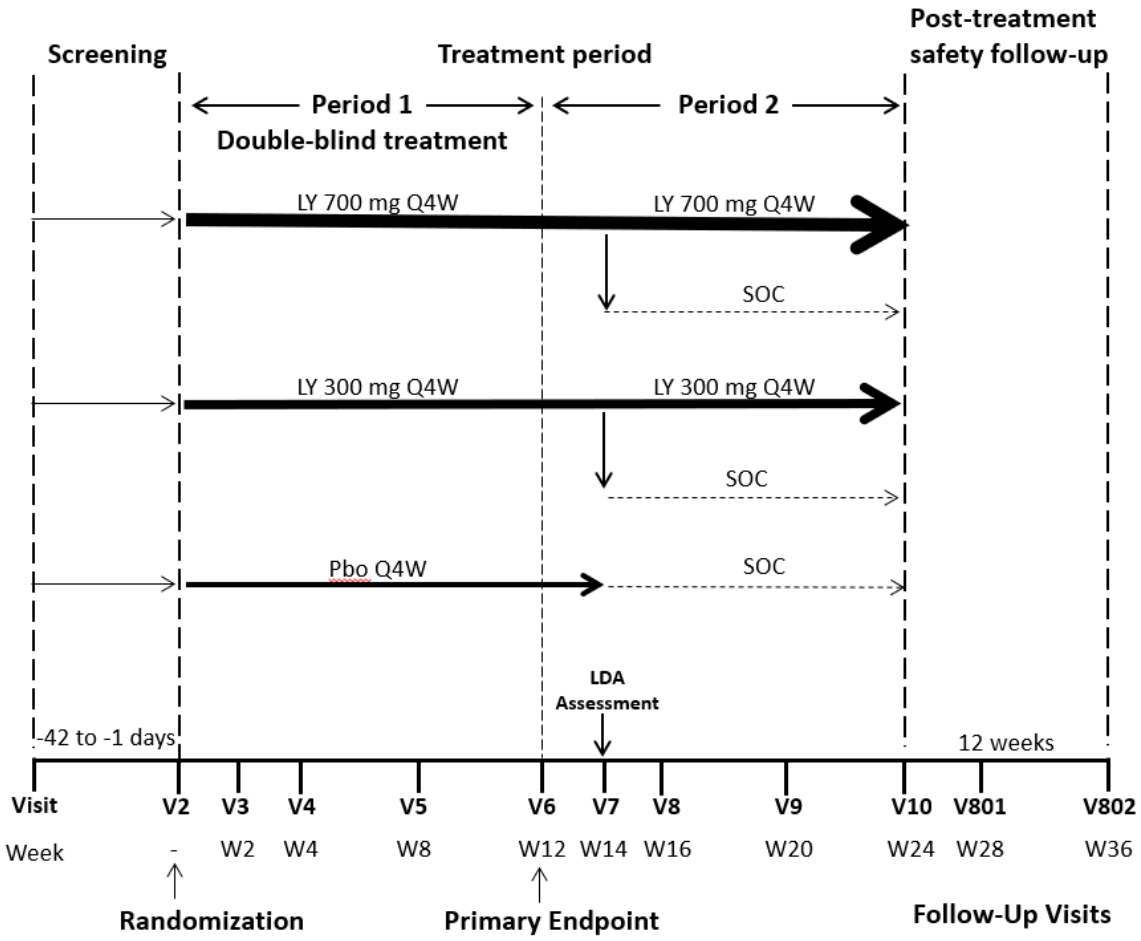
Approximately 80 participants will be randomly assigned to study intervention. At the completion of the study, approximately 40 participants will have been randomized to LY3462817 700 mg and 20 participants will have been randomized to LY3462817 300 mg and placebo during the double-blind treatment.

Intervention Groups and Duration:

Participants will receive 1 of the following study interventions: intravenous LY3462817 300 mg, 700 mg, or placebo every 4 weeks for 12 weeks. Participants assigned to LY3462817 at baseline, and achieving low disease activity (CDAI ≤10) at Week 14 will continue to receive LY3462817 through Week 24.

Data Monitoring Committee: No data monitoring committee, but there will be an internal assessment committee.

1.2. Schema



Notes:

For details about the study intervention doses, see Section 6.1.

Diagonal dashed arrows indicate transition to SOC therapy at Week 14. For details about SOC therapy, see Section 6.5.3.

Abbreviations: Pbo = placebo; LDA = Low Disease Activity; LY = LY3462817; mg = milligrams; Q4W = once every 4 weeks; SOC = Standard of Care; V = visit; W = week.

1.3. Schedule of Activities (SoA)

The SoA should be followed for all participants enrolled in Study KDAD. If participation in this study is affected by exceptional circumstances, such as a pandemic or natural disaster, please refer to Section 10.8, Appendix 8, for additional guidance.

Study J1A-MC-KDAD	**Screen**	**Period 1: Double-blind treatment**					**Period 2**				**ED**	**Post-treatment follow-up**		**Comments**
Day ± Visit Tolerance	**-42 to -1**	**1**	**14 ± 7**	**28 ± 7**	**56 ± 7**	**84 ± 7**	**98 ± 7**	**112 ± 7**	**140 ± 7**	**168 ± 7**	Any	**196 ± 7**	**252 ± 7**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the tolerance window.
Week		**-**	**2**	**4**	**8**	**12**	**14**	**16**	**20**	**24**	**-**	**28**	**36 or ETV + 12**	
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET	V801	V802	
Procedures														
Informed Consent	X													Written informed consent must be obtained before any study procedures or assessments.
Inclusion and exclusion criteria, review and confirm	X	X												
Demographics	X													
Preexisting conditions and medical history, including relevant surgical history	X													
Prespecified medical history (indication and history of interest)	X													
Substance use (alcohol, caffeine, tobacco use)	X	X												
Prior treatments for RA	X													Any previous therapy for RA in the past 15 years that has now been discontinued.

Study J1A-MC-KDAD	**Screen**	**Period 1: Double-blind treatment**					**Period 2**				**ED**	**Post-treatment follow-up**		**Comments**
Day ± Visit Tolerance	**-42 to -1**	**1**	**14 ± 7**	**28 ± 7**	**56 ± 7**	**84 ± 7**	**98 ± 7**	**112 ± 7**	**140 ± 7**	**168 ± 7**	Any	**196 ± 7**	**252 ± 7**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the tolerance window.
Week		**-**	**2**	**4**	**8**	**12**	**14**	**16**	**20**	**24**	**-**	**28**	**36 or ETV + 12**	
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET	V801	V802	
Procedures														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	For concomitant medications of interest (such as background therapies), additional data are collected.
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	AE collection begins when ICF is signed (Section 10.3). For AESIs, additional data are collected (Section 8.3.6).
Participant-Reported Outcomes (Electronic)														
Patient's Global Assessment of Arthritis Pain (VAS)	X	X	X	X	X	X	X	X	X	X	X	X	X	Administer before any clinical assessments and dosing
Health Assessment Questionnaire-Disability Index (HAQ-DI)	X	X	X	X	X	X	X	X	X	X	X	X	X	Administer before any clinical assessments and dosing
Patient's Global Assessment of Disease Activity (PaGADA_VAS)	X	X	X	X	X	X	X	X	X	X	X	X	X	Administer before any clinical assessments and dosing
Medical Outcomes Study 36-Item Short Form Health Survey (SF-36 v2, Acute)		X				X				X	X		X	Administer before any clinical assessments and dosing

Study J1A-MC-KDAD	**Screen**	**Period 1: Double-blind treatment**					**Period 2**				**ED**	**Post-treatment follow-up**		**Comments**
Day ± Visit Tolerance	**-42 to -1**	**1**	**14 ± 7**	**28 ± 7**	**56 ± 7**	**84 ± 7**	**98 ± 7**	**112 ± 7**	**140 ± 7**	**168 ± 7**	Any	**196 ± 7**	**252 ± 7**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the tolerance window.
Week		**-**	**2**	**4**	**8**	**12**	**14**	**16**	**20**	**24**	**-**	**28**	**36 or ETV + 12**	
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET	V801	V802	
Procedures														
Physical Evaluation														
Height		X												
Weight		X				X				X	X			
Vital Signs (BP, PR, T)	X	X	X	X	X	X	X	X	X	X	X	X	X	Supine or sitting blood pressure and PRs obtained at approximately same time as the ECG, prior to blood sampling.
Complete physical examination	X					X				X				Excludes pelvic, rectal, and breast examinations.
Symptom-directed physical examination		X	X	X	X		X	X	X		X	X	X	Performed at the discretion of the investigator. Assess prior to dosing.
12-lead ECG (local)	X									X	X		X	Participants to be supine for at least 5 minutes before ECG and remain supine but awake during ECG. Assess prior to blood sampling.
Chest x-ray (posterior-anterior and lateral view; local)	X													Documentation of radiologic reports/films taken within 3 months prior to screening is acceptable. Lateral view is optional or according to local guidelines.
MRI (Hand/Wrist)	X					X								Performed only after the all eligibility criteria are met except: criterion 6. Evaluate the same hand/wrist at screening and Week 12 prior to dosing.

Study J1A-MC-KDAD	**Screen**	**Period 1: Double-blind treatment**					**Period 2**				**ED**	**Post-treatment follow-up**		**Comments**
Day ± Visit Tolerance	**-42 to -1**	**1**	**14 ± 7**	**28 ± 7**	**56 ± 7**	**84 ± 7**	**98 ± 7**	**112 ± 7**	**140 ± 7**	**168 ± 7**	Any	**196 ± 7**	**252 ± 7**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the tolerance window.
Week		**-**	**2**	**4**	**8**	**12**	**14**	**16**	**20**	**24**	**-**	**28**	**36 or ETV + 12**	
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET	V801	V802	
Procedures														
Health Care Professional RA Assessments (Electronic)														
Clinician-Administered Tender/Swollen Joint Count (TSJC) (68/66)	X	X	X	X	X	X	X	X	X	X	X	X	X	Collected via an electronic tablet device. These joint counts will be performed by the Joint Assessor (Section 6.3). Determine prior to dosing
Physician's Global Assessment of Disease Activity (PhGADA_VAS)	X	X	X	X	X	X	X	X	X	X	X	X	X	Determine prior to dosing
Clinician-Administered Assessments (Paper)														
C-SSRS Screening/Baseline	X													Administer before any clinical assessments and dosing
C-SSRS Since Last Assessed		X	X	X	X	X	X	X	X	X	X	X	X	Administer before any clinical assessments and dosing
Self-harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	X	
Self-Harm Follow-Up Form	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Tests and Sample Collections														
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	Collect prior to dosing
Clinical Chemistry	X	X		X	X	X	X	X	X	X	X	X	X	In addition to scheduled assessments, these laboratory tests may also be performed as clinically indicated. Collect prior to dosing.

Study J1A-MC-KDAD	**Screen**	**Period 1: Double-blind treatment**					**Period 2**				**ED**	**Post-treatment follow-up**		**Comments**
Day ± Visit Tolerance	**-42 to -1**	**1**	**14 ± 7**	**28 ± 7**	**56 ± 7**	**84 ± 7**	**98 ± 7**	**112 ± 7**	**140 ± 7**	**168 ± 7**	Any	**196 ± 7**	**252 ± 7**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the tolerance window.
Week		**-**	**2**	**4**	**8**	**12**	**14**	**16**	**20**	**24**	**-**	**28**	**36 or ETV + 12**	
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET	V801	V802	
Procedures														
Urinalysis	X	X			X			X		X	X		X	In addition to scheduled assessments, these laboratory tests may also be performed as clinically indicated. Collect prior to dosing.
Serum pregnancy	X													For all women of childbearing potential (Section 10.4).
Urine pregnancy (local)		X		X	X	X		X	X	X	X	X	X	Determine results prior to dosing
Follicle Stimulating Hormone (FSH)	X													For women who are considered postmenopausal to confirm postmenopausal status.
C-Reactive Protein, high-sensitivity (hsCRP)	X	X	X	X	X	X	X	X	X	X	X	X	X	Collect prior to dosing
Erythrocyte sedimentation rate (ESR)	X	X				X				X	X	X	X	Collect prior to dosing
Rheumatoid factor (RF)	X	X				X				X	X	X	X	Collect prior to dosing
Anticyclic citrullinated peptide (anti-CCP)	X	X				X				X	X	X	X	Collect prior to dosing
Soluble PD-1		X	X	X	X	X		X		X	X	X	X	Collect prior to dosing
Soluble PD-L1		X	X	X	X	X		X		X	X	X	X	Collect prior to dosing.

Study J1A-MC-KDAD	**Screen**	**Period 1: Double-blind treatment**					**Period 2**				**ED**	**Post-treatment follow-up**		**Comments**
Day ± Visit Tolerance	**-42 to -1**	**1**	**14 ± 7**	**28 ± 7**	**56 ± 7**	**84 ± 7**	**98 ± 7**	**112 ± 7**	**140 ± 7**	**168 ± 7**	Any	**196 ± 7**	**252 ± 7**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the tolerance window.
Week		**-**	**2**	**4**	**8**	**12**	**14**	**16**	**20**	**24**	**-**	**28**	**36 or ETV + 12**	
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET	V801	V802	
Procedures														
Tuberculosis (TB) test	X													See Section 8.2.7 for details of TB testing. Participants will return 48 to 72 hours after a tuberculin test (TST) for their test results. If the QuantiFERON®-TB Gold test or T-SPOT® TB test is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB test is done centrally or locally; the T-SPOT® TB test must be done locally.
Human immunodeficiency virus (HIV) screening tests	X													
Hepatitis C virus (HCV) screening tests	X													
Hepatitis B virus (HBV) screening tests	X													Includes HBsAg and anti-HBc.
Hepatitis B virus (HBV) DNA	X					X				X	X		X	Any enrolled participant who is HBcAb+ will undergo monitoring of HBV DNA during the study treatment.
Flow cytometry panel		X		X		X		X		X	X		X	Includes: TBNK, collect prior to dosing
Cytokine panel		X		X		X		X		X	X		X	Collect prior to dosing

Study J1A-MC-KDAD	**Screen**	**Period 1: Double-blind treatment**					**Period 2**				**ED**	**Post-treatment follow-up**		**Comments**
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Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ET	V801	V802	
Procedures														
Immunoglobulin panel		X				X				X	X		X	Includes: IgG, IgM, and IgA Collect prior to dosing
Pharmacokinetic samples		X	X	X	X	X		X		X	X	X	X	Collect prior to dosing
Immunogenicity samples		X		X		X		X		X	X	X	X	Collect prior to dosing
Receptor occupancy		X	X	X	X	X				X	X	X	X	Collect prior to dosing
Peripheral helper T cells		X	X	X	X	X				X	X	X	X	Collect prior to dosing
Stored samples														
Genetics sample		X												Collect prior to dosing
Exploratory biomarker samples		X	X	X	X	X	X	X		X	X		X	See Section 10.2 for details Collect prior to dosing
Randomization and dosing														
Randomization		X												
Administer study drug		X		X	X	X		X	X	X				During Weeks 16 - 24 administer study drug only if participant achieved low disease activity at Week 14.

Abbreviations: AESI = adverse event of special interest; anti-HBc = hepatitis B core antibody; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation visit; ET = early termination; ETV = early termination visit; HBcAb+ = hepatitis B core antibody positive; HBsAg = hepatitis B surface antigen; ICF = informed consent form; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; MRI = magnetic resonance imaging; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PPD = purified protein derivative; PR = pulse rate; RA = rheumatoid arthritis; T = temperature; TBNK = T cells, B cells, natural killer cells; V = visit; VAS = visual analog scale.

2. Introduction

2.1. Study Rationale

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common, systemic autoimmune inflammatory disease, characterized by synovial inflammation leading to pain, swelling, stiffness, and progressive destruction and deformity of small and large joints. Patients experience impaired physical function, social participation, and health-related quality of life. Patients also have increased risk of significant nonmusculoskeletal comorbidities (Mutru et al. 1985; Doran et al. 2002; Sihvonen et al. 2004; Aviña-Zubieta et al. 2008, 2012; Choi et al. 2013; Kim et al. 2013; Lee and Pope 2014; Picerno et al. 2015; Simon et al. 2015; Ogdie et al. 2018).

Current treatment of RA

Current treatment of RA prioritizes timely initiation and modification of disease-modifying antirheumatic drugs (DMARD) therapy to bring patients to a target of sustained low disease activity (LDA) or remission (Singh et al. 2016; Smolen et al. 2020). Achievement of these targets improves short- and long-term patient health outcomes, including prevention of progressive, irreversible structural joint damage (Maini et al. 2004; Smolen et al. 2020).

The treatment target can be met in most patients with the therapeutic options currently available, which include conventional synthetic DMARDS (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). However, 20 to 30% of the patients with RA remain refractory to current therapies. For these patients, new treatment options are needed (Smolen et al. 2020).

Study KDAD

This study aims to evaluate the efficacy of LY3462817 in adult participants with moderately to severely active RA who have had an inadequate response to csDMARDs, or to bDMARDs/tsDMARDs.

2.2. Background

LY3462817 is a humanized immunoglobulin (Ig) G1 monoclonal antibody that binds to and is an agonist to human programmed cell death protein 1 (PD-1). CCI

[redacted]

PD-1 pathway in autoimmune diseases

Programmed cell death protein 1 expression was found to be high and programmed cell death ligand 1 (PD-L1) (which binds to PD-1) expression low in the synovium of patients with RA (Guo et al. 2018). Characterization of pathogenic, highly PD-1-expressing T-cell subsets within

the synovium of patients with RA showed them to be uniquely poised to promote B-cell responses and antibody production (Rao et al. 2017). Additionally, patients with RA tend to have autoantibodies to PD-L1 and increased soluble PD-1 (sPD-1) and PD-L1 (Wan et al. 2006), all of which correlate with disease activity.

Evidence of the PD-1 pathway pathology having a significant role in autoimmune diseases has also been demonstrated in psoriasis (Gulati et al. 2015), psoriatic arthritis (Bommarito et al. 2017), giant cell vasculitis (Zhang et al. 2017), multiple sclerosis (Trabattoni et al. 2009), and systemic sclerosis (Fukasawa et al. 2017).

LY3462817

Information on the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3462817 comes from the completed study J1A-MC-KDAB (KDAB) and from the ongoing study J1A-MC-KDAC (KDAC).

Study	Study design	Population	Study interventions
KDAB	Single ascending dose, first in human, Phase 1	Healthy participants	LY3462817: 0.1, 0.4, 2, 8, 30, 120, 350, or 700 mg IV 120 mg SC
KDAC	Double-blind, multiple ascending dose, placebo-controlled, Phase 1b.	Participants with psoriasis	LY3462817: 75, 300, or 700 mg Q4W IV for 12 Weeks

Abbreviations: IV = intravenous; Q4W = once every 4 weeks; SC = subcutaneous.

As of 02 September 2020, 47 healthy participants in Study KDAB have received LY3462817. Six participants received 75 mg and 7 participants have received 300 mg LY3462817 in Study KDAC.

No deaths or serious adverse events (SAEs) were reported so far in these studies, and no participants discontinued because of an adverse event (AE). Overall, no clinically significant safety concerns were identified with single-dose intravenous (IV) administration of LY3462817 up to 700 mg and subcutaneous (SC) administration of LY3462817 120 mg. Also, no clinically significant safety concerns have been identified with multiple-dose administration of LY3462817 up to 300 mg in Study KDAC.

The PK of LY3462817 has been evaluated following single doses (Study KDAB) and a small subset of the 75 mg multiple dose (Study KDAC) cohort. Nonlinear disposition that is characteristic of many monoclonal antibodies was observed at lower doses and the PK was approximately dose-proportional at doses equal to and greater than 30 mg. Based on noncompartmental analysis, in the dose linear range (≥30 mg), LY3462817 has estimated clearance of 10.9 mL/hr, volume of distribution of 3.9 L, and a terminal half-life of approximately 10 days. A comparison of exposure from the single dose 120 mg IV and SC cohorts indicates a bioavailability of approximately 60%. Across the IV cohorts, the median time to reach C_{max} ranges between 2 to 8 hours while for 120 mg SC, the median is approximately 9.5 days. Given the limited PK data in the multiple dose cohort (75 mg IV once every 4 weeks [Q4W]), results were not statistically analyzed. Additionally, in Study KDAB, receptor occupancy (RO) and sPD-1 concentrations in healthy volunteers following single IV doses of LY3462817 were collected and analyzed. Together, both are interpreted as measures of target engagement. Across all dose levels tested, RO and sPD-1 increased in both extent and duration with increasing dose level.

In Study KDAC, the 75-mg cohort (N=8) and 300-mg cohort (N=10) were fully enrolled. By the data cutoff date, some subjects had received a minimum of 2 doses, while some subjects had received a maximum of 4 doses (every-4-week dosing schedule).

A decision was made to dose escalate to 700 mg on 08 September 2020. Given the overall safety profile of LY3462817 to date, the sponsor believes the decision to dose escalate to 700 mg in Study KDAC provides sufficient safety data to initiate this study, KDAD.

A detailed description of the chemistry, pharmacology, toxicology, efficacy, and safety of LY3462817 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

Manageable risks associated with most therapeutic monoclonal antibodies are the potential for infusion-related hypersensitivity and cytokine release reactions. The infusions in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made and/or the infusion stopped, if indicated. Additional information regarding infusion reaction and hypersensitivity management options is located in Section 8.3.6.

No clinically significant safety concerns (including infusion or injection site reactions) were observed in Study KDAB, or have been observed in the Study KDAC as of 02 September 2020.

The efficacy of LY3462817 in RA has not been established. Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

In summary, in the context of the cumulative knowledge for LY3462817, the benefit/risk balance for this study is assessed to be acceptable for testing in Phase 2.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3462817 may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints and Estimands
Comparison Groups: Placebo vs LY3462817 **[time frame for endpoint evaluation: 12 weeks from randomization, unless stated otherwise]**	
Primary	
To evaluate the efficacy of LY3462817 in adult participants with moderately to severely active RA	Change from baseline in DAS28-CRP The primary comparison will be assessed using a hypothetical efficacy estimand strategy to address the intercurrent event of early discontinuation where the mean change from baseline will be evaluated using only data up until discontinuation as if all subjects remained on randomized treatment.
Secondary	
To describe the safety and tolerability of LY3462817 compared to placebo	Safety assessments such as AEs, SAEs

To evaluate the effect of LY3462817 on measures of disease activity	• Proportion of participants achieving ACR20, ACR50, and ACR70
	• Change from baseline for physician-assessed individual components:
	  o 68 tender joint count
	  o 66 swollen joint count
	  o physician's global assessment of disease activity (VAS)
	• Change from baseline for mean SDAI
	• Change from baseline for mean CDAI

To describe the effect of LY3462817 on PROs	Change from baseline for:
	• Individual components of the ACR core set:
	  o patient's global assessment of disease activity (VAS),
	  o patient's global assessment of arthritis pain (VAS), and
	  o patient's assessment of physical function (HAQ-DI)
	• SF-36

To characterize the pharmacokinetics of LY3462817	Observed drug concentration
Exploratory	
To explore the effect of LY3462817 on other measures of disease activity	• Proportion of participants achieving LDA or remission using the following measures: DAS28-CRP, DAS28-ESR, SDAI, and CDAI at all time points collected • Change from baseline in the RAMRIS synovitis score by MRI imaging
To explore the durability of effect of LY3462817	• Proportion of participants achieving LDA (with the following measures: DAS28-CRP, DAS28-ESR, SDAI, and CDAI) at Week 12 and maintaining LDA through Week 24 • Proportion of participants that achieve remission (with the following measures: DAS28-CRP, DAS28-ESR, SDAI, and CDAI) at Week 12 and maintaining remission through Week 24

Abbreviations: ACR = American College of Rheumatology; ACR20 = 20% improvement in American College of Rheumatology criteria; ACR50 = 50% improvement in American College of Rheumatology criteria; ACR70 = 70% improvement in American College of Rheumatology criteria; AE = adverse event; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; LDA = low disease activity; MRI = magnetic resonance imaging; PRO = patient-reported outcome; RA = rheumatoid arthritis; RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system; SAE = serious adverse event; SDAI = Simplified Disease Activity Index; SF-36 = Study 36-Item Short Form Health Survey; VAS = visual analog scale.

4. Study Design

4.1. Overall Design

This is a Phase 2, proof-of-concept, placebo-controlled, double-blind, randomized study in adult participants with moderately to severely active RA who have had an inadequate response to csDMARDs, or to bDMARDs/tsDMARDs. Participants will be administered LY3462817 or placebo IV Q4W.

Screening Period (Visit 1, Days -42 to -1)

Participants will sign the informed consent document(s) at Visit 1, prior to completion of any procedures. Participants will be evaluated for study eligibility ≤42 days prior to the baseline visit (Visit 2).

Period 1: Double-blind Treatment (Visits 2 to 6; 12 weeks)

At the baseline visit (Visit 2), participants who fulfill the eligibility criteria will be randomized to receive LY3462817 700 mg, LY3462817 300 mg, or placebo in an allocation ratio of 2:1:1.

The double-blind treatment period will establish the clinical efficacy and safety of LY3462817. The study will be evaluated for the primary objective at the end of the double-blind treatment period.

Period 2 (Visits 6 to 10; 12 weeks)

Data from a Study KDAC interim analysis that includes Week 12 data from participants in the KDAC 700-mg cohort, must be reviewed prior to a participant proceeding to Period 2 in Study KDAD.

At Week 14, participants will be evaluated for clinical benefit.

Participants assigned to LY3462817 at baseline, and achieving low disease activity (CDAI ≤10) at Week 14 will continue to receive LY3462817 at the randomized dose through Week 24 to assess safety and tolerability and evaluate efficacy.

All other participants at Week 14, regardless of baseline treatment assignment, will stop study drug infusions and should receive standard of care treatment at the investigator's discretion.

Posttreatment Safety Follow-up Period (Visits V801 and 802; 12 weeks)

Following Period 2, participants will be followed posttreatment for 12 weeks to assess safety, study drug exposure, and clinical disease activity measures. Participants who discontinue the study intervention per Section 7 will have their last visit at 12 weeks from the last administration of the study intervention.

4.2. Scientific Rationale for Study Design

Appropriateness of study population

Patients with RA are treated with the oral csDMARD methotrexate (MTX) as the first-line therapy either by itself or in combination with other therapies (Smolen et al. 2020). If the treatment target is not achieved with the initial csDMARD strategy, treatment modification often

involves use of bDMARDs, including tumor necrosis factor-α (TNF-α) inhibitors, or targeted synthetic tsDMARDs, in combination with csDMARDs (Smolen et al. 2020).

LY3462817 is being investigated to modulate the underlying immune dysregulation in the PD-1 pathway for the treatment of RA. Enrolling a mixed RA population who have had an inadequate response to csDMARDs, or to bDMARDs/tsDMARDs would allow patients with inadequate response to the current standard of care for RA across the disease spectrum to be included in the study.

Duration of treatment period and post-treatment follow-up

The placebo-controlled treatment period (Period 1) lasts 12 weeks. Participants randomized to LY3462817 at baseline can continue to receive treatment though Week 24 if achieving low disease activity by Week 14. Per current RA treatment guidelines (Smolen et al. 2020), therapy should be adjusted if no improvement is achieved by approximately ≤3 months within initiation, or if the target has not been reached by 6 months (Smolen et al. 2020). All participants randomized to placebo, and participants randomized to LY3462817 not achieving low disease activity by Week 14 should be switch to SOC RA therapy at the investigator's discretion. The length of the study placebo-controlled period falls within those guidelines.

The 12-week follow-up duration after 24 weeks of treatment is considered to be sufficient to evaluate safety and to explore the durability of biomarker and clinical disease activity changes achieved during the 24-week treatment period. Participants with disease activity that require any other treatment may discontinue the study at any time (Section 7.2).

Change from baseline in DAS28-CRP as the primary endpoint

The primary endpoint of this study is the change from baseline at Week 12 in the Disease Activity Score - C-reactive protein (DAS28-CRP) (Sections 3 and 8.1.1) and is a continuous measure that enables evaluation across multiple time points.

MRI

Magnetic resonance imaging (MRI) allows detailed assessment of the synovial joint. Magnetic resonance imaging features are frequently used as outcome measures in RA clinical trials. The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) RA MRI Scoring system (RAMRIS) outlines semiquantitative scoring of 5 RA pathologies: bone erosions, joint space narrowing, synovitis, tenosynovitis, and bone marrow edema in the wrist and metacarpophalangeal joints.

The primary interest in this study is to evaluate the effectiveness of LY3462817 in reducing inflammation in the joints. Enrolling study participants with active synovitis as determined by MRI will support overall evaluation of LY3462817 in reducing inflammation. Exploratory evaluation of a change in RAMRIS synovitis score at Week 12 will provide an objective measure of reduction in inflammation.

4.3. Justification for Dose

In this study, 2 dose levels of LY3462817 will be evaluated: 300 mg and 700 mg. These dose levels were selected based on preclinical pharmacology and toxicology data, and available clinical PK, target engagement, and safety data.

In Study KDAB, single LY3462817 IV doses of 350 and 700 mg have been evaluated in healthy subjects with no clinical significant safety concerns. The ongoing Study KDAC, is designed to evaluate multiple doses (4 total doses) of 75 mg, 300 mg, and 700 mg of LY3462817 IV Q4W in participants with psoriasis. The data from these studies and the plan to initiate KDAD is discussed in Section 2.2.

From available human PK and preclinical monkey toxicology data, the estimated margins of safety for 300 mg and 700 mg LY3462817 IV Q4W are ≥24 and >10-fold, respectively, based on both dose and steady-state exposure multiples.

The planned dose levels were also selected to evaluate an exposure range that is anticipated to be pharmacologically active. Receptor occupancy was used as a surrogate for pharmacological activity to help assess dose levels that saturate the target over the planned dosing interval. Doses of 350 mg and 700 mg have both been shown to saturate the receptor in plasma over 4 weeks and longer. However, significant uncertainties exist in translating RO profile in plasma to tissue with respect to drug concentration and receptor density (Chen et al. 2015; Rao et al. 2017). The 2 dose levels help account for these uncertainties, both of which directionally point to a decrease in extent and duration in tissue RO relative to plasma. Additionally, inclusion of 2 dose levels in KDAD will allow for a direct comparison with the corresponding dose levels in KDAC for assessing the impact, if any, of disease state on PK, RO, and sPD-1. If there is impact, having an additional dose level in KDAD will provide more data and confidence when projecting forward to a dose level or regimen ranging study.

4.4. End of Study Definition

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

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the trial globally.

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Are ≥18 years of age, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Have a diagnosis of adult onset RA as defined by the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria (Aletaha et al. 2010) for at least 3 months prior to screening
3. Have moderately to severely active RA defined by the presence of ≥6 swollen joints (based on 66 joint count) and ≥6 tender joints (based on 68 joint count) at screening and baseline. The distal interphalangeal joint should be evaluated but not included in the total count to determine eligibility
4. Have at least 1 of the following:
   - positive test results for rheumatoid factor or anti-citrullinated peptide antibodies at screening,
     OR
   - previous radiographs documenting bony erosions in hands or feet consistent with RA
5. Have C-reactive protein (CRP) >1.2 times upper limit of normal (ULN) per the central laboratory at screening
6. Have active synovitis in ≥1 joint in hands or wrists at screening as demonstrated by a MRI synovitis RAMRIS score (Østergaard et al. 2017) of ≥1 determined from central reading of images
7. Vaccinations of study subjects should be up to date per regional and national guidelines, specifically influenza, pneumonia, and zoster. All should be administered ≥30 days before randomization and no live vaccines should be used within 3 months of randomization
8. Have clinically acceptable central laboratory test results at screening (retesting is allowed for hematology and chemistry), as assessed by the investigator, including:

   Hematology

   - absolute neutrophil count ≥1.5 × 10^9/L (≥1.5 × 10^3/μL or ≥1.5 GI/L)
   - platelet count ≥100 × 10^9/L (≥100 × 10^3/μL or ≥100 GI/L)
   - hemoglobin level ≥10.0 g/dL

- lymphocyte count >500 cells/μL (>0.50 × 10^3/μL or >0.50 GI/L)
- total leukocyte count ≥3.0 × 10^9/L (≥3.0 × 10^3/μL or ≥3.0 GI/L)

Clinical chemistry test results

- serum creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels ≤2 × ULN
- total bilirubin level (TBL) and alkaline phosphatase (ALP) <1.5 × ULN (patients with Gilbert's syndrome must have serum direct bilirubin <1.5 mg/dL)

Concomitant Therapy

9. Demonstrated an inadequate response to, or loss of response or intolerance to:
   - at least 1 csDMARD treatment
     OR
   - at least 1 bDMARD/tsDMARD treatment

   This is defined as signs and symptoms of persistently active disease despite a history of treatment with at least 1 of the following: azathioprine, MTX, hydroxychloroquine, leflunomide, sulfasalazine, bDMARDs, or tsDMARDs

10. The following therapies are permitted during the study, if the dose is stable for ≥4 weeks prior to the screening MRI:
    - parenteral MTX up to 20 mg/week OR oral MTX up to 25 mg/week. Subjects on MTX should receive supplementation with folic acid according to local standard of care
    - hydroxychloroquine up to 400 mg/day
    - leflunomide up to 20 mg/day
    - oral sulfasalazine up to 3000 mg/day
    - oral prednisone ≤10 mg daily or other equivalent corticosteroid dose

Contraception

11. To participate in the study, participants must agree to the reproductive and contraceptive agreements and guidance provided in Section 10.4, Appendix 4.

    Contraceptive use by men or women should be consistent with local regulations for those participating in clinical studies.

Informed Consent

12. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

13. Class IV RA according to ACR revised response criteria
14. Have an abnormality in the 12-lead electrocardiogram (ECG) that, in the opinion of the investigator, increases the risks associated with participating in the study
15. Have presence of 1 or more significant concurrent medical conditions per investigator judgment, including but not limited to the following: poorly controlled diabetes or hypertension; chronic kidney disease stage IIIb, IV, or V; symptomatic heart failure (New York Heart Association class II, III, or IV); myocardial infarction or unstable angina pectoris within the past 12 months prior to randomization; severe chronic pulmonary disease (e.g., requiring oxygen therapy); and major chronic inflammatory disease or connective tissue disease other than RA
16. Have a history of chronic alcohol abuse, IV drug abuse or illicit drug abuse within 1 year before screening.
    Note: Marijuana use is prohibited during participation in this study, regardless of local laws or if used for medical purposes. Cannabidiol (CBD) products may be used during the study if they are derived exclusively from hemp. Participants who use hemp-based CBD products must be on a stable dose for at least 10 days prior to randomization, and participants must remain on that stable dose during the study.
17. Have a Columbia-Suicide Severity Rating Scale (C-SSRS) ideation within 1 month prior to screening or any suicidal behavior within 3 months prior to screening and either ideation or suicidal behavior during screening prior to Visit 2
18. Have donated blood of more than a single unit of blood within 4 weeks before randomization (Visit 2) or intent to donate blood during the course of the study
19. Have a diagnosis or history of malignant disease within 5 years prior to baseline, with the exceptions of:
    - basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years, or
    - cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline
20. Have presence of confirmed cervical dysplasia
21. Have had any surgical procedure (except for minor surgery requiring local or no anesthesia and without any complications or sequelae) within 12 weeks prior to screening, or any planned surgical procedure scheduled to occur during the study

22. Have received a Bacillus Calmette-Guerin (BCG) vaccination or BCG treatment within 12 months of screening; or received any other live vaccine(s) (i.e., live attenuated) within 3 months of screening, or intend to receive a live vaccine during the study

23. Have had any of the following types of infection within 3 months of screening or develops any of these infections before the randomization visit:
    - Serious (requiring hospitalization, and/or IV or equivalent oral antibiotic treatment)
    - Opportunistic (as defined in Winthrop et al. 2015)
        - Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over
    - Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
    - Recurring (including, but not limited to herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis)
        - Subjects with recurrent nonserious infections such as cellulitis and uncomplicated orolabial and/or genital herpes may be enrolled at the discretion of the investigator when deemed not to place subjects at an increased risk of complications

24. Have any of the following:

    - Human immunodeficiency virus (HIV) infection
    - Current infection with hepatitis B virus (HBV) (i.e., positive for hepatitis B surface antigen and/or polymerase chain reaction [PCR] positive for HBV DNA)
    - Current infection with hepatitis C virus (HCV) (i.e., positive for HCV RNA)
    - Active tuberculosis (TB)

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

26. Current or recent acute active infection, or fever of 100.5°F (38°C) or above, at screening or baseline. For at least 30 days prior to screening, participants must have no symptoms and/or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment

27. Have estimated glomerular filtration rate from serum creatinine using the Modification of Diet in Renal Disease method of <60 mL/minute

28. Participants having contraindications to MRI (for example, claustrophobia, pacemakers, aneurysm clips, intraocular metallic fragments) or IV gadolinium diethylenetriamine penta-acetic acid ([Gd-DTPA]; moderate or severe renal insufficiency, prior allergic reaction to gadolinium-containing contrast media)

29. Are women who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study drug.

Prior/Concomitant Therapy

30. Currently receiving or have received any of the following therapies within 28 days prior to the screening MRI:

    - MTX, hydroxychloroquine, sulfasalazine, or leflunomide at an unstable dose (defined as a change in prescription).
      This also includes a planned dose change during the study (including initiation or discontinuation)
    - Cyclophosphamide, azathioprine, cyclosporine, gold, mycophenolate mofetil, Prosorba column, or Tacrolimus
    - Oral Janus kinase inhibitor (e.g., tofacitinib, baricitinib)
    - Parenteral corticosteroids, including initiation of planned treatment during the study
      Note: A single intra-articular corticosteroid injection is permitted within 28 days prior to the screening MRI if no more than 40 mg triamcinolone (or equivalent) is administered and no further injections are planned during the study. The treated joint should be excluded from any joint-specific evaluations during the study.
    - A chronic narcotic drug at an unstable dose. This also includes planned increase/new prescription during the study

31. Have received any of the following biologic immunosuppressive therapies under the defined conditions or plan any such treatments during the study (other biologic agents may be allowed after discussion with the sponsor and upon agreement in writing):

    - Etanercept, adalimumab, anakinra, infliximab, certolizumab pegol, golimumab, abatacept, or tocilizumab within 8 weeks prior to screening MRI
    - B-cell–depleting agents (such as rituximab) or other cell-depleting biologics (e.g., anti-CD3 antibody) within 12 months prior to screening MRI

32. Have failed more than 2 bDMARDs or tsDMARDs (e.g. excluded if have failed 2 bDMARDs and 1 tsDMARD)

33. Have previously completed a clinical trial investigating any other molecule targeting PD-1 or have previously discontinued from this study after receiving LY3462817

Prior/Concurrent Clinical Study Experience

34. Are currently enrolled in any other clinical trial involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study

35. Have participated, within the last 30 days, in a clinical trial involving study intervention. If the previous study intervention has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening

36. Have previously completed or withdrawn from this study

Other Exclusions

37. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
38. Are Lilly employees or employees of third-party organizations involved with the study that require exclusion of their employees
39. Are not willing to receive IV injections
40. Are unsuitable for inclusion in the study, in the opinion of the investigator or sponsor, for any reason that may compromise the participant's safety or confound data interpretation

5.3. Lifestyle Considerations

All study participants should be instructed not to donate blood or blood products during the study or for 6 months after the last dose of the study intervention.

Reproductive and Contraceptive guidance is provided in Section 10.4, Appendix 4.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once for failure due to any of the following criteria: 2, 8, 21, 22, 23, 26, 34, or 35. Individuals who failed criterion 25 can be rescreened once if appropriate treatment for LTBI is underway. Rescreened participants should be assigned a new participant number. Each time rescreening is performed, the individual must sign a new ICF.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

Study interventions

Each participant will receive multiple IV infusions of placebo, LY3462817 300 mg, or LY3462817 700 mg.

Intervention Name	Placebo	LY3462817	LY3462817
Dose Formulation	0.9% sodium chloride solution	Solution	Solution
Unit Dose Strengths	-	50 mg/mL in a 3-mL vial	
Dosage Level(s) (mg)	Not applicable	300	700
Use	Placebo	Experimental	
IMP and NIMP	IMP	IMP	
Sourcing	Commercially available 0.9% sodium chloride solution sourced centrally by Lilly	From Lilly	
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study intervention will be provided in glass vials and will be labeled as required per country requirement	

Abbreviations: IMP = Investigational Medicinal Product; NIMP = Noninvestigational Medicinal Product.

Study intervention will be prepared by an unblinded pharmacy staff or pharmacist who is not involved in any other study-related procedures.

The study intervention is planned to be administered as an IV infusion.

The infusion rate may be reduced as deemed necessary if an infusion reaction is observed (Section 8.3.6). Participants will be monitored for signs and symptoms of infusion reaction:

- during the infusion, and
- for at least 1 hour after completion of the infusion.

Infusion information may be found in the pharmacy binder.

Resuscitation equipment, emergency drugs, and appropriately trained medical staff must be available during the infusion and for at least 1 hour after the completion of the infusion.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized study staff or designee may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study staff or designee.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

To preserve the blinding of the study, a minimum number of Lilly personnel who are not directly involved with investigational sites will see the randomization table and treatment assignments before the study is complete.

Joint, disease activity, and safety assessments

Joint Assessor

To prevent potential bias due to observed efficacy or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety. The Joint Assessor (or designee) should be a rheumatologist or skilled arthritis assessor. The Joint Assessor will be responsible for completing the joint counts. To ensure consistent joint evaluation throughout the trial, individual participants should be evaluated by the same Joint Assessor for all study visits. The Joint Assessor must not access or discuss with the participant the patient-reported assessments, Physician's Global Assessment of Disease Activity (PhGADA_VAS), and safety assessments.

Safety Assessor

The Safety Assessor (or designee) should be a rheumatologist (or medically qualified physician) and will have access to both safety and efficacy data. The Safety Assessor may be the principal investigator. The Safety Assessor will be responsible for completing the PhGADA_VAS. To ensure consistent PhGADA_VAS throughout the trial, the instrument should be evaluated by the same physician at all study visits. The Safety Assessor will have access to source documents, laboratory results, and electronic case report forms (eCRFs) and will be responsible for making treatment decisions based on a participant's clinical response and laboratory parameters.

Method of treatment assignment

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

Participants will be stratified by prior use of csDMARD only or by tsDMARD/bDMARDs use (yes versus no).

Emergency unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, the sponsor must be notified immediately.

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

6.4. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The date and time of each dose administered will be recorded in the source documents and in the case report form (CRF). The dose of study intervention and study participant identification will be confirmed prior to the time of dosing.

6.5. Concomitant Therapy

Participants will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical condition. Investigators should follow local guidelines for the management of lipid disorders. If the need for other concomitant medications arises, discontinuation of the participant from study intervention or the study will be at the discretion of the investigator in consultation with sponsor (or designee).

All medications, whether prescription or over-the-counter, used at screening and/or during the study must be documented in the eCRF with start and stop dates.

6.5.1. Permitted Rheumatoid Arthritis Concomitant Therapy

Treatment with the following concomitant medications for RA during the study are permitted as outlined below and in the inclusion/exclusion criteria. This applies to all participants during Period 1 and any participant that remains on LY3462817 during Period 2.

Concomitant therapy	Permitted	Not permitted
Methotrexate (MTX)	If parenteral, up to 20 mg/week If oral, up to 25 mg/week Subjects on MTX should receive supplementation with folic acid according to local standard of care	
Hydroxychloroquine	up to 400 mg/day	
Oral sulfasalazine	up to 3000 mg/day	

Concomitant therapy	Permitted	Not permitted
Leflunomide	up to 20 mg/day	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Permitted during the Period 1 only if the participant was on a stable dose for at least 7 days before planned randomization.	Increase of NSAID dose and/or introduction of new NSAIDs are not permitted during the Period 1 or in participants receiving LY3462817 in Period 2
Analgesics	Dose reductions and/or termination of analgesics are permitted at any time.	
Corticosteroids	Prednisone (or equivalent) at doses up to 10 mg per day is allowed during this study but must be maintained at stable levels from ≥4 weeks prior to the screening magnetic resonance imaging (MRI) through Period 1 or in participants receiving LY3462817 in Period 2. Topical, intranasal, intraocular, and inhaled corticosteroids are permitted. **Directions for use of intra-articular glucocorticoids**: If an unforeseen intra-articular glucocorticoid injection is required during the study, it will be noted as a protocol deviation. Any joints that had been injected with intra-articular corticosteroids within 42 days prior to the screening MRI will be censored from the clinician-administered Tender Joint Counts (TJCs) and Swollen Joint Counts (SJCs) (68/66) for the duration of the study.	Participants who were not previously on prednisone (or equivalent) prior to randomization should not initiate corticosteroid therapy during the study during Period 1 or in participants receiving LY3462817 in Period 2, Participants should not receive other systemic corticosteroids during the study including intra-muscular or intra-articular corticosteroids during Period 1 or in participants receiving LY3462817 in Period 2.
Folic acid	Local standard of care should be followed for concomitant administration of folic acid.	

6.5.2. Prohibited Concomitant Therapy

Live vaccinations are not allowed up to 3 months prior to screening or at any time during the study. Live herpes zoster vaccination is not permitted within 30 days of planned randomization or at any time during the study.

Nonlive seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed.

6.5.3. Standard of Care Therapy after Week 14

All placebo patients should begin SOC therapy at Week 14 at the investigator's discretion.

Participants randomized to LY3462817 at baseline and not achieving low disease activity (CDAI ≤10) at Week 14 will no longer receive study drug infusions and should receive SOC therapy at the investigator's discretion.

Participants who achieve low disease activity at Week 14, and maintain treatment with LY3462817 during Period 2, can be switched to SOC prior to Week 24 if the participant stops receiving clinical benefit. Name(s) and dosage regimen(s) must be recorded for the SOC therapy. Standard of care medications will not be supplied by the sponsor.

6.6. Dose Modification

Dose modifications during the treatment period will not be allowed.

6.7. Intervention after the End of the Study

No continued access is planned after completion of this study, as additional efficacy would be needed to demonstrate continued access criteria.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The sections below describe reasons for a participant's

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

Discontinuation of specific sites or of the trial as a whole are handled as part of regulatory, ethical, and trial oversight considerations in Section 10.1, Appendix 1.

7.1. Discontinuation of Study Intervention

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

Participants who permanently discontinue study intervention early will undergo early termination procedures, which include an early termination visit and a posttreatment follow-up visit (V801) as described in the SoA (Section 1.3).

The investigator will complete any AE reporting and follow-up (Section 8.3).

7.1.1. Criteria for Temporary Interruption (Withholding) of Study Intervention

Study treatment may be temporarily discontinued if the participant requires surgery. Administration of the study intervention may be restarted only after adequate wound healing.

This and other situations that may merit temporary discontinuation of the study intervention should be discussed with the sponsor. The investigator should consult with the Medical Monitor and then determine when it is appropriate to recommence study treatment.

7.1.1.1. Infection-related Criteria for Temporary Withholding of Study Intervention

Study intervention will be temporarily withheld if any of the following infection-related criteria occur during the study:

1. Serious or opportunistic infections, as defined in Exclusion Criteria (Section 5.2). Study intervention can be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment (exception for LTBI, noted below). The investigator should consult with the Medical Monitor and then determine when it is appropriate to recommence study treatment.
2. If a participant is diagnosed with LTBI during the study and is treated for LTBI as follows:
   a) Study intervention is temporarily held for at least the first 4 weeks of LTBI treatment.
   b) If there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance after receiving at least 4 weeks of appropriate LTBI therapy (as per WHO and/or CDC guidelines), then study intervention may be resumed.
   c) The participant must complete appropriate LTBI therapy during the course of the study to remain eligible to continue to receive study intervention.
3. HBV DNA results reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. The Medical Monitor should be contacted regarding study status

of the participant. Hepatitis B virus DNA testing should be repeated as soon as possible. If HBV DNA is confirmed positive, then study intervention should be discontinued.

7.1.2. Criteria for Permanent Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will be encouraged to remain in the study. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Permanent discontinuation of study intervention should occur if the scenarios described occur during the study.

Participant decision

- The participant requests to discontinue the study intervention.

Investigator decision

- The investigator decides that the participant should be discontinued from the study intervention.

Pregnancy

- The participant becomes pregnant during the study (see Section 8.3.5 and Section 10.4, Appendix 4).

Safety considerations

The participant:

- Has a malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- Answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS
- Answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS
  A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.
- Is diagnosed with LTBI during the study and are not a candidate for treatment as described in Section 7.1.1.1, or
- Has a serious or opportunistic infection that in the opinion of the investigator merits the study intervention being discontinued. Such infections may include, but are not limited to:
  - HIV/acquired immune deficiency syndrome (AIDS) infection
  - active TB infection or untreated LTBI (see Sections 7.1.1 and 8.2.6)
  - HCV RNA positive (Section 8.2.8)
  - HBV DNA positive (Section 8.2.7).

The participant should be referred to, evaluated and managed by a specialist physician with expertise in evaluation and management of viral hepatitis prior to discontinuation of any

immunomodulatory and/or immunosuppressive therapy, including study intervention. Timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

Hepatic event or liver test abnormality

Participants who are discontinued from intervention due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF. The investigator should consult with the medical monitor to determine if discontinuation of the intervention for abnormal liver tests **should be** considered if a participant meets one of these conditions (see Section 10.7, Appendix 8):

- ALT or AST >8 times ULN
- ALT or AST >5 times ULN for more than 2 weeks
- ALT or AST >3 times ULN and TBL >2 times ULN or international normalized ratio (INR) >1.5
- ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 times ULN
- ALP >2.5 times ULN and TBL >2 times ULN, or
- ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

Discontinuation is expected to be uncommon.

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. Additional country-specific requirements for discontinuation of inadvertently enrolled participants is provided in Section 10.10, Appendix 10.

The investigator should consult with the Medical Monitor, then determine if it is medically appropriate to continue. The investigator must obtain documented approval from the Medical Monitor to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product.

Safety follow up is as outlined in:

- Section 1.3 (SoA)
- Section 8.2 (Safety Assessments), and
- Section 8.3 (Adverse Events and Serious Adverse Events).

7.3. Lost to Follow up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1, Appendix 1.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Monitoring of blinded safety data will continue throughout the study and will be conducted by blinded study team members. Details of the blinded safety reviews, including the frequency and approximate timing, are specified in the trial level safety review plan.

8.1. Efficacy Assessments

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

8.1.1. Disease Activity Score–High-Sensitivity C-Reactive Protein (DAS28-hsCRP)

The DAS28-hsCRP measures disease activity in 28 joints using a composite numeric score of the following variables (Vander Cruyssen et al. 2005):

- TJC (see Section 8.1.4)
- SJC (see Section 8.1.4)
- high sensitivity C-reactive protein (hsCRP), and
- Patient's Global Assessment of Disease Activity (PaGADA_VAS; see Section 8.1.7).

The 28 joints examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC include 14 joints on each side of the participant's body (Smolen et al. 1995):

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

8.1.2. Disease Activity Score–Erythrocyte Sedimentation Rate (DAS28-ESR)

The DAS28-ESR measures disease activity in 28 joints using a composite numeric score of the following variables (Vander Cruyssen et al. 2005):

- TJC (Section 8.1.4)
- SJC (Section 8.1.4)
- Erythrocyte sedimentation rate (ESR), and
- PaGADA_VAS (Section 8.1.7).

For description of the 28 joints to be examined, see Section 8.1.1.

The DAS28-ESR remission is defined as DAS28-ESR <2.6, and DAS28-ESR LDA is defined as DAS28-ESR ≤3.2.

8.1.3. American College of Rheumatology Criteria (ACR20, ACR50, and ACR70)

The ACR20 is defined as at least 20% improvement in the ACR core set values. Similarly, ACR50 and ACR70 are defined as at least 50% and 70% improvement in the ACR core set values.

This is defined as:

- an improvement of at least 20%, 50%, or 70% in the TJC and SJC (68/66; Section 8.1.4) AND
- an improvement of at least 20%, 50%, or 70% in at least 3 of the following 5 assessments:
  1. Patient's Global Assessment of Arthritis Pain (visual analog scale [VAS]; Section 8.1.6)
  2. PaGADA_VAS (Section 8.1.7)
  3. PhGADA_VAS (Section 8.1.5)
  4. Patient's Assessment of Physical Function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI; Section 8.1.8)
  5. Acute phase reactant as measured by hsCRP

8.1.4. Tender Joint Count and Swollen Joint Count

The joint exam will be performed by the Joint Assessor and reviewed by the Safety Assessor (Section 6.3).

8.1.5. Physician's Global Assessment of Disease Activity (PhGADA_VAS)

The PhGADA_VAS is used as a component of ACR (Section 8.1.3) as well as a separate efficacy assessment.

The PhGADA_VAS is a single item that asks the physician to assess the patient's current disease activity on a 0- to 100-mm VAS, with anchors of 0 = "no disease activity" and 100 = "extremely active disease."

8.1.6. Patient's Global Assessment of Arthritis Pain (Visual Analog Scale)

The Patient's Global Assessment of Arthritis Pain (VAS) is used as a component of ACR (Section 8.1.3) as well as a separate efficacy assessment.

The Patient's Global Assessment of Arthritis Pain (VAS) is a single item that asks the patient to rate the current severity of their pain in relation to their RA on a 0- to 100-mm VAS, with anchors of "no pain" and "worst possible pain."

8.1.7. Patient's Global Assessment of Disease Activity (PaGADA_VAS)

The PaGADA_VAS is used as a component of ACR (Section 8.1.3) as well as a separate efficacy assessment.

The PaGADA_VAS is a single item that asks the patients to indicate how they feel their RA is today on a 0- to 100-mm VAS, with anchors of 0 = "very well" and 100 = "very poor."

8.1.8. Health Assessment Questionnaire - Disability Index (HAQ-DI)

The HAQ-DI is used as a component of ACR (Section 8.1.3) as well as a separate efficacy assessment.

The HAQ-DI is a patient-reported questionnaire that is commonly used in RA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains (Fries et al. 1980, 1982; Ramey et al. 1996):

1. dressing/grooming
2. arising
3. eating
4. walking
5. hygiene
6. reach
7. grip, and
8. activities.

Participants use a scale from 0 to 3 to score difficulty when performing these and other daily activities over the past week (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do). The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. Higher scores indicate more limitations in physical function. The scores for each of the functional domains will be averaged to calculate the functional disability index.

8.1.9. Simplified Disease Activity Index (SDAI)

The SDAI is a tool for measurement of disease activity in RA that integrates measures of physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI is calculated by adding together scores from the following assessments:

- number of swollen joints (0 to 28)
- number of tender joints (0 to 28)
- CRP in mg/dL (0.1 to 10.0)
- PaGADA_VAS (0 to 100 mm), and
- PhGADA_VAS (0 to 100 mm) (Aletaha and Smolen 2005).

Disease remission according to ACR/EULAR index-based definition of remission is defined as an SDAI score of ≤3.3 (Felson et al. 2011). Low disease activity is defined as an SDAI score of ≤11.

8.1.10. Clinical Disease Activity Index (CDAI)

The CDAI is similar to the SDAI, but it allows for immediate scoring because it does not use a laboratory result. The CDAI is calculated by adding together scores from the following assessments:

- number of swollen joints (0 to 28)
- number of tender joints (0 to 28)
- PaGADA_VAS (0 to 100 mm), and
- PhGADA_VAS (0 to 100 mm) (Aletaha and Smolen 2005).

Remission is defined as a CDAI score of ≤2.8 (Felson et al. 2011). Low disease activity is defined as a CDAI score of ≤10.

8.1.11. Medical Outcomes Study 36-Item Short Form Health Survey

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36v2) Acute measure is a subjective, generic, health-related quality of life instrument that is patient-reported and consists of 36 questions covering 8 health domains:

- physical functioning
- bodily pain
- role limitations due to physical problems
- role limitations due to emotional problems
- general health perceptions
- mental health
- social function, and
- vitality.

Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status or functioning.

In addition, 2 summary scores, the physical component score and the mental component score, will be evaluated based on the 8 SF-36v2 Acute domains (Brazier et al. 1992; Ware and Sherbourne 1992).

8.1.12. MRI Imaging and Synovitis Score

Magnetic resonance imaging is a more sensitive, noninvasive imaging technique that can provide cross-sectional images in any plane allowing for simultaneous examination of all the components of the diarthrodial joint (including soft tissues, articular cartilage, and bone) without the need for ionizing radiation (McQueen and Dalbeth 2009). Specifically, both inflammatory changes (as represented by synovitis and osteitis) and structural changes (as represented by erosion and joint space narrowing) are characteristic features of RA that may be detected in patients by MRI imaging (Klarlund et al. 2000).

Magnetic resonance imaging scans will be conducted on hand/wrist determined by the investigator at the site, during screening and at the Week 12 visit. Screening scans will be evaluated to determine the presence of synovitis for study eligibility. Screening and Week 12 scans will be read and scored in pairs for each subject by 2 assessors at a central vendor, blinded to each subject's treatment and the temporal order of the scans. A detailed charter from the central reading laboratory will outline the MRI procedures including image acquisition, image analysis, and data transfer.

Synovitis, osteitis, bone erosion, and joint space narrowing scores are planned to be determined using the OMERACT RAMRIS system for synovitis, osteitis, and bone erosion (Østergaard et al. 2017).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

A complete physical examination will be performed at the screening visit according to the SoA (Section 1.3). This examination excludes pelvic, rectal, and breast examinations unless clinically indicated.

A symptom directed physical examination will be performed at other visits, as specified in the SoA and as clinically indicated. A complete physical examination may be repeated at the investigator's discretion at any time a participant presents with physical complaints.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3). Vital signs include body temperature, blood pressure, and pulse rate (PR). Participants should be seated and relaxed with both feet on the floor for at least 5 minutes before measurements are taken. Blood pressure and pulse should be measured using either automated or manual equipment. If measurements are machine averaged, the average blood pressure reading should be recorded on the eCRF.

Measurements should be taken before any scheduled blood draws.

Additional vital signs may be measured at the discretion of the investigator.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, and QRS and QT intervals.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The

laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within approximately 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then these would be reported in the AE section of the CRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with the study intervention should be monitored appropriately and observed for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Families and caregivers of participants being treated with the study intervention should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior and treatment emergent suicidal ideation and behavior will be monitored during Study KDAD using the C-SSRS.

C-SSRS Self-Harm Supplement and Follow-Up forms

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

Consistent with Food and Drug Administration (FDA) regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the SoA (Section 1.3).

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have

occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

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

8.2.6. Tuberculosis Testing and Monitoring

Tuberculosis testing at screening Visit 1

Medical history will determine the lifetime risk factors for TB infection, for TB progression, and for symptoms and/or signs of active TB.

A physical examination will determine symptoms of active TB, including measurement of body temperature (Section 8.2.2) and assessment of peripheral lymph nodes.

A chest x-ray (CXR) will be interpreted and reported by a radiologist or pulmonologist, as specified in the SoA (Section 1.3). Participants do not need to have a CXR at screening if results from a CXR within 3 months prior to the study are available.

All participants with no history of LTBI or active TB, and no history of positive Mantoux tuberculin skin test (TST) using purified protein derivative (PPD) or positive *Mycobacterium tuberculosis* interferon gamma release assay (IGRA), must have either a PPD TST or IGRA for *M. tuberculosis*.

PPD TST

An induration of 5 or more millimeters is considered positive in:

- HIV-infected persons
- persons with a recent contact with a person with TB disease
- persons with fibrotic changes on chest radiograph consistent with prior TB
- persons with organ transplants
- persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)

An induration of 10 or more millimeters is considered positive in all other potential clinical trial participants.

Two-step testing (repeat TST from 1 to 3 weeks after the first TST) is recommended for certain participant groups, including:

- persons receiving immunosuppressant treatment
- persons with a history of temporally remote increased risk of TB infection
- persons for whom the first test is negative, as per local public health and/or professional medical society recommendations.

IGRA for M. tuberculosis

Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.

Diagnosed LTBI

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

- After receiving at least 4 weeks of appropriate LTBI therapy (as per WHO and/or the CDC guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN), or other treatment intolerance.
- The participant must continue and complete appropriate LTBI therapy in order to remain eligible to continue to receive study intervention.

Monitoring during the study

At a minimum, each participant will have the following documented at least every 3 months:

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

8.2.7. Hepatitis B Testing and Monitoring

Initial testing for HBV infection includes hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).

If…	Then…
If HBsAg is positive	the participant is excluded
If HBsAg is negative and anti-HBc is negative	the participant is not excluded
If HBsAg is negative and anti-HBc is positive	further testing for HBV DNA is required
If the screening HBV DNA is positive	the participant is excluded (see Section 5.2)

Participants who are hepatitis B core antibody-positive and HBV DNA-negative (undetectable) at Visit 1 are not excluded but will require HBV DNA monitoring every 3 months and at the participant's last visit.

The following actions should be taken in response to HBV DNA test results.

If…	Then…
If a single result is obtained with a value "below limit of quantitation"	the test should be repeated within approximately 2 weeks
If the repeat test result is "target not detected"	monitoring may resume according to the study schedule
If the participant has 2 or more test results with a value "below limit of quantitation" during the study	HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended
If a result is obtained with a value "above limit of quantitation" at any time during the study	the participant will be permanently discontinued from the study intervention (see Section 7.1) and should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study intervention in accordance with current immunomodulator management in the setting of HBV DNA positivity. This option may be considered in

If…	Then…
	consultation with the sponsor (or its designee) and after evaluation of individual participant's risks and benefits.

8.2.8. Hepatitis C Testing and Monitoring

Initial testing for HCV infection includes testing for antibodies to HCV.

If…	Then…
If anti-HCV is positive	HCV RNA testing should be performed
If HCV RNA test is negative	the participant is not excluded
If HCV RNA test is positive	the participant is excluded (see Section 5.2)

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

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

8.3. Adverse Events and Serious Adverse Events

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

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

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

All SAEs will be collected from the signing of the ICF until participation in study has ended.

All AEs will be collected from the signing of the ICF until participation in study has ended.

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

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

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3, Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after

a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS.

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

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3, Appendix 3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (AESIs) (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3, Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 8 weeks after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4, Appendix 4.

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

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for this study include:

- hypersensitivity
- infusion site reactions
- infections, and
- malignancy.

Hypersensitivity

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 study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Section 10.6, Appendix 6, Recommended Laboratory Testing for Hypersensitivity Events. Laboratory results are provided to the sponsor via the central laboratory.

Infusion Site Reactions

Symptoms of a local infusion site reaction may include erythema, induration, pain, pruritus, and edema. If an infusion site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the eCRF.

Infections

Participants will be monitored for symptoms and signs of infection after administration of LY3462817. More detailed information may be found in the IB.

Opportunistic Infections

The sponsor will identify infections considered to be opportunistic based on the publication "Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance" (Winthrop et al. 2015).

Malignancy

Participants will be monitored for symptoms and signs of malignancy after administration of LY3462817. More detailed information may be found in the IB.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

Sponsor collects product complaints on investigational products used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

NOTE: Adverse events/serious adverse events that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Section 10.3, Appendix 3 of the protocol.

8.3.7.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the intervention is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

8.3.7.2. Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the sponsor by the method designated by the sponsor. If the primary method is unavailable, the sponsor will designate an alternative method.

8.3.7.3. Follow-up of Product Complaints

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

The signs and symptoms of LY3462817 overdose are not known. There is no known antidote for LY3462817 overdose.

In the event of an overdose, the investigator should contact the Medical Monitor immediately. Hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care should be provided as necessary.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the serum concentrations of LY3462817.

Samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time of each sampling will be recorded.

LY3462817 concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3462817 will be assayed using a validated enzyme-linked immunosorbent assay method. Analyses of samples collected from placebo-treated participants are not planned.

Sample retention is described in Appendix 1, Section 10.1.12. During this time, samples remaining after the bioanalyses may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

8.6. Pharmacodynamics

Samples for assessment of target engagement (RO and sPD-1) will be collected at the times specified in the SoA (Section 1.3). Sample retention is described in Appendix 1, Section 10.1.12. Remaining samples may be used for additional exploratory studies to better understand LY3462817 and/or the disease.

8.7. Genetics

A whole blood sample will be collected for genetic analysis where local regulations allow.

See Section 10.2, Clinical Laboratory Tests, and Section 1.3, the SoA for sample collection information.

See Section 10.5, Genetics for genetic research, custody, and sample retention information.

8.8. Biomarkers

See the SoA (Section 1.3) for the frequency of collection of the biomarker samples.

Efficacy-related biomarkers

Certain biomarkers will be collected to evaluate their association with observed clinical responses to the study intervention. These biomarkers include:

- hsCRP, and
- ESR

RA characteristics biomarkers

The following biomarker samples will be collected to describe the disease characteristics of the randomized population:

- Rheumatoid Factor, and
- Anticyclic citrullinated peptide

Exploratory biomarkers

Serum, plasma, and whole blood RNA and DNA (to enable epigenetic analyses) samples will be collected at the times specified in the SoA (Section 1.3) where local regulations allow.

Samples may be used for research on the drug target, disease process, pathways associated with disease state, mechanism of action of LY3462817, and/or research method or in validating diagnostic tools or assay(s) related to RA.

Sample retention is described in Appendix 1, Section 10.1.12.

8.9. Immunogenicity Assessments

All samples for immunogenicity should be taken predose when applicable at the visits and times specified in the SoA (Section 1.3). Venous blood samples will be collected and evaluated to determine antibody production against LY3462817. To interpret the results of immunogenicity, venous blood samples will be collected at the same time points to determine the concentrations of LY3462817. Antidrug antibodies may be further characterized for their ability to neutralize the activity of LY3462817.

Treatment-emergent antidrug antibody (TE-ADA) classifications are described in Section 9.4.6.

Sample retention is described in Appendix 1, Section 10.1.12.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis for the primary endpoint is that there is no difference between LY3462817 and placebo in reducing the signs and symptoms of RA as measured by the mean change from baseline in DAS28-CRP at Week 12.

9.2. Sample Size Determination

Approximately 80 participants will be randomly assigned to study intervention. At the completion of the study, approximately 40 participants will have been randomized to LY3462817 700 mg and 20 participants will have been randomized to LY3462817 300 mg and placebo during the double-blind treatment. All randomized participants in the modified intent-to-treat (mITT) population will be considered evaluable.

Assuming -1.80 and -0.75 as the DAS28-CRP change from baseline for LY3462817 700 mg and placebo, respectively, with standard deviation equal to 1.25, a 2-sided t-test with $\alpha = 0.05$ has greater than 80% power to detect a statistically significant difference in DAS28-CRP change from baseline at Week 12. The t-test provides an approximation to the power calculation for the primary analysis, which will use MMRM as described in Section 9.4.1. The comparison of LY3462817 300 mg and placebo for the DAS28-CRP change from baseline at Week 12 is exploratory, and therefore, no formal sample size calculation was performed for this comparison. Comparisons of LY3462817 700 mg and 300 mg for the DAS28-CRP change from baseline will also be considered exploratory, and again therefore, no formal sample size calculation was performed for this comparison.

9.3. Populations for Analyses

The following populations are defined:

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

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of sponsor or its designee. The independent variable, previous RA therapy population, is defined as only csDMARD experienced or bDMARD/tsDMARD experienced participants. Unless otherwise indicated in the statistical analysis plan (SAP), the analyses will be conducted as follows:

Analysis for	Description
Primary and secondary endpoint analyses comparing LY3462817 to placebo	Tested at a 2-sided α level of 0.05 for frequentist analyses.
Adjustments for multiplicity	None to be performed since this a proof of concept Phase 2 study.
Baseline	Defined as the last available value before the first dose of study intervention for both efficacy and safety analyses. In most cases, this value will be what is recorded at the randomization visit (Visit 2).
Change from baseline	Will be calculated as the visit value of interest minus the baseline value.
Efficacy and patient-reported outcome (PRO) analysis	Analysis models may contain the independent variables such as treatment group, baseline disease activity, and previous RA therapy population. Endpoint analyses will use the mITT population unless otherwise specified.
Dichotomous responder endpoints	Missing data will be imputed using the nonresponder imputation (NRI) method. Will be analyzed using a logistic regression model with treatment group, baseline disease activity, and previous RA therapy population as model covariates.
NRI analysis	Participants will be considered nonresponders if: • they do not meet all the clinical response criteria • they are noncompliant with concomitant medication rules (Section 6.5) • they permanently discontinue study intervention at any time before the end of the treatment period for any reason, or • they are randomized and do not have at least 1 postbaseline observation.
Continuous efficacy endpoints	Mixed-effects model for repeated measures (MMRM) will be used. The MMRM model will include treatment, strata (previous RA therapy population), baseline value, visit, treatment-by-visit interaction in the model as fixed factors, and patient as a random factor. An unstructured covariance matrix will be used to model the within-subject errors. If this analysis fails to converge, other structures will be tested (in this order: Toeplitz, Autoregressive with

Analysis for	Description
	heterogeneity, etc.). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least squares means and Type III tests.
Participant Disposition	A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete the study or discontinue, both overall and by reason for discontinuation. A summary of important protocol deviations will be provided.
Participant Characteristics	Demographic data are collected and responded to demonstrate that the study population represents the target patient population. A summary of baseline participant characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by treatment group using descriptive statistics. Other participant characteristics will be summarized by treatment group as deemed appropriate.
Concomitant Therapy	Previous and concomitant medications will be summarized by treatment group and will be presented by Anatomical Therapeutic Chemical drug classes using the latest version of the WHO drug dictionary.
Treatment Compliance	No analyses are planned to assess treatment compliance, given that participants will receive study intervention directly from the investigator or designee at the study site, under medical supervision (Section 6.4).

Additional imputation methods may be considered for all endpoint types.

Estimands for Double-Blind Treatment Period

Endpoints	Estimand strategy	Estimand description	Use post-discontinuation data?	Imputation	Possible analysis method (estimator)
Primary endpoint and all other continuous efficacy and PRO endpoints	Hypothetical efficacy	Mean change from baseline (and mean scores) had all subjects remained on randomized treatment.	No, only use data up until discontinuation	Participants who discontinue study intervention have remaining data imputed* to reflect the expected outcome had the subject remained on the study treatment without using restricted medications** (assume missing at random [MAR])	MMRM model under MAR is applied to the data prior to treatment discontinuation
All dichotomous efficacy and	Composite responder	Proportion of responders where	No, only data up until discontinuation	Participants who start restricted medication** or discontinue study	Endpoint definition effectively

Endpoints	Estimand strategy	Estimand description	Use post-discontinuation data?	Imputation	Possible analysis method (estimator)
PRO endpoints		participants who start restricted medication or discontinue study intervention are considered treatment failures	is required to define endpoint	intervention are defined as nonresponders	gives complete data

*Note: No actual imputed value per participant, mixed model used to derive result at treatment group level.

** Restricted medications include prohibited medications (Section 6.5.2) and permitted medications above the allowable dose range (Section 6.5.1).

Any change to the data analysis methods described in the protocol will require an amendment only if the change affects a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to unblinding. It will include a more technical and detailed description of the statistical analyses described in this section.

9.4.2. Primary Endpoint(s)

The primary endpoint is DAS28-CRP change from baseline at Week 12.

A restricted maximum likelihood based, MMRM analysis will be used to analyze the primary endpoint using the primary estimand as described in Section 9.4.1.

9.4.3. Secondary Endpoint(s)

Key secondary efficacy endpoints include the following at Week 12:

- Proportion of participants achieving:
  - ACR20
  - ACR50, and
  - ACR70
- Change from baseline in:
  - TJC
  - SJC
  - PhGADA_VAS (VAS)
  - PaGADA_VAS (VAS)
  - patient's global assessment of arthritis pain (VAS), and
  - patient's assessment of physical function (HAQ-DI)
  - SF-36

- Change from baseline in mean score:
  - SDAI
  - CDAI

Continuous secondary endpoints will be analyzed using the model specified for the primary analysis described in Section 9.4.2. Dichotomous secondary endpoints will be analyzed using the logistic regression model described in Section 9.4.2.

9.4.4. Exploratory Endpoint(s)

Key exploratory efficacy endpoints include the following:

- Proportion of participants at Week 12 achieving:
  - DAS28-CRP remission defined as DAS28-CRP <2.6
  - DAS28-CRP LDA defined as DAS28-CRP ≤3.2
  - DAS28-ESR remission defined as DAS28-ESR <2.6
  - DAS28-ESR LDA defined as DAS28-ESR ≤3.2
  - SDAI remission defined as SDAI ≤3.3
  - SDAI LDA defined as SDAI ≤11
  - CDAI remission defined as CDAI ≤2.8
  - CDAI LDA defined as CDAI ≤10
- Change from baseline at Week 12 in the RAMRIS synovitis score from centrally read MRI images
- Measures of disease activity and PROs at all visits including mean scores, mean change from baseline, and proportion of participants achieving desired response

Details of exploratory analyses will be described in the SAP that is finalized before database lock.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

LY3462817 concentrations will be illustrated graphically and summarized descriptively. To facilitate the planning of future clinical studies, a model-based approach implemented using nonlinear mixed effects modeling (NONMEM) or other appropriate software may be conducted. Receptor occupancy data over time will be summarized by dose level. Exploratory PK/PD analyses may be conducted to evaluate the relationship between LY3462817 exposure and selected measures of response (for example, RO, sPD-1, clinical endpoints, and/or biomarkers). As appropriate, data from the present study may be combined with data from other studies in model-based analyses.

Additional analyses may be conducted if deemed appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

9.4.6. Evaluation of Immunogenicity

Treatment-emergent antidrug antibodies (ADAs) are defined as participants

- with a 2-fold (1 dilution) increase in titer than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or

- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADA and who are TE-ADA positive (TE-ADA+) to LY3462817 will be tabulated.

For the TE ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies, if assessed, may also be tabulated for the TE-ADA+ participants.

The relationship between the presence of antibodies and LY3462817 concentrations and PD response, including safety and efficacy, may also be assessed. Additional details may be provided in the SAP.

9.4.7. Other Safety Analyses

Analyses/measures	Presented…
Safety analyses: AEs, SAEs, C-SSRS, vital signs, ECGs, and laboratory analytes	Descriptively summarized by treatment group, will use the safety population data
Categorical safety measures	Summarized with counts by visit
Continuous safety measures	Summarized as mean change by visit
Exposure to study intervention	Calculated for each participant and summarized by treatment group by treatment period

Adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, severity, and relationship to the study intervention. All AEs, including pre-existing conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

Treatment-emergent adverse events

A TEAE is defined as an event that first occurred or worsened in severity after baseline, with baseline defined as all pre-existing conditions recorded at Visit 1 and any AEs recorded before the first dose of study intervention (that is, during the interval between Visits 1 and 2 and recorded with the time of onset before the first dose of study intervention). For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

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

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

Adverse events of special interest will be identified by a standardized MedDRA query or a Lilly-defined MedDRA preferred term listing.

Suicide-related thoughts and behaviors

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (Columbia Lighthouse Project WWW).

Follow-up emergent adverse events

Follow-up emergent AEs, SAEs including deaths, and AEs that lead to study discontinuation will be summarized.

9.4.8. Other Analyse(s)

9.4.8.1. Subgroup Analyses

Summaries of subgroups will be provided. Subgroup analyses may be conducted for the primary endpoint DAS28-CRP change from baseline using the mITT population.

Subgroups that may be evaluated include

- previous RA therapy population
- gender
- race
- geographic region
- previous therapies, and
- disease duration.

Detailed description of the summaries and/or statistical analyses are provided in the SAP.

9.4.8.2. Supplemental Analyses

Supplemental analyses may be performed as deemed necessary.

9.5. Interim Analyses

Analyses for the primary database lock will be conducted as described in Section 9.4 when all participants have completed the double-blind treatment period or discontinued treatment.

One interim analysis of the safety and efficacy data be planned prior to database lock, to support planning activities. This will be done when approximately 40% to 60% of participants have completed Period 1 (double-blind treatment) or have discontinued treatment. Bayesian posterior probabilities will be calculated to assess the efficacy of LY3462817 700 mg versus placebo for DAS28-CRP for Period 1 at the interim analysis. The decision rules based upon the posterior probability results will help in deciding whether to support further clinical development of LY3462817. Additionally, this interim analysis will aid in the development of PK/PD modeling.

Other interim analyses may be conducted as needed. All interim analyses will be used to support planning activities associated with the clinical development program and to aid in the development of PK/PD modeling. Since the study may terminate early only for safety and/or futility, no adjustment of type I error will be performed. Information about interim futility and decision rules will be provided in the SAP.

Internal assessment committee

Assessment of unblinded interim data will be conducted by an internal assessment committee (AC) with a limited number of prespecified members who do not have direct site contact or data entry or validation responsibilities (see Section 10.1.5, Appendix 1). Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding document. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Evaluation of unblinded safety data by the internal AC will occur if any of the following events are observed following review by the blinded safety review team:

- three or more participants experience TEAEs in the same system organ class, and these TEAEs assessed as severe by the investigator and are judged as related to blinded study treatment by the investigator.
- a malignancy SAE occurs during the study.

Pending the evaluation by the internal AC, enrollment and/or further dosing may be stopped.

Unblinding during the interim analyses

Prior to any interim or the final database lock, a limited number of preidentified individuals may gain access to the unblinded data for internal decision making or to initiate the final population PK/PD model development processes for interim or final analyses. To minimize bias, the SAP and PK/PD analysis plan will be finalized and approved before any unblinding. Unblinding details will be specified in the SAP or in a separate unblinding document. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the prespecified milestone for unblinding of study results.

9.6. Data Monitoring Committee (DMC)

Not applicable. An internal AC will be used to conduct the interim analysis (Section 9.5).

Overall committee structure information is in Section 10.1.5, Appendix 1. Details of the internal AC will be provided in the internal AC charter.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

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

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

When rescreening is performed, the individual must sign a new ICF, repeat all screening procedures as described in the SoA (Section 1.3), and will be assigned a new identification number (see Section 5.4).

10.1.4. Data Protection

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

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

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

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

10.1.5. Committees Structure

The internal AC will consist of a limited number of prespecified members not part of the blinded study team who do not have direct site contact or data entry or validation responsibilities. Further details will be provided in the internal AC charter.

10.1.6. Dissemination of Clinical Study Data

A clinical study report will be provided for this study and a summary of study information provided on publicly available websites.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

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

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

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

Data Capture System

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

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

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

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant and investigator site personnel, into an instrument (for example, tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

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

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

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

10.1.8. Source Documents

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

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

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

10.1.9. Study and Site Start and Closure

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

Physicians with a specialty in rheumatology and with other specialties and experience in treatment of patients with RA will participate as investigators in this clinical trial.

10.1.12. Long-Term 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 the intervention or after the intervention becomes commercially available.

This table describes the retention period for potential sample types.

Sample Type	Custodian	Retention Period After Last Participant Visit
Pharmacodynamic samples	Sponsor or designee	up to 7 years
Genetics sample	Sponsor or designee	up to 7 years
Exploratory Biomarker samples	Sponsor or designee	up to 15 years
Immunogenicity (ADA) sample	Sponsor or designee	up to 15 years
Pharmacokinetic (PK) sample	Sponsor or designee	up to 1 year

Abbreviations: ADA = antidrug antibody.

10.2. Appendix 2: Clinical Laboratory Tests

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

If the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

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

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

Pregnancy testing will be performed according to the SoA (Section 1.3).

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

Refer to Section 10.6, Appendix 6 for recommended laboratory testing for hypersensitivity events.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - Red Blood Cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - White Blood Cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell Morphology (RBC and WBC)	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	

Clinical Laboratory Tests	Comments
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Glomerular filtration rate (GFR)	Only performed at screening
Albumin	
Calcium	
Phosphorus	
Glucose	
Cholesterol	
Triglycerides	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	
Hormones (female)	
Serum Pregnancy	Assayed by Lilly-designated laboratory
Urine Pregnancy	Evaluated locally
Follicle stimulating hormone (FSH)	Assayed by Lilly-designated laboratory. Optional, performed as needed to confirm participant's postmenopausal status.
Serology	Assayed by Lilly-designated laboratory
Tuberculosis (TB) testing	See the protocol (Section 8.2.6) for more information about TB testing.
QuantiFERON-TB Gold test	Assayed by Lilly-designated laboratory. Testing can be performed by local laboratory if the site prefers.
T-SPOT or TST	Evaluated locally
Human immunodeficiency virus (HIV) testing	Assayed by Lilly-designated laboratory
Hepatitis C virus (HCV) testing	
HCV antibody	Assayed by Lilly-designated laboratory. Will be confirmed with an additional testing method
Hepatitis B virus (HBV) testing	Assayed by Lilly-designated laboratory
HBV DNA	Performed only for participants who test positive for anti-HBc

Clinical Laboratory Tests	Comments
Hepatitis B core antibody (Anti-HBc)	
Hepatitis B surface antigen (HBsAg)	
Pharmacokinetic Samples	
LY3462817 concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Flow Cytometry Panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
T cells, B cells, natural killer cells (TBNK)	
Peripheral helper T cells	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Receptor occupancy	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
C-reactive protein, high-sensitivity (hsCRP)	
Erythrocyte sedimentation rate (ESR)	
Soluble programmed cell death ligand – 1 (sPD-L1)	
Soluble programmed cell death protein – 1 (sPD-1)	
Anti-cyclic citrullinated peptide (anti-CCP)	
Rheumatoid factor (RF)	
Immunoglobulin Panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
IgG	
IgM	
IgA	
Cytokine Panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Genetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory storage samples:	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
Plasma (EDTA)	
Whole blood (EDTA)	
PAXgene (RNA)	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3462817 antibodies	
Anti-LY3462817 antibodies neutralization	

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is

appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

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

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

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the sponsor or designee will request the investigator to provide a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

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

SAE Reporting via Paper CRF

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

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

Women

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman Not of Childbearing Potential

Women in the following categories are not considered WOCBP:

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

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as, women with:
   - 12 months of amenorrhea for women >55, with no need for follicle stimulating hormone (FSH)
   - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced amenorrhea)

Participation in the Study

Women of child-bearing potential may participate in this study.

Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test prior to exposure. Women of child-bearing potential must test negative for pregnancy prior to administration of the study drug intervention at each visit by a negative urine pregnancy test.

Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual

lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males.

All other WOCBP must agree to use 2 forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate), for the entirety of the study.

Abstinence or contraception must continue following completion of study drug administration for at least 8 weeks or 5 half-lives, whichever is longer.

Acceptable Methods of Contraception

Highly effective methods of contraception (less than 1% failure rate) comprise, but are not limited to:

- combination oral contraceptives
- implanted contraceptives, or
- intrauterine devices.

Effective methods of contraception comprise but are not limited to male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges.

Not Acceptable Methods of Contraception

Use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men

Men, regardless of their fertility status, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception or effective method of contraception with nonpregnant WOCBP partners for the duration of the study and until their study drug concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 5 half-lives plus 90 days following the last dose of study intervention.

Acceptable Methods of Contraception

Highly effective methods of contraception (less than 1% failure rate) comprise, but are not limited to:

- combination oral contraceptives
- implanted contraceptives, or
- intrauterine devices.

Effective methods of contraception comprise but are not limited to diaphragms with spermicide or cervical sponges.

Men and their partners may choose to use a double–barrier method of contraception that must include use of a spermicide.

Not Acceptable Methods of Contraception

Use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Other Guidance

Men should refrain from sperm donation for the duration of the study and until their study drug concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 5 half-lives plus 90 days following the last dose of study intervention.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

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

Female Participants who become pregnant

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

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

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

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

Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study intervention, the participant should remain in the study if possible and complete the posttreatment safety follow-up procedures detailed in the SoA (Section 1.3).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to LY3462817 or RA and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3462817 and RA. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

DNA samples will be analyzed for genetic variants thought to play a role in RA. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3462817 or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on LY3462817 or study interventions of this class or RA continues but no longer than 7 years or other period as per local requirements.

10.6. Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events

Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected:

- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

Hypersensitivity Tests	**Notes** Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
LY3462817 antidrug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3462817 concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **Note:** If a tryptase sample is obtained more than 2 hours after the event (i.e., within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine sample for N-methylhistamine testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for N-methylhistamine testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **NOTE:** The basophil activation test 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.
Complement (C3, C3a, and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Abbreviations: ADA = antidrug antibody; IgE = immunoglobulin E; PK = pharmacokinetic.

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments

Close hepatic monitoring

This table describes when close hepatic monitoring should occur.

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

The laboratory tests listed under Hepatic Evaluation and Testing below, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

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

Comprehensive hepatic evaluation

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

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

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

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

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

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF)

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

If a participant with baseline...	**has the following elevations…**
ALT <1.5 ×ULN	ALT ≥5 × ULN on 2 or more consecutive blood tests
ALP <1.5 × ULN	ALP ≥2 × ULN on 2 or more consecutive blood tests
TBL <1.5 × ULN	TBL ≥2 × ULN, except for cases of known Gilbert's syndrome
ALT ≥1.5 × ULN	ALT ≥3 × baseline on 2 or more consecutive blood tests
ALP ≥1.5 × ULN	ALP ≥2 × baseline on 2 or more consecutive blood tests
TBL ≥1.5 × ULN	TBL ≥2 × baseline

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

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

Hepatic Evaluation Testing

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

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

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

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, international normalized ratio (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA; quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG; quantitative)
HAV total antibody	Immunoglobulin M (IgM; quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Antinuclear antibody (ANA)
Hepatitis B core IgG antibody	Antismooth muscle antibody (ASMA)[a]
HBV DNA[d]	Anti-actin antibody[b]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if antiactin antibody is tested.

[b] Not required if antismooth muscle antibody (ASMA) is tested.

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

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

10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

In rare, exceptional circumstances, barriers may occur that prevent completion of mandatory visits at study sites.

When allowed by local regulations, remote visits performed by trained site personnel, including telehealth (telephone or technology-assisted virtual) visits or visits at locations other than the site (e.g. participant's home) performed by a mobile healthcare service provider, or alternate methods of study intervention delivery and administration may be considered as alternatives to replace on-site visits after consultation and written approval from the sponsor.

Once written approval is granted for changes in study conduct, additional written guidance will be provided by the sponsor.

The changes in study conduct captured in this Appendix will not be considered protocol deviations. Missing data will be captured as protocol deviation(s). Such changes are intended to mitigate risks of participants missing visits, allow participants to continue safely in the study, and maintain the data integrity of the study. Good Clinical Practice compliance and minimization of risk to study integrity are important considerations. Ensuring the safety of study participants is the prevailing consideration.

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor. Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

Informed Consent and Ethical Review Boards

Additional written consent from the participant will be obtained for those who participate in mobile health services, and a method of study intervention administration other than on-site visits. The site should also document the participant's verbal consent for having telehealth visits and alternate study intervention delivery prior to implementation of these activities.

Ethical review boards and regulatory bodies will be notified as soon as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation.

Study Intervention Administration

In cases when a participant is unable to come to the site to receive study intervention during normal on-site visit, the site should work with the sponsor to determine appropriate actions to administer the study intervention to the participant. This may include administration of study intervention to the participant during a mobile health visit, provided these requirements are met prior to administration of intervention:

1. sponsor approves the alternative method to on-site administration, taking local regulatory requirements into consideration
2. participant consent must include provision of any personal information

3. delivery of intervention does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged
4. investigator/sponsor provides oversight of the transport process to ensure accountability and product quality (i.e., storage conditions and intact packaging upon receipt)
5. only authorized study staff or designee may supply or administer study intervention, and
6. resuscitation equipment, emergency drugs, and appropriately trained medical staff must be available during the infusion and for at least 1 hour after the completion of the infusion, in case of hypersensitivity or infusion site reactions.

Concomitant medications may be recorded during a remote visit.

Study Assessments and Procedures

Remote visits to complete appropriate assessments are acceptable. Site staff should capture the visit location and method with a specific explanation for any possible data missing in the source document and eCRF.

Visit Windows

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

Except for Visits 6 and 7, flexibility in visit windows can be considered following consultation with and prior approval by the sponsor.

Efficacy Assessments

Conduct or review of participant-reported outcomes may be completed during a telehealth visit. These activities and health care professional RA evaluations, including assessments of the disease activity by a blinded assessor, may be conducted during a mobile health visit.

Safety Assessments

Adverse events/serious adverse events, product complaints, and C-SSRS-related assessments need to be completed during a telehealth visit. These activities and physical examinations may be completed during a mobile health visit.

Requirements related to the reporting of SAEs remain unchanged.

Sample Collection

In exceptional circumstances, to ensure participant safety and with the sponsor's prior written approval, local laboratory testing may be conducted in lieu of central laboratory testing only if it is determined that central laboratory testing cannot be conducted. The local laboratory must also be qualified in accordance with applicable local regulations. Clinically significant laboratory findings must be recorded as an AE in the AE CRF.

Documentation of Changes to Study Conduct

Sites must identify and document the details of how all participants, visits, methods, and activities conducted were affected by exceptional circumstances.

Consent to be obtained and documented as above.

Source document(s) that are generated at the participant's home or any remote location should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Missing Data and Other Protocol Deviations

Sites should capture specific explanations for any missing data and other protocol deviations in source documents, eCRFs, and other data capture systems. While protocol deviations may be unavoidable in an exceptional circumstance, documentation of deviations and missing data will be important for data analysis and reporting.

10.9. Appendix 9: Abbreviations

Term	Definition
AC	assessment committee
ACR	American College of Rheumatology
ACR20	20% improvement in American College of Rheumatology criteria
ACR50	50% improvement in American College of Rheumatology criteria
ACR70	70% improvement in American College of Rheumatology criteria
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ALP	alkaline phosphatase
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guerin
bDMARD	biologic disease-modifying antirheumatic drug
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CBD	cannabidiol
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDAI	Clinical Disease Activity Index
CDC	United States Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, GCP, and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CXR	chest x-ray
DAS28-CRP	Disease Activity Score - C-reactive protein
DAS28-ESR	Disease Activity Score - erythrocyte sedimentation rate
DAS28-hsCRP	Disease Activity Score - high sensitivity C-reactive protein
Device Deficiencies	Equivalent to product complaint
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	electronic data capture system
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration

FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Gd-DTPA	gadolinium diethylenetriamine penta-acetic acid
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
Ig	immunoglobulin
IGRA	interferon gamma release assay
IL	interleukin
IMP	Investigational Medicinal Product
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Boards

IV	intravenous
IWRS	interactive web-response system
LDA	low disease activity
LTBI	latent tuberculosis infection
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
Medical monitor	Individual responsible for the medical conduct of the study. Responsibilities of the medical monitor may be performed by a clinical research physician, clinical research scientist, global safety physician, or other medical officer designated by the sponsor.
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MRI	magnetic resonance imaging
MTX	methotrexate
NIMP	Noninvestigational Medicinal Product
NONMEM	nonlinear mixed effects modeling
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PaGADA_VAS	Patient's Global Assessment of Disease Activity
participant	Equivalent to Clinical Data Interchange Standards Consortium (CDISC) term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PhGADA_VAS	Physician's Global Assessment of Disease Activity
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
PR	pulse rate

PRO	patient-reported outcomes
Q4W	once every 4 weeks
RA	rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDAI	Simplified Disease Activity Index
SERM	selective estrogen receptor modulators
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SJC	Swollen Joint Counts
SoA	Schedule of Activities
sPD-1	soluble programmed cell death protein 1
TB	tuberculosis
TBL	total bilirubin level
TE-ADA	treatment-emergent antidrug antibody
TE-ADA+	treatment-emergent antidrug antibody positive
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.
TJC	Tender Joint Counts
TNF-α	tumor necrosis factor-α
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
TST	tuberculin skin test
ULN	upper limit of normal

VAS	visual analog scale
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.10. Appendix 10: Country Specific Requirements

Discontinuation of Inadvertently Enrolled Patients in the United Kingdom

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

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Leo Document ID = 033f1066-c461-41b4-a3d7-b8b045063e6b

Approver: PPD

Approval Date & Time: 10-Dec-2020 14:53:30 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 11-Dec-2020 01:38:45 GMT

Signature meaning: Approved