LY3541860 KIAB(d) Harmonized Clinical Protocol

An Adaptive Phase 2a/2b, Randomized, Double-Blind, Parallel-Group Study to Investigate the Safety and Efficacy of LY3541860 Compared to Placebo in Slowing the Occurrence of New T1 Gadolinium-Enhancing Lesions in Adult Participants with Relapsing Multiple Sclerosis

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Title Page

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Protocol Title: An Adaptive Phase 2a/2b, Randomized, Double-Blind, Parallel-Group Study to Investigate the Safety and Efficacy of LY3541860 Compared to Placebo in Slowing the Occurrence of New T1 Gadolinium-Enhancing Lesions in Adult Participants with Relapsing Multiple Sclerosis

Protocol Number: J3K-MC-KIAB

Amendment Number: d

Compound: CD19 Antibody, LY3541860

Brief Title: An Adaptive Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of LY3541860 in Adult Participants with Relapsing Multiple Sclerosis

Study Phase: 2

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Numbers:

IND: 156942

EU trial number: 2023-503289-22-00

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

Document ID: VV-CLIN-115001

Medical Monitor Name and Contact Information will be provided separately.

Approved on 23 Apr 2025 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	*13-Dec-2024*
Amendment b	*07-Nov-2023*
Amendment a	*25-Aug-2023*
Original Protocol	*14-Feb-2023*

Amendment [d]

This amendment is considered to be substantial.

Overall rationale for the amendment

The purpose of this amendment is to expand the proposed population, improve study enrollment, and generate additional data in participants exposed to LY3541860 in the Phase 2a portion of the study.

The table below outlines a high-level description of changes, with a brief rationale.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 4.1.2 Treatment Period	The randomization ratio for Phase 2a portion has been updated from CCI to CCI	To improve study enrollment and generate additional data in participants exposed to LY3541860.
Section 1.3.1 Schedule of Activities for Phase 2a of Study J3K-MC-KIAB, and 1.3.2. Schedule of Activities for Phase 2b of Study J3K-MC-KIAB	• EDSS will be performed by an independent rater and not by an investigator. • Updated CCI [redacted]	• To maintain consistency with the protocol body. • Clarification.
Section 5.2 Exclusion Criteria	Daclizumab has been removed from the list of prior/concomitant therapy listed in Exclusion Criterion number 12.	To allow enrollment of participants with daclizumab treatment.
Section 9.3.1 General Considerations	The 2-sided alpha level has been updated from 0.05 to 0.10 and the confidence level has been updated from 95% to 90%.	To maintain more than 80% power after switching to a CCI randomization ratio.
Section 9.3.2 Primary Endpoint/Estimand Analysis	It has been clarified that, for Phase 2a, a binary indicator will be included as a covariate in the model for participants randomly assigned to study intervention before and	This covariate is being added to control for potential differences in prognostic factors across patients enrolled before and after protocol amendment (d).

Section # and Name	Description of Change	Brief Rationale
	after this Protocol Amendment (d).	
Section 9.4 Interim Analysis	• The number of anticipated interim analyses during Phase 2a has been updated from 3 to 2. • Updated the timing of interim analyses for Phase 2a.	Timing of interim analyses was updated to enable earlier decision-making.
Section 9.5 Sample Size Determination	For Phase 2a part of the study • the sample size calculation has been updated to clarify that the first 40 participants will be randomly assigned in a CCI ratio, and the remaining 60 participants will be randomly assigned in a CCI ratio, and • updated the 2-sided Type I error from 0.05 to 0.10. For Phase 2b part of the study • updated 2-sided Type I error from 0.05 to 0.10 and power has been updated from 83% to greater than 80%, and • number of participants in the combined placebo group has been changed from 54 to 36.	The sample size was updated to address the change from CCI to CCI randomization in the Phase 2a portion of the study.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: An Adaptive Phase 2a/2b, Randomized, Double-Blind, Parallel-Group Study to Investigate the Safety and Efficacy of LY3541860 Compared to Placebo in Slowing the Occurrence of New T1 Gadolinium-Enhancing Lesions in Adult Participants with Relapsing Multiple Sclerosis

Brief Title: An Adaptive Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of LY3541860 in Adult Participants with Relapsing Multiple Sclerosis

Regulatory Agency Identifier Numbers:

IND: 156942

EU trial number: 2023-503289-22-00

Rationale:

LY3541860 is a B cell nondepleting anti-CD19 IgG4-variant monoclonal antibody. LY3541860 is highly selective for CD19, which is found on plasmablasts and plasma cells. LY3541860 may therefore be efficacious in patients with relapsing multiple sclerosis (RMS).

Study J3K-MC-KIAB (KIAB) will evaluate the efficacy of multiple dose levels of LY3541860 versus placebo over 36 weeks of treatment in study participants with RMS. Findings from the study will be used to assess the utility of LY3541860 for the treatment of RMS and advance understanding of the benefit/risk relationship for LY3541860 and inform the doses and design of future studies of LY3541860.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To evaluate the efficacy of LY3541860 versus placebo on the number of new T1 GdE MRI brain lesions in participants with RMS	The cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12[a]
Secondary	
To evaluate the efficacy of LY3541860 versus placebo on other measures of MRI activity in participants with RMS	The cumulative number of total T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 The cumulative number of new or enlarging T2 lesions, as measured by MRI scans, over Weeks 4, 8, and 12

To characterize the PK of LY3541860 in participants with RMS	Plasma trough concentrations of LY3541860
To describe the safety of LY3541860 in participants with RMS	Summary of safety data, including number and incidence of • TEAEs • SAEs • discontinuations due to AE

Abbreviations: AE = adverse event; GdE = gadolinium-enhancing; MRI = magnetic resonance imaging; PK = pharmacokinetics; RMS = relapsing multiple sclerosis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] When counting the number of new T1 GdE lesions at each postbaseline visit, the baseline (Visit 1) scan will be used as the reference (see Section 9.3.2 for details). Lesions persisting for more than 4 weeks will be counted only once.

Primary Estimand

The primary estimand is defined to represent the primary clinical question of interest: what is the difference in cumulative number of new T1 GdE lesions over 12 weeks of treatment with LY3541860 versus placebo among participants with RMS if use of prohibited medication or discontinuing the study intervention had not happened?

Overall Design:

J3K-MC-KIAB (KIAB) is an adaptive Phase 2a/2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of multiple dose levels of LY3541860 versus placebo in adult participants with RMS.

This study has 2 phases that differ from one another by purpose and dose levels being tested. This table notes these differences.

	Phase 2a portion	**Phase 2b portion**
Purpose	Proof of concept	Dose ranging[a]
LY3541860 dose levels	CCI mg CCI mg	Dose Level 3 Dose Level 4

[a] Phase 2b doses will be no higher than CCI mg.

Results of interim analyses from the Phase 2a portion of this study will determine whether the Phase 2b portion will be initiated and, if so, what doses of LY3541860 will be used.

Both portions will have these study periods:

- Screening period: Visit 1 from 35 to 14 days before Visit 2 (Week 0, baseline)
- Treatment period: Visit 2 (Week 0, baseline) through Visit 11 (Week 36), and
- Follow-up period: Visit 801 (12 weeks after Visit 11) and Visit 802 (24 weeks after Visit 11)
    - the follow-up period will take longer CCI [redacted]

This study includes investigator and participant blinding (masking). An Internal Assessment Committee (IAC) will exist for the purpose of reviewing the data in an unblinded fashion.

Brief Summary:

Multiple sclerosis is a chronic inflammatory disease characterized by demyelinating lesions throughout the central nervous system. Abnormalities of B cell function has been implicated in the pathophysiology of multiple sclerosis. LY3541860 is a monoclonal antibody that inhibits primary human B cell activation, proliferation, and differentiation without causing B cell depletion or inducing B cell apoptosis. LY3541860 may therefore be efficacious in patients with RMS.

The primary objective of this study is to measure the number of new gadolinium-enhancing T1 lesions on brain MRI with various dose levels of LY3541860 given by CCI [redacted] CCI [redacted] compared with placebo also given by CCI [redacted] in study participants with RMS. The presence of new gadolinium-enhancing T1 lesions in the brain is accepted in clinical trials and in clinical practice as a marker of recent disease activity in multiple sclerosis.

This study has 2 portions: a proof-of-concept Phase 2a portion, and a dose-ranging Phase 2b portion. In both portions, participants who are randomly assigned to LY3541860 will be given LY3541860 every CCI [redacted] by CCI [redacted] and participants randomly assigned to placebo will be given placebo for 12 weeks, followed by LY3541860 CCI [redacted]

This table notes the LY3541860 dose levels to be used in each portion.

	Phase 2a portion	**Phase 2b portion**[a]
LY3541860 dose levels	CCI [redacted] mg	Dose Level 3
	CCI [redacted] mg	Dose Level 4

[a] Phase 2b doses will be no higher than CCI [redacted] mg.

Results of interim analyses from the Phase 2a portion of this study will determine whether the Phase 2b portion will be initiated and, if so, what doses of LY3541860 will be used.

Whether enrolled in the Phase 2a or Phase 2b portion, the total duration of an individual's participation will be from approximately 62 to 65 weeks, inclusive of the screening period, treatment period, and follow-up period.

Treatment is administered from Visit 2 (Week 0) through the last dose given at Visit 10 (Week 32), with the final treatment period evaluation occurring at Visit 11 (Week 36).

After Visit 2 (Week 0), the visit frequency is every 4 weeks until Visit 11 (Week 36).

Follow-up visits occur at approximately 12 weeks after Visit 11 and again approximately 24 weeks after Visit 11.

Study Population:

The study population includes male or female participants from 18 to 55 years of age, inclusive, who have RMS and meet 1 or more of these criteria:

at least 1 relapse within the previous year

at least 2 relapses within the previous 2 years, or

at least 1 active gadolinium-enhancing lesion in the past 180 days prior to screening.

Participants will be excluded from this study if they

have a diagnosis of primary progressive or nonactive secondary progressive multiple sclerosis

have had a confirmed relapse (flare) less than 30 days before randomization

have an Expanded Disability Status Scale (EDSS) score >5.5 at screening

have been treated with certain therapies, including but not limited to these within the specified time frame:

Therapy	Exclusionary if given in this time frame
Bruton tyrosine kinase inhibitors, such as ibrutinib and fenebrutinib	at any time
B-cell depleting therapies, such as inebilizumab, ocrelizumab, ofatumumab, rituximab, and ublituximab	at any time
fingolimod or ozanimod	within 10 weeks prior to randomization
ponesimod, siponimod, or natalizumab	within 60 days prior to randomization
intravenous immunoglobulin	within 60 days prior to randomization
teriflunomide or leflunomide	within 2 years prior to randomization or 30 days prior to randomization if the participant undergoes accelerated elimination with documented teriflunomide plasma level below 0.02 mg/L prior to randomization
dimethyl fumarate, diroximel fumarate, monomethyl fumarate, or laquinimod	within 30 days prior to randomization
systemic corticosteroids	within 30 days prior to screening MRI
interferons or glatiramer acetate treatments	on the day of randomization

Number of Participants:

In the Phase 2a portion, a total of approximately 100 participants will be randomly assigned to study intervention.

If the Phase 2b portion is implemented, approximately 100 additional participants will be randomly assigned to study intervention.

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Intervention Groups and Duration:

Whether enrolled in the Phase 2a or the Phase 2b portion of the study, the duration of an individual's participation will be from approximately 62 to 65 weeks:

- Screening period: 2 to 5 weeks
- Treatment period: 36 weeks
- Follow-up period: 24 weeks

In the Phase 2a portion, participants who fulfill the eligibility criteria will be randomized in a CC ratio to receive

- LY3541860 CCI mg CCI for 36 weeks, or
- placebo for 12 weeks followed by LY3541860 CCI mg CCI

In the Phase 2b portion, participants who fulfill the eligibility criteria will be randomized in a CCI ratio to receive

- LY3541860 Dose Level 3 CCI for 36 weeks
- LY3541860 Dose Level 4 CCI for 36 weeks, or
- placebo for 12 weeks followed by, in a CC ratio, either
  - LY3541860 Dose Level 3 CCI or
  - LY3541860 Dose Level 4 CCI

The Phase 2b doses of LY3541860 will be determined based on the interim analyses from Phase 2a and recommendations of the sponsor's IAC.

Ethical Considerations of Benefit/Risk:

Administration of LY3541860 may increase the risk of developing infections, may increase the risk of an infection becoming more serious, or may change the effectiveness of vaccines administered. The administration of therapeutic monoclonal antibodies to humans can be associated with hypersensitivity reactions. Depression and suicidality may be increased with certain immune-mediated disorders. Participants may benefit by receiving personal health information from the physical examinations and other routine safety assessments performed in this study. Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with LY3541860 are justified by the anticipated benefits that may be afforded to the RMS patient population. Based on available clinical and nonclinical data, there are no anticipated risks that would require safety monitoring in this study beyond what is typical for clinical studies involving therapeutic monoclonal antibodies.

Data Monitoring Committee: Yes (Internal Assessment Committee [IAC])



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1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities for Phase 2a of Study J3K-MC-KIAB

Schedule follow-up visits from last dose received. Visit 1 may be conducted over more than 1 day.

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the 'CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Consent and demographics															
Informed consent	X														The ICF must be signed before any protocol-specific tests or procedures are performed.
Inclusion/exclusion criteria; confirmation of eligibility	X	X													Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.
Demographics	X														Includes ethnicity (where permitted), year of birth, sex, and race.

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Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted]. *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Preexisting conditions and medical history	X														Collect all conditions ongoing and relevant past surgical and medical history.
Prespecified medical history	X														Includes history of hysterectomy and autoimmune diseases.
Prior treatments for indication	X														
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE collection begins when the ICF is signed. Additional data are collected for certain adverse events of special interest.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Evaluation															
Height	X														
Weight	X							X			X	X			

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Include pulse rate, blood pressure, respiratory rate, and temperature. Measure after participant has been sitting at least 5 min. Measure both predose and postdose if study intervention is administered.
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	At Visits 2-10, perform prior to administration of study intervention. Assess for signs and symptoms of active infection or tuberculosis (TB), as well as TB risk factors, including examination of peripheral lymph nodes. See Section 8.2.5.

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Assessments															
CCI [redacted]															

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
[redacted] CCI															
C-SSRS Baseline and Screening	X														AE collection should occur prior to the collection of the C-SSRS.

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
C-SSRS Since Last Assessed		X	X	X	X	X	X	X	X	X	X	X	X	X	AE collection should occur prior to the collection of the C-SSRS.
Expanded Disability Status Scale (EDSS)	X	X	X		X			X			X	X			If new neurological symptoms are present that would suggest a relapse or if relapse is detected, the independent rater is to perform an EDSS. If there is any concern that a relapse may have occurred between the protocol-required visits, the participant is to have an unscheduled visit at which an EDSS is to be assessed.
[redacted] CCI															

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			

[redacted]
CCI

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Imaging															
ECG	X	X	X		X			X			X	X		X	A local 12-lead ECG will be performed at designated visits. ECGs should be collected at least 30 min before collection of blood samples for laboratory testing, including PK samples. Participants should be supine for approximately 5 to 10 min before ECG collections and should remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit.

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Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
MRI of brain	X		X	X	X	X	X	X	X	X	X	X		X	MRI of brain with gadolinium to be performed. The participant should meet all other eligibility criteria before the screening MRI. Visit 1 MRIs need to be obtained at least 10 days before Visit 2. For Visits 3 through 11 and ED, MRIs can be performed within 5 days before or after the scheduled visit date.

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Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
X-ray of chest	X														Posterior – anterior and, if needed, lateral. Interpreted and reported by a radiologist or pulmonologist. Required only if not already done within 90 days before Visit 1. Variations on the view requirements will be permitted only as necessary to conform to local guidelines of care for
CCI [redacted]															

Approved on 23 Apr 2025 GMT

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
[redacted]															
Laboratory Samples															At dosing visits, samples are to be collected predose.
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine clearance	X							X							

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Coagulation	X														Assessed locally at Visit 1 and as clinically indicated, for example, if a significant bleeding event occurs.
C-reactive protein (CRP)	X							X			X	X			
Lipids	X										X	X			Fasting not required.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Reticulocyte count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X			
Follicle-stimulating hormone (FSH)	X														Optional; performed as needed to confirm postmenopausal status.
Serum pregnancy test	X														Collect for WOCBP only.

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Urine pregnancy test (local)		X	X	X	X	X	X	X	X	X	X	X	X	X	Collect for WOCBP only. Additional pregnancy testing should be performed at any time during the study if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.
HIV testing	X														

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Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Tuberculosis (TB) test	X														Lilly-designated laboratory preferred; may be completed locally. Participants who had a tuberculin skin test (TST) will return 48 to 72 hr after placement to have their test results read. TST does not need to be read at the site but must be read by a trained professional, and results must be presented to the site prior to randomization.
Hepatitis B virus (HBV) screening tests	X														See Section 8.2.7.
Hepatitis C virus (HCV) screening tests	X														See Section 8.2.8.
CCI [redacted]															

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
[redacted]															

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Pharmacokinetics (PK) samples		X**	X***		X***	X***		X***			X***	X	X	X	In the event of a systemic drug hypersensitivity reaction (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Appendix 2, Section 10.2.1. ** Collect post dose after the completion of the infusion. ***Samples should be taken before the dose is administered. For each PK sample collected, record time and date of previous dose administration.

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Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Immunogenicity		X	X		X	X		X			X	X		X	In the event of a systemic drug hypersensitivity reaction (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Appendix 2, Section 10.2.1.
Stored samples															At dosing visits, samples are to be collected predose.
CCI [redacted]															
Genetics sample		X													
Participant education															
Paper diary education	X														Conduct additional training as needed.

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the 'CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Participant paper diary															
Paper diary dispense	X			X			X			X					Paper diary collects FCCI [redacted] symptom domain information starting six days prior to participant's next visit.
Paper diary review		X			X			X			X	X			The site coordinator should contact and remind participants to start completion of their diary 6 days prior to these scheduled visits.
Paper diary return		X			X			X			X	X			
Investigational product															
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization via IWRS		X													

Schedule of Activities for Phase 2a of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24**	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted]. *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
CCI [redacted]															
Observe after administering study intervention		X	X	X	X	X	X	X	X	X					Observe for at least 1 hour after completion of dosing.

Abbreviations: anti-HBc = hepatitis B core antibody; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation visit; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; CCI [redacted] MRI = magnetic resonance imaging; RNA = ribonucleic acid; WOCBP = women of childbearing potential.

1.3.2. Schedule of Activities for Phase 2b of Study J3K-MC-KIAB

Schedule follow-up visits from last dose received. Visit 1 may be conducted over more than 1 day.

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Consent and demographics															
Informed consent	X														The ICF must be signed before any protocol-specific tests or procedures are performed.
Inclusion/exclusion criteria; confirmation of eligibility	X	X													Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.
Demographics	X														Includes ethnicity (where permitted), year of birth, sex, and race.

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Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Preexisting conditions and medical history	X														Collect all conditions ongoing and relevant past surgical and medical history.
Prespecified medical history	X														Includes history of hysterectomy and autoimmune diseases.
Prior treatments for indication	X														
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE collection begins when the ICF is signed. Additional data are collected for certain adverse events of special interest.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Evaluation															
Height	X														

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Weight	X							X			X	X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Include pulse rate, blood pressure, respiratory rate, and temperature. Measure after participant has been sitting at least 5 min. Measure both predose and postdose if study intervention is administered.
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	At Visits 2-10, perform prior to administration of study intervention. Assess for signs and symptoms of active infection or tuberculosis (TB), as well as TB risk factors, including examination of peripheral lymph nodes. See Section 8.2.5.

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Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Assessments															
CCI [redacted]															

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
CCI [redacted]															
C-SSRS Baseline and Screening	X														AE collection should occur prior to the collection of the C-SSRS.

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Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
C-SSRS Since Last Assessed		X	X	X	X	X	X	X	X	X	X	X	X	X	AE collection should occur prior to the collection of the C-SSRS.
Expanded Disability Status Scale (EDSS)	X	X	X		X			X			X	X			If new neurological symptoms are present that would suggest a relapse or if relapse is detected, the independent rater is to perform an EDSS. If there is any concern that a relapse may have occurred between the protocol-required visits, the participant is to have an unscheduled visit at which an EDSS is to be assessed.
CCI [redacted]															

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			

[redacted]
CCI

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Imaging															
ECG	X	X	X		X			X			X	X		X	A local 12-lead ECG will be performed at designated visits. ECGs should be collected at least 30 min before collection of blood samples for laboratory testing, including PK samples. Participants should be supine for approximately 5 to 10 min before ECG collections and should remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit.

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Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
MRI of brain	X		X	X	X	X	X	X	X	X	X	X		X	MRI of brain with gadolinium to be performed. The participant should meet all other eligibility criteria before the screening MRI. Visit 1 MRIs need to be obtained at least 10 days before Visit 2. For Visits 3 through 11 and ED, MRIs can be performed within 5 days before or after the scheduled visit date.

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
X-ray of chest	X														Posterior – anterior and, if needed, lateral. Interpreted and reported by a radiologist or pulmonologist. Required only if not already done within 90 days before Visit 1. Variations on the view requirements will be permitted only as necessary to conform to local guidelines of care for standard tuberculosis screening.
CCI [redacted]															

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
[redacted]															
Laboratory Samples															At dosing visits, samples are to be collected predose.
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine clearance	X							X							

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Coagulation	X														Assessed locally at Visit 1 and as clinically indicated (for example, if a significant bleeding event occurs).
C-reactive protein (CRP)	X							X			X	X			
Lipids	X										X	X			Fasting not required.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Reticulocyte count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X			
Follicle-stimulating hormone (FSH)	X														Optional; performed as needed to confirm postmenopausal status.
Serum pregnancy test	X														Collect for WOCBP only.

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Urine pregnancy test (local)		X	X	X	X	X	X	X	X	X	X	X	X	X	Collect for WOCBP only. Additional pregnancy testing should be performed at any time during the study if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.
HIV testing	X														

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Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Tuberculosis (TB) test	X														Lilly-designated laboratory preferred; may be completed locally. Participants who had a tuberculin skin test (TST) will return 48 to 72 hr after placement to have their test results read. TST does not need to be read at the site but must be read by a trained professional, and results must be presented to the site prior to randomization.
Hepatitis B virus (HBV) screening tests	X														See Section 8.2.7.
Hepatitis C virus (HCV) screening tests	X														See Section 8.2.8.

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Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
[redacted]															
Pharmacokinetics (PK) samples		X**	X***		X***	X***		X***			X***	X	X	X	In the event of a systemic hypersensitivity reaction (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Appendix 2, Section 10.2.1.

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
															** Collect post dose after the completion of the infusion. ***Samples should be taken before the dose is administered. For each PK sample collected, record time and date of previous dose administration.
Immunogenicity		X	X		X	X		X			X	X		X	In the event of a systemic hypersensitivity reaction (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Appendix 2, Section 10.2.1.

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Stored samples															At dosing visits, samples are to be collected predose.
CCI [redacted]															
Genetics sample		X													
Participant education															
Paper diary education	X														Conduct additional training as needed.
Participant paper diary															
Paper diary dispense	X			X			X			X					Paper diary collects FSIQ-RMS symptom domain information starting six days prior to participant's next visit.

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Paper diary review		X			X			X			X	X			The site coordinator should contact and remind participants to start completion of their diary 6 days prior to these scheduled visits.
Paper diary return		X			X			X			X	X			
Investigational product															
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization via IWRS		X													
Re-randomize via IWRS					X										
[redacted]															

Schedule of Activities for Phase 2b of Study J3K-MC-KIAB															
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**V801**	**V802**	**Notes**
Weeks	-35 to -14 days*	0	4	8	12	16	20	24	28	32	36	—	+12	+24	* See the MRI row. ** The follow-up may take longer; see the "CCI [redacted] *** See the pharmacokinetics (PK) samples row
Visit interval tolerance (+/- days)	—	—	3	3	3	3	3	3	3	3	3	—	7	7	
Fasting visit	X										X	X			
Observe after administering study intervention		X	X	X	X	X	X	X	X	X					Observe for at least 1 hour after completion of dosing.

Abbreviations: anti-HBc = hepatitis B core antibody; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation visit; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ICF = informed consent form; CCI [redacted] MRI = magnetic resonance imaging; RNA = ribonucleic acid; WOCBP = women of childbearing potential.

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2. Introduction

2.1. Study Rationale

LY3541860 is a B cell nondepleting anti-CD19 IgG4-variant mAb. LY3541860 is highly selective for CD19, which is found on plasmablasts and plasma cells. LY3541860 may therefore be efficacious in patients with RMS.

Study J3K-MC-KIAB (KIAB) will evaluate the efficacy of multiple dose levels of LY3541860 versus placebo over 36 weeks of treatment in study participants with RMS. Findings from the study will be used to assess the utility of LY3541860 for the treatment of RMS and advance understanding of the benefit/risk relationship for LY3541860 and inform the doses and design of future studies of LY3541860.

2.2. Background

MS is a chronic inflammatory demyelinating CNS disease. It is characterized by demyelinating lesions throughout the CNS, including the optic nerves, cerebrum, brainstem, cerebellum, periventricular white matter, and spinal cord (Ford 2020).

According to The Multiple Sclerosis International Federation (2020), MS was estimated to affect 2.8 million people worldwide. The prevalence of MS population is higher in Europe (133/100,000) and in the Americas (112/100,000) than in Africa (5/100,000) or Southeast Asia (9/100,000). RMS accounts for 85% of MS cases at disease onset. MS affects women more frequently than men, in a ratio of up to 3:1 (Ford 2020).

In the past, therapies for MS have been designed to suppress effector T-cell responses. The approach for the treatment of MS has shifted due to greater understanding of the role of B cells in the pathophysiology of MS. Current therapies include anti-CD20 chimeric monoclonal antibody treatments, which bind to CD20 and deplete B cell populations.

LY3541860 is an anti-CD19 IgG4-variant mAb, which inhibits primary human B cell activation, proliferation, and differentiation without causing B cell depletion or inducing B cell apoptosis. It does not depend on antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity for functional activity and inhibits both circulating and tissue-resident B cells.

Additional information regarding LY3541860, including nonclinical data and in vitro and in vivo PK and PD, may be found in the IB.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3541860 may be found in the IB.

2.3.1. Risk Assessment

As with other immunomodulatory therapies, LY3541860 may increase the risk of developing infections or may increase the risk of an infection becoming more serious or may change the effectiveness of vaccines administered, or both. Opportunistic infections and reactivation of

latent infections may include HBV. Participants will therefore be screened for HBV, HCV, and HIV. In addition, all participants should be monitored for symptoms and signs of infection after administration of LY3541860.

Administration of this study drug, as with any mAb, may result in hypersensitivity reactions, including IRRs. These reactions, if they occur, will prompt additional participant management, testing, and data collection (Sections 6.1 and 8.3.5.1) and could lead to a participant's discontinuation from study drug (Section 7.1).

Depression and suicidality may be increased with certain immune-mediated disorders. Participants should be monitored for signs and symptoms of suicidal ideation or behavior (Section 8.2.4).

CCI [redacted]

2.3.2. Benefit Assessment

The efficacy of LY3541860 in RMS has not yet been established. Participants may benefit by receiving personal health information from the physical examinations and other routine safety assessments performed in this study.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with LY3541860 are justified by the anticipated benefits that may be afforded to the RMS patient population.

3. Objectives, Endpoints, and Estimands

This table lists objectives and endpoints of this study.

Objectives	Endpoints
Primary	
To evaluate the efficacy of LY3541860 versus placebo on the number of new T1 GdE MRI brain lesions in participants with RMS	• The cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12[a]
Secondary	
To evaluate the efficacy of LY3541860 versus placebo on other measures of MRI activity in participants with RMS	• The cumulative number of total T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 • The cumulative number of new or enlarging T2 lesions, as measured by MRI scans, over Weeks 4, 8, and 12
To characterize the PK of LY3541860 in participants with RMS	Plasma trough concentrations of LY3541860
To describe the safety of LY3541860 in participants with RMS	Summary of safety data, including number and incidence of • TEAEs • SAEs • discontinuations due to AE
[redacted]	

Objectives	Endpoints
CCI	

Abbreviations: AE = adverse event; EDSS = Expanded Disability Status Scale; CCI ; GdE = gadolinium-enhancing; CCI MRI = magnetic resonance imaging; CCI PD = pharmacodynamic; PK = pharmacokinetics; CCI ; RMS = relapsing multiple sclerosis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] When counting the number of new T1 GdE lesions at each postbaseline visit, the baseline (Visit 1) scan will be used as the reference (see Section 9.3.2 for details). Lesions persisting for more than 4 weeks will be counted only once.

Primary estimand

Unless otherwise specified, the information in this section applies to both phases of this study.

The primary estimand is defined to represent the primary clinical question of interest: what is the difference in cumulative number of new T1 GdE lesions over 12 weeks of treatment with LY3541860 versus placebo among participants with RMS if use of prohibited medication or discontinuing the study intervention had not happened?

- Treatment: Each dose of LY3541860 versus placebo
- Population: defined through appropriate inclusion and exclusion criteria (Sections 5.1 and 5.2) to reflect the targeted patient population with RMS.



Secondary estimand

Unless otherwise specified, the information in this section applies to both phases of this study.

The secondary estimand is defined to represent the secondary clinical question of interest: what is the difference in other MRI lesions over 12 weeks of treatment with LY3541860 versus placebo among participants with RMS if use of prohibited medication or discontinuing the study intervention had not happened?

- Treatment: LY3541860 versus placebo.
- Population: defined through appropriate inclusion and exclusion criteria (Sections 5.1 and 5.2) to reflect the targeted patient population with RMS.





Supportive estimands

Additional details on supportive estimands for primary and secondary objectives will be provided in the SAP.

4. Study Design

4.1. Overall Design

Study KIAB is an adaptive Phase 2a/2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of multiple dose levels of LY3541860 versus placebo in adult participants with RMS.

As an adaptive study, Study KIAB has 2 phases that differ from one another by purpose and dose levels being tested. This table notes these differences.

	Phase 2a portion	Phase 2b portion
Purpose	Proof of concept	Dose ranging[a]
LY3541860 dose levels	CCI mg CCI mg	Dose Level 3 Dose Level 4

[a] Phase 2b doses will be no higher than CCI mg.

Results of interim analyses from the Phase 2a portion of this study will determine whether the Phase 2b portion will be initiated and, if so, what doses of LY3541860 will be used.

There are no differences in the study entry criteria for the Phase 2a and Phase 2b portions. In both portions, participants in the placebo group will receive treatment with LY3541860 after 12 weeks of having received placebo.

4.1.1. Screening Period

Participants will sign the ICF(s) at Visit 1, prior to the start of any study procedures. At Visit 1, participants will be evaluated for study eligibility. The MRI at Visit 1 is to be performed after all other eligibility criteria are confirmed and after screening laboratory results have been reviewed. Visit 1 procedures may be conducted over a period of more than 1 day.

4.1.2. Treatment Period

At the baseline visit (Visit 2), eligibility criteria should be reviewed and confirmed again.

In the Phase 2a portion, participants who fulfill the eligibility criteria will be randomized in a CC ratio to receive

- LY3541860 CCI mg CCI for 36 weeks, or
- placebo for 12 weeks followed by LY3541860 CCI mg CCI

In the Phase 2b portion, participants who fulfill the eligibility criteria will be randomized in a CCI ratio to receive

- LY3541860 Dose Level 3 CCI for 36 weeks
- LY3541860 Dose Level 4 CCI for 36 weeks, or
- placebo for 12 weeks followed by, in a CC ratio, either
  - LY3541860 Dose Level 3 CCI or
  - LY3541860 Dose Level 4 CCI

In both the Phase 2a and 2b portions, participants will have scheduled visits approximately every 4 weeks, at which safety and clinical assessments and procedures, including brain MRIs, will be conducted according to the SoA (Section 1.3). The primary endpoint of new T1 GdE lesions on brain MRI will be evaluated based on data generated during the treatment period.

4.1.3. Follow-Up

Both the Phase 2a and 2b portions have a follow-up period. That is, after completing the treatment period, all participants, including those who discontinue study intervention early, will return at Visit 801 (approximately 12 weeks after Visit 11 or from last dose received) and Visit 802 (approximately 24 weeks after Visit 11 or from last dose received) so that safety assessments and other procedures can be conducted according to the SoA (Section 1.3). The follow-up period will take longer than 24 weeks CCI [redacted]

4.2. Scientific Rationale for Study Design

Primary endpoint measure

The primary endpoint is based on T1 GdE lesions on brain MRI, which is widely used as a primary or secondary outcome measure in Phase 2 trials in RMS. Because of its high sensitivity for detecting disease activity and correlation with clinical disease activity, it is an appropriate endpoint for a Phase 2 study to demonstrate initial proof-of-concept (van Munster and Uitdehaag 2017). As multiple MRI scans are desirable to account for variability in MRI lesions, the primary endpoint is calculated as the mean of 2 scans, as specified in Section 3.

Appropriateness of study population

The study inclusion criteria will enable enrollment of participants who are representative of the general population of adults with RMS. The McDonald diagnostic criteria (Thompson et al. 2018) for the diagnosis of multiple sclerosis are widely accepted.

Rationale for placebo control and number of treatment groups

The double-blind, placebo-controlled design of this study limits potential bias in investigator assessments and enables a clearer interpretation of the effects of LY3541860 compared to placebo.

The use of multiple dose levels of LY3541860 will allow for an evaluation of safety and efficacy across a broad dose range and thus provide information to guide dose selection for future studies.

Duration of treatment period

The treatment period of this study is 36 weeks, with an MRI at baseline and at every fourth week thereafter, to provide sufficient time to observe treatment effects with LY3541860. To limit exposure to placebo, participants who receive placebo for the first 12 weeks will receive LY3541860 for the remainder of the treatment period. The primary endpoint will document the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12.

Duration of follow-up period

The follow-up period allows for continued safety monitoring after the last dose. The second of the 2 follow-up visits, occurring 24 weeks after the Week 36 visit, is CCI [redacted]

CCI . The follow-up period will take longer than 24 weeks CCI

Collection of race and ethnicity data

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

Adaptive design

An adaptive study design provides advantages relative to sequential studies such as improved efficiency in use of operational resources by the sponsor and sites.

4.3. Justification for Dose

This study will evaluate up to CCI

The Phase 2a portion will evaluate 2 dose levels of LY3541860 administered every 4CCI CCI Doses were selected based on current nonclinical pharmacology and toxicology data and available clinical data from the SAD/MAD study, KIAA.



The Phase 2b portion of the study will evaluate up to CCI Doses will be administered by CCI Safety, efficacy, PK, and PD data from Phase 2a of the study will inform the dosing regimens to evaluate in Phase 2b, but the dosing regimens selected will be predicted to not exceed exposures associated with the maximum dose being evaluated in Phase 2a (CCI

See the IB for additional details.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

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 these criteria apply.

Age

1. Participants must be 18 to 55 years of age, inclusive, at the time of signing the ICF.

Type of participant and disease characteristics

2. Participants must meet criteria for relapsing forms of multiple sclerosis, including relapsing-remitting multiple sclerosis or active secondary progressive multiple sclerosis, based on the 2017 revision of the McDonald diagnostic criteria (Thompson et al. 2018) with a relapsing course (RMS) activity according to Klineova and Lublin 2018.
3. Participants must have 1 of these:
   at least 1 documented relapse within the previous year
   at least 2 documented relapses within the previous 2 years, or
   at least 1 active GdE brain lesion on an MRI scan in the past 180 days prior to screening.
4. Have an EDSS ’v–‘x'–ỿ AZA't „,'’v‘xx–•–z and randomization.

Sex and contraceptive/barrier requirements

5. Males and females may participate in this study.
   a. WOCBP and WNOCBP may participate in this trial. Contraception use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. See Appendix 4, Section 10.4, for definitions and additional requirements related to contraception.
   b. Males may participate in this study.
   See Appendix 4, Section 10.4, for definitions and additional guidance related to contraception.

Informed consent

6. Capable of giving signed informed consent as described in Appendix 1, Section 10.1 and Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of these criteria applies.

MS-related history

7. Have had a diagnosis of
   primary progressive MS according to the 2017 revision of McDonald diagnostic criteria (Thompson et al. 2018), or
   nonactive secondary progressive MS (Klineova and Lublin 2018).
8. Meet criteria for neuromyelitis optica spectrum disorder (Wingerchuk and Lucchinetti 2022).
9. Have a history of clinically significant CNS disease (for example, stroke, traumatic brain injury, or spinal injury) or neurological disorders that may mimic MS or interfere with MRI or with clinical assessments in this study.
10. Have had a confirmed relapse with systemic corticosteroid administration <30 days prior to randomization.
11. Have more than 20 active GdE brain lesions on screening MRI scan.

Prior/concomitant therapy

12. Have received any of these medications or treatments:

The participant is excluded if the participant has received this	**I I I I o**	**Note**
alemtuzumab, mitoxantrone, cyclophosphamide, or cladribine	at any time	Individuals who have used 1 or more of these therapies are not eligible for this study.
lymphoid irradiation, bone marrow transplant, or chemotherapeutics	at any time	
Bruton tyrosine kinase inhibitors, such as ibrutinib and fenebrutinib	at any time	
B-cell-depleting therapies, such as inebilizumab, ocrelizumab, ofatumumab, rituximab, and ublituximab	at any time	
purine analogues or calcineurin inhibitors such as methotrexate, azathioprine, and cyclosporine	within 6 months prior to randomization	
fingolimod or ozanimod	within 10 weeks prior to randomization	
intravenous immunoglobin	within 60 days prior to randomization	
plasmapheresis	within 60 days prior to randomization	
ponesimod, siponimod, or natalizumab	within 60 days prior to randomization	Participants who have discontinued natalizumab in the 6 months prior to randomization should be evaluated to rule out PML prior to screening.

The participant is excluded if the participant has received this	I I I I o	Note
teriflunomide or leflunomide	'● •,~•– 2 years prior to randomization or 30 days prior to randomization if the participant undergoes accelerated elimination with documented teriflunomide plasma level below 0.02 mg/L prior to randomization	
dimethyl fumarate, diroximel fumarate, monomethyl fumarate, or laquinimod	within 30 days prior to randomization	
systemic corticosteroids or adrenocorticotropic hormone	within 30 days prior to screening MRI	
interferons or glatiramer acetate treatments	on the day of randomization	No washout is required.

13. Have received a BCG vaccination or treatment within less than 28 days before randomization, or intend to receive BCG vaccination or treatment during the study.
14. Have received any live vaccine (that is, live attenuated) within less than 28 days before randomization, or intend to receive a live vaccine during the study, or within 28 days after receiving the last dose of study intervention.

Infections

15. A history of PML, or neurological or MRI findings suggestive of PML.
16. Have a current or recent acute, active infection. For at least 30 days prior to screening and up to the randomization visit, participants must have not symptoms or signs of confirmed or suspected infection and must have completed any appropriate anti-infective treatment.

    Note: Participants who have upper respiratory infection, a vaginal candida infection, or an oral candida infection and who are being treated only symptomatically and not requiring system anti-infectives may be considered for enrollment if other study eligibility criteria are met. Enrollment of participants with other uncomplicated local infections should be discussed with the ’“—’—‘ ’'wx’•z–t ,xw'..xw•vt µ…—•„–‘7
17. Have had any of these types of infections within 90 days prior to screening visit or develops any of these infections before the randomization visit:

    serious (requiring hospitalization, or intravenous or equivalent oral antibiotic treatment, or both)

    opportunistic (as defined in Winthrop et al. 2015; see Appendix 8, Section 10.8)

    Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.

    chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer), and

recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, and chronic osteomyelitis).

Note: Participants with only recurrent, mild, and uncomplicated orolabial herpes or genital herpes, or both, ..t κ'ux'w•'v×''xw'● •,~',,~x''"—'—‘ ''wx'•z–xw'..xw•vt µ monitor and considered for enrollment if other study eligibility criteria are met.

18. Have active TB or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and the United States CDC (Section 8.2.5).
19. Have any of these infections:
    current infection with HBV or evidence of past infection with HBV, that is, positive for HBsAg or t–,• TNv (Section 8.2.7)
    evidence of current or prior infection with HCV, that is, positive for HCV RNA or HCV antibody (Section 8.2.8), or
    HIV infection.

Other medical conditions

20. Have a contraindication for gadolinium-based contrast agents or MRI, such as presence of a pacemaker, metallic implants (for example, artificial heart valves or aneurysm clips) in high-risk areas, or metallic material (for example, shrapnel) in high-risk areas, and history of claustrophobia that would prevent completion of all protocol-scheduled MRIs.
21. Have any active concomitant illness that is anticipated to require the use of systemic corticosteroids or other immunosuppressant, for example, rheumatoid arthritis or systemic lupus erythematosus.
22. Have a bleeding disorder, anti-phospholipid syndrome, or other hypercoagulable disorder or are on chronic anticoagulation therapy, such as warfarin or heparin, or are on an antiplatelet agent, such as clopidogrel or ticlopidine (a stable regimen of aspirin up to 81 mg/day is permitted).
23. Have current serious or unstable illnesses, including cardiovascular, hepatic (including S •µx‘,, ''' κ–w'—. x2, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than RMS), psychiatric, immunologic, or hematologic disease and other conditions ,,~t ,,5•–',,~x'•–○x',,•zt ,,—‘ ''—“•–•—5v–×µw compromise the participant s safety during the study or interfere with analyses of the study data.
24. Have any other clinically important abnormality at screening or baseline, as determined by the investigator, in physical or neurological examination, vital signs, ECG, MRI, or clinical laboratory test results that, •–',,~x'•–○x',,•zt ,,—‘ ''—“•–•—5could compromise the “t ‘,,•v•“t –,, ''' t yx,,κ'w×‘•–z',,~x'',,×wκ'—‘'•–,,x‘yx‘x'● •,,~',,~x't –t µκ'x''—y',,~x'',,×wκ'wt ,,‡ 7
    Specifically, participants will be excluded if they have the following test results at screening:
    AST or ALT 3 times ULN or greater
    TBL 2 times ULN or greater
    amylase or lipase above the ULN
    IgG or IgM below the LLN, and
    500 ms or greater on QTc.

25. Have a hematology test result at screening:
    lymphocyte count 500 cells/µL 1 97A9' '$10^3$8 X'—'' 97A9'S U8X), and
    total leukocyte count <3.0 × 10^9/L (<3.0 × 10^3/µL or <3.0 GI/L)
26. Have diagnosis or a history of malignant disease, with the exceptions of:
    basal cell or squamous cell epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 1 year
27. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
28. Have t–'●x‘xw' κx' ',„'x•,„~x''d ×x',„•—'='—''d ×x',„•—'A'—',„~x' f ×•v•wt µUwxt,„•— ' portion of the C-SSRS **and** the ideation occurred within the past 1 month prior to screening visit or since last assessed at baseline visit, **OR**
    have answered κx' ',„'t–κ'–y',„~x''×•v•wx-‘xµt,xw'ux~t ○•—‘''—',„~x' '×•v•wt µux~t ○•—‘ ' portion of the C-SSRS **and** the behavior occurred within the past 1 month prior to screening visit or since last assessed at baseline visit.

Prior/concurrent clinical study experience

29. 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.
30. Have participated, within the last 30 days, in a clinical trial involving study intervention. If the previous study intervention has a long half-life, 90 days or 5 half-lives (whichever is longer) should have passed prior to screening.
31. Have previously completed or withdrawn from this study.

Other exclusion criteria

32. Are investigator site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
33. Are Lilly employees or employees of third-party organizations involved with the study that require exclusion of their employees.
34. Are pregnant or are intending to become pregnant or to breastfeed at any time in the study. Note: Individuals of childbearing potential must test negative for pregnancy as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to the first exposure to study intervention.
35. Have experienced allergic or hypersensitivity reaction to any component of LY3541860, including excipients.
36. Have evidence of current or a within 1-year history of any substance use disorder of any severity, as defined by the DSM-V (APA 2013), in the opinion of the investigator, excepting disorders of nicotine or caffeine use.
37. Are unsuitable for inclusion in the study, in the opinion of the investigator or sponsor, for t–κ'‘xt '—',„~t,„'..tκ'v—..:‘'—..•'x',„~x'‘'t ‘,„v•‘'t–„ ''t yx,κ'—''v—y–×–w'wt,‡'•–,x‘'‘x,‡,„•—.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is 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 CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened **1 time**, unless the reason for screen failure is due to GdE lesions >20.

Rescreened participants will be assigned a new participant number.

5.4.1. Allowed Retesting of Screening Investigations

Repeating of screening investigations (without a requirement for screen failure and rescreening) is allowed at the discretion of the investigator. These screening investigations may be retested **1 time** at the discretion of the investigator:

Screening hematology and chemistry laboratory tests: These are allowed when results are outside the acceptable range for study entry but may be within the acceptable range upon retesting, due to test-retest variability.

Retesting or confirmatory testing for TB: One retest is allowed for participants ● •,~'t –' •–wx,x‘…•–t ,x 'd ×t –,•RQe b a ®-TB Gold assay or a u–‘wx‘µ•–x ' T-SPOT®.TB assay. Participants with **2** indeterminate QuantiFERON-TB Gold assays or **2** borderline T-SPOT.TB assays will be excluded.

e x“xt ,•–z'–ẏ–,,~x‘'’v‘xx–•–z'•–○x’,,•zt ,,•—’'’~–×µẇux'w•’v×’’xẇ● •,,~',,~x'’‘“—’—‘ ’'wx’•z–t ,xẇ medical monitor prior to retesting.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal products or medical devices intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This table lists the interventions used in this clinical study.

Interventions for Phase 2a			
Intervention Name	LY3541860	Placebo	Gadolinium-based contrast agents
Dosage Levels	● CCI mg CCI ● CCI mg CCI	Sodium chloride solution 0.9%	Administered according to marketing authorization
Route of Administration	CCI	CCI	IV
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and not used according to EU authorization	Authorized and used according to EU authorization
Interventions for Phase 2b			
Intervention Name	LY3541860	Placebo	Gadolinium-based contrast agents
Dosage Levels	● Dose Level 3 ● Dose Level 4	Sodium chloride solution 0.9%	Administered according to marketing authorization
Route of Administration	CCI	CCI	IV
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and not used according to EU authorization	Authorized and used according to EU authorization

Abbreviations: EU = European Union; IAC = internal assessment committee; IV = intravenous; CCI

Note: Phase 2b doses will be no higher than CCI mg. Phase 2b doses of LY3541860 will be determined based on the interim analyses from Phase 2a and recommendations of the sponsor's IAC.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

Preparing study interventions for dosing

An unblinded pharmacist or other unblinded qualified individual will prepare the study interventions for IV dosing (see Section 6.4).

Monitoring of participants after dosing

As stated in the SoA (Section 1.3), participants will be observed for at least 1 hour after completion of dosing. See Section 8.3.5.1 for additional information on participant monitoring and completing additional data collection for IRRs, if applicable.

6.2. Preparation, Handling, Storage, and 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. Only authorized study personnel may supply, prepare, 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 personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are given in the instructions provided by the sponsor.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention by a computer-generated random sequence using an IWRS.

Before the study is initiated, the login information and directions for the IWRS will be provided to each site.



6.4. Blinding

This is a double-blind study in which participants, care providers, investigators, and outcomes assessors such as Independent EDSS Raters are blinded to study intervention.

To maintain this blind, an otherwise uninvolved party, such as an unblinded pharmacist or other unblinded qualified individual, will be responsible for the preparation and dispensation of all study intervention according to the pharmacy preparation instructions.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately within 24 hours of this occurrence. The date and reason that the blind was broken must be recorded.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study (Section 7.2).

6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. Study participant identification will be confirmed prior to the time of dosing. The dose, date, and time of each dose administered on site will be recorded in the source documents and will be provided to the sponsor as requested.

6.6. Dose Modification

Participants who are randomly assigned to placebo will receive LY3541860 from Week 12 to the end of the treatment period, as described in Section 4.1.

Other dose modifications are not permitted.

6.7. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.8. Treatment of Overdose

In the event of an overdose, the investigator or treating physician should

contact the medical monitor immediately

evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced, and

closely monitor the participant for any AE or SAE as medically appropriate.

6.9. Prior and Concomitant Therapy

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Rescue Medicine

The investigator should attempt to consistently maintain therapies or treatments for symptoms related to MS throughout the study.

Participants who experience an MS relapse during the study treatment period may, if judged clinically appropriate by the investigator, receive treatment with IV or oral corticosteroids. If a participant meets this criterion during the study treatment period, the decision to implement ‘x’v×x'..xw•vt„•—'•’'“x‘',~x'•–○x’„•zt„—‘ ’'≤wz..x–„'and is not a protocol requirement. The standardized treatment regimen of 1 g IV methylprednisolone per day for a maximum of 5 consecutive days should be used as warranted. Corticosteroids may be stopped or tapered over

t'…ŧβ•…×…!–ɣ: 9'wŧκ’ƽt„',„~x'•–○x’„•zt„—‘ ’'w•’v‘x„•—7c t ‘„•v•“t –„’'xβ“x‘•x–v•–z'‘xμt “’x'’~–×μẁ not discontinue the treatment period due to the occurrence of a relapse alone, unless the investigator determines the participant has met any discontinuation criteria (Section 7.1) or the participant requests to discontinue (Section 7.2).

6.9.2. Prohibited Therapy

Therapies listed in Exclusion Criteria #12, #13, #14, and #22 (Section 5.2) are not permitted during the study treatment period, except for systemic corticosteroids for the treatment of a relapse as described in Section 6.9.1.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1, Section 10.1.9.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment) and will remain in the study and follow procedures for all remaining study visits, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
If the investigator determines that a severe or serious systemic hypersensitivity reaction, including IRR, has occurred, the participant may be permanently discontinued from the ’„×wκ'•–„x‘○x–„•—5t –w'„~x'’“—’—‘ ’'wx’•z–ated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.
t –’●x‘xw' κx’ '„–'d ×x’„•—'=’–''d ×x’„•—'A'—',~x' f ×•v•wt µUwxt „•— '“—‘„•—'–ɣ„~x'O-SSRS, **or** t –’●x‘xw' κx’ '„–'t –κ'–ɣ„~x'’×•v•wx-related behaviors on the Suicidal Behavior portion of the C-SSRS.

Note: A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

HBV or HCV: The participant tests positive for HBV DNA or tests positive for HCV RNA.

Note: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification (Section 7.1.2). Prior to discontinuation of any immunomodulatory or immunosuppressive therapy, including study intervention, the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

The participant develops HIV infection.
The participant develops active TB or a new diagnosis of latent LTBI.
The participant develops a malignancy (except for successfully treated basal or squamous cell skin carcinoma).
The participant has a second occurrence of the following:

- ANC $<0.75 \times 10^9$/L
- Platelets $<50.0 \times 10^9$/L

- Hemoglobin <8.0 g/dL
- Total lymphocyte count <200 cells/µL
- SAEs that, in the opinion of the investigator, are related to study intervention and warrant discontinuation.

See Section 7.1.2 for guidance on temporary discontinuation of study intervention in the event of a first occurrence.

7.1.1. Liver Chemistry Stopping Criteria

7.1.1.1. Interrupting Study Drug Based on Elevated Liver Tests

The study drug should be **interrupted** and close hepatic monitoring initiated (Appendix 6, Section 10.6.2) if 1 or more of these conditions occur:

Elevation
ALT or AST >8 times ULN
ALT or AST >5 times ULN for more than 2 weeks
ALT or AST >3 times ULN and either TBL >2 times ULN or INR >1.5
ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
ALP >3 times ULN, when the source of increased ALP is the liver
ALP >2.5 times ULN and TBL >2 times ULN
ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
Source: FDA 2009a and other consensus guidelines, with minor modifications.

7.1.1.2. Resuming Study Drug after Elevated Liver Tests

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

7.1.2. Temporary Discontinuation of Study Intervention

Infection-related criteria for temporary discontinuation

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

Serious or opportunistic infections, as defined in Section 5.2 and Appendix 8, Section 10.8. Study intervention is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment, after which, the participant may continue the study at the discretion of the investigator.

HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV P a M•''uxµ–●',~x'µ○xµ–ƴ"×t–„•y•vt„•—7U–',~•''•,×t„•—5,~x''"—'–‘''
designated medical monitor should be v—,‡ v,,xw‘xzt ‘w•–z',~x'"t ‘,„•v•"t–„ ''',‡,,×'7
HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention as described in Section 7.1.

Other criteria for temporary discontinuation

For the following criteria, suspend study intervention until recovery on the first occurrence and ‘x'×..x'',,×wκ'•–,x‘○x–,„•—'"x''•–○x',•zt„–‘''≤×wz..x–,7b–''xv—w–vv×''x–vx5w•'v—,„•–×x'',,×wκ' intervention permanently (Section 7.1).

ANC <0.75 × 10^9/L
Platelets <50.0 × 10^9/L
Hemoglobin <8.0 g/dL
Total lymphocyte count <200 cells/µL
SAEs that, in the opinion of the investigator, are related to study intervention and warrant discontinuation.

7.1.3. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using R‘•wx‘•v•t ''y–‘..×µ'nd g vR]) after enrollment, the investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant who becomes pregnant will be discontinued from the study.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant will be discontinued from the study.

A participant may also withdraw from the study in these circumstances:

at any time at ,,~x'"t‘,„•v•"t–„’ own request for any reason or without providing any reason

t,',,~x'‘x"×x','–ƴ,~x'"t‘,„•v•"t–„''wx'•z–xx5y–‘'xβt…“µ5"t‘x–,,''—‘'µxzt µz×t‘w•t–

at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons

if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or

if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and follow-up, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

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

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 investigational product. 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.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

MRI will be used to assess new T1 GdE weighted MRI lesions compared with the ones on previous scan. For additional information regarding MRI assessments, see Section 8.3.4.

8.1.2. Secondary Efficacy Assessments

MRI will be used to assess secondary endpoints related to new or total T1 and T2 GdE lesions. See Section 8.3.4.





Approved on 23 Apr 2025 GMT



8.2. Safety Assessments

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

8.2.1. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (Section 1.3). See Section 7.1.3 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.2. Clinical Safety Laboratory Tests

Appendix 2, Section 10.2, lists of clinical laboratory tests to be performed, and see the SoA, Section 1.3, for the timing and frequency.

See Appendix 6, Section 10.6, for clinical safety laboratory tests related to liver safety.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the follow-up time 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 Appendix 2, Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.3. Pregnancy Testing

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

8.2.4. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with study intervention should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated, and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with 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 this study using C-SSRS.

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

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

8.2.5. Tuberculosis Testing and Monitoring

Screening

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

- thorough history to determine the lifetime risk factors for TB infection, for TB progression, and for symptoms or signs of active TB, and
- signs of previous or active TB by means of
  - thorough physical examination for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes, and
  - a high-quality chest X-ray (posterior anterior, including a lateral view if needed) interpreted and reported by a radiologist or pulmonologist.

All participants with no history of LTBI or active TB, and no history of positive Mantoux TST using PPD or positive *Mycobacterium tuberculosis* IGRA must have 1 of these tests:

- PPD TST, or
- IGRA for *Mycobacterium tuberculosis.*

For details about these tests, see Appendix 7, Section 10.7.

Diagnosed LTBI

Participants diagnosed with LTBI are excluded (Section 5.2) unless they have completed appropriate LTBI therapy.

Monitoring during the study

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

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

8.2.6. Chest Imaging

A high-quality chest X-ray (posterior anterior view and, if needed, a lateral view), interpreted and reported by a radiologist or pulmonologist, will be obtained as specified in the SoA (Section 1.3).

Note: Participants do not need to have a chest X-ray at screening if, in the opinion of the investigator, both of these 2 conditions are met:

- the chest X-ray was performed within 3 months before initial screening, and
- documentation of the chest X-ray, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

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

Note: Results of a chest CT scan or other imaging study similar to a chest X-ray may be used instead of the chest X-ray y–‘'g N'x○t µ«t „•—5•–'v—’ ×µ‡ „•—'● •„~',„~x'’“—’—‘ ’'. . xw•vt µ. . .—•„–‘7

8.2.7. Hepatitis B Testing

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

If HBsAg is negative and anti-HBc is negative, the participant is not excluded.

If HBsAg is positive, the participant is excluded.

If HBsAg is negative and anti-HBc is positive, the participant is excluded.

8.2.8. Hepatitis C Testing

As specified in the SoA (Section 1.3), initial testing for HCV infection includes testing for HCV.

If either anti-HCV antibody or HCV RNA is positive, the participant is excluded (Section 5.2).

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

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

The definitions of the following events can be found in Appendix 3, Section 10.3:

AEs
SAEs, and
PCs

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AESIs (as defined in Section 8.3.5) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and causality. Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Backup Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	N/A
SAE and SAE updates after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	N/A
SAE[a] after "t ‘„•v•"t –„ ’' study participation has ended **and** the investigator becomes aware	After pt ‘„•v•"t –„ ’' study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	230 days after the last dose	Within 24 hours (Section 8.3.2)	Pregnancy paper form	N/A

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

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; PC = product complaint; SAE = serious adverse event.

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

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will atte…“,',„–'v–µκv,'"‘xz–t–vκ'•–y–‘..ŧ„•—'—'t–κ'..ŧµκ'"t‘„•v•"t–„ ’'yx..ŧµκ' partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After learning of a pregnancy in the female partner of a study participant, the investigator

will obtain a consent to release information from the pregnant female partner directly, and
within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

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

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

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

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ; 9 weeks gestational age) is always considered to be an SAE and will be reported as such.

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

Any female participant who becomes pregnant while participating in the study will be discontinued from the study (Section 7.2). If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. MS Relapse

See Section 8.1.3.

8.3.4. Magnetic Resonance Imaging

Brain MRI scans will be performed for all participants according to the SoA (Section 1.3).

MRI scans will be read by a centralized reading center blinded to treatment assignment for efficacy and safety endpoints. The reading will be performed in the absence of clinical information. Further details on scanning acquisition sequences, methods, and administrative procedures at the central reading center will be provided in a separate manual.

Each MRI scan performed for the study will be reviewed by a local neuroradiologist or radiologist who is not the investigator. However, the investigator should be contacted in the event of unexpected findings not consistent with MS that is relevant for participant safety. The investigator should not review the MRI unless necessary for participant safety.

In the event a participant requires corticosteroids for treatment of an MS relapse, an MRI should be done prior to the first steroid dose if the scan is within 1 week of the next scheduled visit, whenever possible.

Participants receiving corticosteroids should have an interval of 3 weeks between their last dose of corticosteroids and the MRI scan.

8.3.5. Adverse Events of Special Interest

These are the AESIs for this study:

hypersensitivity reactions, including infusion-related reactions (Section 8.3.5.1)

infections, including opportunistic infections (Section 8.3.5.2)

infusion site reactions (Section 8.3.5.3), and

suicidal ideation and behavior (Section 8.2.4).

8.3.5.1. Hypersensitivity Reactions, Including Infusion-Related Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions, including IRRs. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff, appropriate medical equipment, and emergency medications available when study participants are receiving study intervention and until the completion of all the postdosing activities. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Appendix 2, Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

Premedication for infusions

Premedication for the infusions is not planned. However, if an IRR occurs, appropriate medication may be used for subsequent infusions as determined by the study investigator. Administration of acetaminophen 500 to 1000 mg and/or an antihistamine may be administered orally 30 to 60 minutes prior to the start of infusion.

Any premedications given will be documented as a concomitant therapy (Section 6.9).

Periodic assessments of the potential benefit of implementing required infusion premedication based on safety data collection and evaluation will be conducted.

Management of infusion-related reactions

There is a risk of IRR with any infused biological agent. Therefore, participants should be monitored closely during the infusion and after the infusion.

Symptoms and signs that may occur as part of an IRR include, but are not limited to

fever chills nausea headache bronchospasm hypotension	angioedema throat irritation rash pruritus myalgia, and dizziness.

Manage IRRs as shown in this table.

a significant IRR occurs	Slow the infusion of the study intervention. For example, reduce infusion rate by 50%, that is, an infusion rate of 12 mL/hour becomes 6 mL/hour or slower. The infusion can also be stopped, depending on the symptoms or signs present. If slowed, complete the infusion at the slower rate, as tolerated. If determined by the investigator that the infusion should no longer continue, do not further dose the participant.
	Employ supportive care according to the symptoms or signs at the discretion of the investigator.
t'"t ‘„•v•"t –„ ’ IRR is sufficiently severe to discontinue the infusion	Subsequent infusions may be administered with premedication at the discretion of the investigator.
t'"t ‘„•v•"t –„ ’ infusion rate is reduced due to an IRR	Subsequent infusions may be administered at the discretion of the investigator following agreement with the sponsor.

If…	then…
	• The infusion rate of the subsequent infusions must not exceed the slowest rate used to complete the infusion in the event of an IRR, and • Premedication may be administered at the discretion of the investigator in consultation with the sponsor.
it is determined that the participant should not receive further doses of study intervention	• Permanently discontinue the study intervention. Participants will remain in the study; see Sections 7.1 and 1.3.

8.3.5.2. Infections, Including Opportunistic Infections

Completion of the Infection CRF page is required for each infection reported as an AE or SAE. The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al. (2015) (Appendix 8, Section 10.8).

8.3.5.3. Infusion Site Reactions

Symptoms and signs of a local infusion site reaction may include erythema, induration, pain, pruritus, and edema.

If an INFSR is reported by a participant or site staff, the INFSR CRF will be used to capture additional information about this reaction, for example, infusion site pain, severity and area of erythema, induration, pruritis, and edema.

8.4. Pharmacokinetics

Samples will be collected for measurement of plasma concentrations of LY3541860 as specified in the SoA (Section 1.3). Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of LY3541860 will be assayed using a validated bioanalytical assay. Only samples from participants assigned to treatment with LY3541860 will be analyzed for drug concentrations.

A CCI may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of LY3541860. Samples collected for analyses of LY3541860 plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

See Appendix 1, Section 10.1.12, for details about sample retention and custody.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A whole-blood sample will be collected from participants for pharmacogenetic analysis where local regulations allow according to the SoA (Section 1.3).

See Appendix 5, Section 10.5, for information regarding genetic research. See Appendix 1, Section 10.1.12, for details about sample retention and custody.

8.7. Biomarkers

Blood samples for biomarker research will be collected at the times specified in the SoA (Section 1.3), where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3541860, pathways associated with multiple sclerosis, mechanism of action of LY3541860, CCI

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of CCI after the last patient visit for the study, or for a shorter period if local regulations and IRBs impose shorter time limits (Appendix 1, Section 10.1.12). This retention period enables the use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3541860 or after LY3541860 becomes commercially available.

8.8. Immunogenicity Assessments

Antibodies to study intervention will be evaluated in venous samples collected from all participants according to the SoA (Section 1.3). Additionally, samples will be collected at the final visit from participants who discontinued study intervention or withdrew from the study. These samples will be tested by the sponsor or sponsor's designee using a validated assay designed to detect ADA in the presence of study intervention at a laboratory approved by the sponsor.

Collected samples will be screened for ADA, and the titer of confirmed positive samples may be reported or tabulated. Further analysis including neutralizing capability may be performed. TE ADA are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADA were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared with baseline if ADA were detected at baseline (treatment-boosted ADA).

All samples collected for detection of ADA will also be evaluated for study intervention plasma concentration to enable interpretation of the data. All samples for immunogenicity should be

collected predose when applicable and possible. See Appendix 1, Section 10.1.12, for details about sample retention and custody.

8.9. Medical Resource Utilization and Health Economics

Health economics or medical resource utilization parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to first unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

Phase 2a

The null hypothesis for the primary objective is that there is no difference in reducing the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with LY3541860 CCI mg versus placebo.

Phase 2b

The null hypothesis for the primary objective is that there is no difference in reducing the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with at least 1 dose of LY3541860 versus placebo.

Multiplicity Adjustment

Adjustment for multiple comparisons will not be employed in the analysis for this study.

9.2. Analyses Sets

For the purposes of analysis, these analysis sets are defined:

Participant Analysis Set	Description
mITT	All participants randomly assigned to study intervention and receive at least 1 dose of the study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Safety	All participants randomly assigned to study intervention and receive at least 1 dose of the study intervention. Participants will be analyzed according to the intervention they actually received within each study period.
PK	All participants randomly assigned to study intervention and receive at least 1 dose of the study intervention and with at least 1 postbaseline evaluable PK sample.

Efficacy analyses will be conducted on the mITT analysis set, unless otherwise specified, and will combine efficacy data collected in Phase 2a and Phase 2b, as appropriate. Separate efficacy analyses by study phases may be provided on the mITT analysis set if deemed necessary. Safety summaries and analyses will be provided on the safety analysis set by study phases. More detailed definitions of analysis sets will be provided in the SAP.

9.3. Statistical Analyses

9.3.1. General Considerations

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Prior to first unblinding of the database, a detailed SAP will be developed by sponsor or its designee.

Efficacy and safety data will be analyzed and summarized by phases:

- Phase 2a: Proof-of-concept study
- Phase 2b: Dose-ranging study

For Phase 2b efficacy analysis, Phase 2a efficacy data will be combined, as appropriate, to assist with the Phase 2b analysis. More details will be provided in the SAP.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.10, unless otherwise stated. All confidence intervals will be given at a 2-sided 90% level. No adjustments for multiplicity will be performed. Alternative or additional statistical methods may be used as appropriate as outlined in the SAP. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data will report the number of participants and incidence as a frequency and as a percentage. All participants will be included in individual participant data listings.

Baseline will be defined as the last available value before the first dose of study intervention for both efficacy and safety analyses. In most cases, this value will be what is recorded at the randomization visit (Visit 2, with the exception of MRI). Any assessment collected after the first dosing is defined as postbaseline for the treatment period. Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline value or the value at the visit is missing for a particular variable, then the change from baseline is defined as missing.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.3.2. Primary Endpoint/Estimand Analysis

Definition of primary endpoints

Phase 2a

The primary endpoint is the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with LY3541860 CCI mg versus placebo.

Phase 2b

The primary endpoint is the cumulative number of new T1 GdE lesions, as measured by MRI scans, over Weeks 4, 8, and 12 with each 1 dose of LY3541860 versus placebo.

Analysis of primary estimands



CCI [redacted]

When counting the number of new T1 GdE lesions at each postbaseline visit, the baseline (Visit 1) scan will be used as the reference to determine whether a lesion was new and the lesions that persist for more than 4 weeks were counted only once. No missing data imputation will be performed in the primary estimand analysis. Additional imputation methods and deviations from assumptions may be tested in sensitivity analyses specified in SAP.

9.3.3. Secondary Estimands Analysis

The secondary estimands on MRI lesions will be analyzed using the same way as the primary estimand. Additional details will be provided in the SAP that is finalized before the first unblinding.

9.3.4. Exploratory Endpoints and Patient-Reported Outcomes

Analyses for exploratory endpoints and patient-reported outcomes will be further described in the SAP that is finalized before the first unblinding.

9.3.5. Pharmacokinetic/Pharmacodynamics Analysis

Observed plasma concentrations of LY3541860 will be summarized by time point and by dose using descriptive statistics and may be illustrated graphically.

Mean population PK parameters for LY3541860 in plasma (for example, clearance, exposure, and volume of distribution) and inter-individual PK variability may be determined using a population PK approach with nonlinear mixed-effect modeling (NONMEM) software. The PK data from this study may be combined with data from other studies in the clinical development program to improve PK parameter estimation.

Relationships between LY3541860 exposure and select biomarkers and clinical efficacy endpoints may also be explored using graphical or modeling approaches if warranted.

Additional analyses may be conducted if they are deemed appropriate.

9.3.6. Safety Analyses

Safety data will be assessed by evaluating exposure, AEs, laboratory analytes, vital signs, and AESIs.

Duration of exposure to therapy will be calculated for each participant and summarized by treatment group.

The AEs will be coded according to the MedDRA and summarized by system organ class, preferred term, severity, and relationship to the study intervention. All AEs, including preexisting conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

A TEAE is defined as an event that first occurred or worsened in severity after baseline, with baseline defined as all preexisting conditions recorded at Visit 1 and any AEs recorded before the first dose of study intervention (that is, during the interval between Visits 1 and 2, and recorded with the time of onset before the first dose of study intervention). The treatment period

will be used as the postbaseline period for the analysis. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

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

Treatment-related TEAEs, that is, TEAEs related to study intervention, are defined as events that are indicated by the investigator on the CRF to be related to treatment.

AESIs or special safety topics will be identified by a standardized MedDRA query or a sponsor-defined MedDRA-preferred term listing.

Follow-up emergent AEs, SAEs including deaths, and AEs that lead to study discontinuation will be summarized for the follow-up period separately and also in combination with events from the treatment period. All AEs, including preexisting conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

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

9.3.7. Other Analyses

9.3.7.1. Subgroup Analyses

Subgroup analyses may be conducted for the primary endpoint to assess the effects of various demographic and baseline characteristics for both Phase 2a and Phase 2b, separately or combined. Subgroups to be evaluated may include previous therapy use, gender, age, race, geographic region, compliance with study intervention, reason for discontinuation, and so on. The specific grouping of patients based on these variables, as well as the detailed description of the summaries and statistical analyses, will be outlined in the SAP.

9.4. Interim Analysis

Analyses for the primary database locks for Phase 2a and Phase 2b will be conducted as described in Section 9.3, when all participants in each phase have completed the Week 36 visit or have discontinued from study intervention.

Potential prespecified interim analyses

Any of the predefined interim analyses may be conducted at the discretion of the sponsor.

Phase 2a

Two interim analyses may be conducted during Phase 2a period to evaluate the benefit/risk and inform internal business decision making. At the discretion of the sponsor, the prespecified interim analyses below may not be conducted.

CCI [redacted]

Results of interim analyses from the Phase 2a portion of this study will determine whether the Phase 2b portion will be initiated and, if so, what doses of LY3541860 will be used.

Phase 2b

Three interim analyses may be conducted during Phase 2b period prior to the primary database lock to evaluate the benefit/risk and inform internal business decision making. At the discretion of the sponsor, the prespecified interim analyses below may not be conducted.

CCI [redacted]

Relevant Phase 2a data may be considered for inclusion in the interim analyses in Phase 2b.

Other interim analyses may be conducted at the discretion of the sponsor. All interim analyses will be used to support planning activities associated with the clinical development program.

Assessment of unblinded interim data

Assessment of unblinded interim data will be conducted by an IAC with a limited number of prespecified team members who do not have direct site contact or data entry or validation responsibilities (Section 10.1.5). Only the IAC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Prior to the interim or final database lock, a limited number of preidentified individuals may gain access to the unblinded data 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 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. Study sites will receive information about interim results only if they need to know for the safety of their participants.

9.5. Sample Size Determination

Phase 2a

The first approximately 40 participants will be equally randomly assigned to LY3541860 CCI mg or placebo (approximately 20 participants per arm). Thereafter, approximately 60 participants will be randomly assigned to LY3541860 dose of CCI mg or placebo using a CC randomization ratio. The total sample size will be approximately 100 participants, with approximately 70 participants on LY3541860 dose of CCI mg and 30 participants on placebo.

All randomized participants in the mITT analysis set will be considered evaluable. At the time of primary outcome, the sample sizes of the LY3541860 CCI mg and placebo groups will be approximately 63 and 27, respectively, assuming a 10% drop-out rate from the study intervention.

The sample size calculation is based on the primary efficacy estimand and its endpoint, the cumulative number of new T1 GdE lesions over Weeks 4, 8 and 12. CCI [redacted]

Phase 2b

Approximately 100 participants will be randomly assigned to either LY3541860 Dose Level 3, or LY3541860 Dose Level 4, or placebo in a ratio of CCI . All randomized participants in the mITT analysis set will be considered evaluable.

The power calculations for Phase 2b study assume the following:

- At the time of primary outcome, the LY3541860 Dose Level 3 and LY3541860 Dose Level 4 groups will each have a sample size of approximately 40 participants, and the placebo group will have a sample size of approximately 9 participants, assuming 10% drop-out rate from the study intervention.
- For simplicity in the power calculation, these are assumed:

CCI [redacted]

- As noted in Section 9.3.1, Phase 2a efficacy data will be combined, as appropriate, to assist with the Phase 2b analysis, and the placebo group will be combined from both phases, which will have a total sample size of approximately 36 participants at the time of the primary outcome.
- The power is calculated under a negative binomial regression model with a 2-sided Type I error of 0.10.

Given these assumptions, the power to reject the null hypothesis under the pairwise comparison for the LY3541860 treatment groups with sample sizes equal to 40 compared to a combined placebo group with sample size of 36 is greater than CCI

Approved on 23 Apr 2025 GMT

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

applicable ICH GCP Guidelines, and

applicable laws and regulations.

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

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

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

The investigator will be responsible for

providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and

reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity

Investigator sites are compensated for participation in the study as detailed in the CTA.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or „~x'•–○x',•zt „–‘ ’ representative will explain the nature of the study, including the risks and benefits, to the potential participant –‘',~x'“–„x–„•t µ“t ‘„•v•“t –„ ’'µκzt µκ' authorized representative and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection 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.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant –‘',~x'“t ‘„•v•“t –„ ’'µκzt µκ't ×,~–‘•-xẁ representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

c t ‘„•v•“t –„,'● •µµlux't ’'•z–xẁt'×–•”×x'•wx–„•y•x‘'uκ',~x'’“—’–‘',–'“‘–„xv,',~x'“t ‘„•v•“t –„ ’' personal data. Any participant information, such as 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 „~x'“t ‘„•v•“t –„ ’ 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. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their 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 information security, data integrity, and data protection, including data transfer, unauthorized access, disclosure, dissemination, alteration, or loss of information or personal data. These processes include appropriate contingency plans for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements t–ẁ“‘–vx’’x’7g~x'’“—’–‘ ’'“‘–vx’’x’'t ‘x'v–.:“µt–„'● •,~'µ–vt µ“‘•○t vκ'µt ● ’'t–ẁ‘xµκ○t–„' legislations, including the GDPR.

10.1.5. Committees Structure

Internal Assessment Committee

The primary responsibility of the IAC is to review unblinded safety, PK/PD, and efficacy reports from interim analyses and to provide a recommendation to senior management regarding future study conduct and for internal clinical development planning.

CCI [redacted] The IAC will have a charter, which will be approved prior to the first unblinding, that includes details about IAC membership, purpose, responsibilities, and operation. Information about interim analyses will be shared with investigators and site personnel only if necessary for the safety of their study participants.

In addition to the predefined interim analyses, the IAC will evaluate unblinded data if the blinded safety review team observes any of the following events regardless of the relatedness to the study intervention:

CCI [redacted]

The IAC would review the unblinded data and determine if stopping the study is warranted. Enrollment and dosing may be paused during review by the IAC. Case unblinding may be performed for the described reviews, if necessary.

Sponsor's blinded internal safety review team

Participant safety will be continuously monitored by the sponsor's blinded internal safety review team, which includes safety signal detection at any time during the study.

All safety data collected will be summarized and reviewed by the sponsor's internal safety review committee for agreement of next steps.

10.1.6. Dissemination of Clinical Study Data

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

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

10.1.7. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

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

QTLs will be predefined to identify systematic issues that can impact participant safety or reliability of study results. These predefined parameters will be monitored during the study, and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.

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

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

The sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

The sponsor or designee will perform monitoring to confirm that data transcribed 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 CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Data capture system

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

An EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment data (participant-focused outcome instrument) and other data will be collected by the participant via a paper source document and will be transcribed by the authorized study personnel into the EDC.

Data collected via the sponsor-provided data capture systems will be stored at a third party. 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 or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in ,˜x'vx–,‘t µ○x–w—‘ ’'wt ,‡ ut ’x'’κ’,ɤ..5t –ẇreports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the •–,ɤz‘•,ɤ'–y,,˜x'wt ,‡'v–µκv,ɤw7f –×‘vx'w–v×..x–,,’'t ‘x'y•µκw't ,',,˜x'•–○x’,,•zt ,,—‘ ’'’•,ɤ7

Data reported on or entered in the CRF and 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, Pausing, and Closure

First act of recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Pausing of enrollment to the study

In the event any of the below criteria are observed, the IAC members individually will review unblinded safety data before determining whether study enrollment should be paused or whether any other study parameters should be modified.
AEs that require pausing of enrollment to the study include the following, regardless of the relatedness to the study intervention:

1 death

3 participants experience a severe AE of the same preferred term

3 or more participants meet the liver chemistry stopping criteria (Section 7.1.1), or

3 or more participants meet hematology laboratory discontinuation criteria in any of the laboratory abnormalities detected and confirmed, with no other obvious cause in the opinion of the investigator (Section 7.1.2).

Study or site termination

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

For study termination

discontinuation of further study intervention development

For site termination

failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor s procedures, or GCP guidelines

inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and

total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations

used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and 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

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.12. Sample Retention

Sample Type	Custodian	Retention Period after Last Patient Visit
Exploratory Biomarkers	Sponsor or Designee	CCI
Pharmacokinetics	Sponsor or Designee	
Genetics	Sponsor or Designee	
Immunogenicity	Sponsor or Designee	

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed centrally or locally as defined by the table below.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

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.

Investigators must document their review of the laboratory safety results.

Laboratory and analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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	
Absolute neutrophil count (segmented and bands) (calculation)	
Leukocytes (WBCs [white blood cells])	
Differential	
Percent and absolutes count of	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	Reflex if abnormalities are present

Clinical Laboratory Tests	Comments
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Amylase	
Lipase	
Lipid Panel	Assayed by Lilly-designated laboratory
High-density lipoprotein (HDL)	
Low-density lipoprotein (LDL-C)	If triglycerides are >400, direct LDL will be measured.
Very low-density lipoprotein (VLDL-C)	
Cholesterol	
Triglycerides	
Coagulation	Assayed locally
Prothrombin time, INR (PT-INR)	
Partial thromboplastin time (PTT)	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	

Clinical Laboratory Tests	Comments
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	
Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory
Urine pregnancy	Assayed and evaluated locally
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory
Calculations	Generated by Lilly-designated laboratory
Creatinine clearance - Cockcroft-Gault	
TB, HIV, and Hepatitis Serology	
Tuberculosis (TB) testing:	
QuantiFERON-TB® Gold test	Assayed by Lilly-designated laboratory
T-SPOT®.TB	May be tested and evaluated locally. Local laboratory must be qualified by local regulations.
TST	Tested and evaluated locally. Local staff must be qualified to administer and interpret the test.
HIV testing	Assayed by Lilly-designated laboratory
Hepatitis C Virus (HCV) testing:	Assayed by Lilly-designated laboratory
HCV antibody	
HCV RNA	
Hepatitis B Virus (HBV) testing:	Assayed by Lilly-designated laboratory
Hepatitis B core antibody (anti-HBc)	
Hepatitis B surface antigen (HBsAg)	
Other Testing	Assayed by Lilly-designated laboratory
C-reactive protein (CRP)	
Reticulocyte count	
CCI [redacted]	Results will not be provided to the investigative sites.
Pharmacokinetic Samples – LY3541860 concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Immunogenicity (ADA) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3541860 antibodies	
Anti-LY3541860 antibodies neutralization	

Clinical Laboratory Tests	Comments
CCI	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
	Assayed by Lilly-designated laboratory. Screening results will be reported to investigative sites for eligibility. All other 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.
CCI	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

Timing	Laboratory Test[a]
Collect from 30 min to 4 hr after the start of the event. Note: The optimal collection time is from 1 to 2 hr after the start of event.	Total tryptase
	Complements (C3, C3a, and C5a)
	Cytokine panel (IL-B5UX : 5UX : 9, or any cytokine panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. Note: If collecting, collect up to 12 hr after the start of the event.	LY3541860 ADA
	LY3541860 concentration

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

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Adverse Events and Serious 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 participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.

Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

New condition 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.

Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical 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 that are associated with the underlying disease, unless judged by the •–○x’,,•zt ,,—',,—'ux'…–‘x'’x○x‘x',,~t–'xβ“xv,,xw'y—',,~x'“t ‘,,•v•“t–,, ’'v—w•,,•—7

The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the “t ‘,,•v•“t–,, ’'v—w•,,•—7

Medical or surgical procedure, for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of preexisting diseases or conditions present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

Results in death

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.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the “~κ’•v•t– ’'–yy•vx'–‘'–×,,“t ,,•x–,,'’x,,,•–z7O–.. :“µ•vt ,,•—’',,~t ,,'–v×‘'w×‘•–z' hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

Results in persistent disability or incapacity

The term disability met –’'t'’×u’,ŧ–,,•t µw•’‘×“,,•—'–ɣt'“x‘’— ’'t u•µ•,ĸ',,–' conduct normal life functions.

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

Is a congenital anomaly/birth defect

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

Other situations:

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

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

10.3.3. Definition of 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 study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

deficiencies in labeling information, and

use errors for device or drug-device combination products due to ergonomic design elements of the product.

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

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

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

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

AE, SAE, and Product Complaint Recording

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

The investigator will then record all relevant AE/SAE/product complaint information in the “t ‘„•v•“t –„ ’'. . xw•vt µ‘xv–‘w’ 5•–'t vv–‘wt –vx'● •„~'„~x'•–○x’„•zt „–‘ ’'—‘. . t µvµ–•vt µ‘“‘t v„•vx. AE/SAE information is recorded on the appropriate CRF page, and product complaint information is reported on the PC Form.

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

It is **not** t vvx“,‡ uµ'y—‘',~x'•–○x’,•zt ,,—‘',,—'’x–w‘“~—,, v—“•x’'—¥',~x'“t ‘,•v•“t –,, ’'..xw•vt µrecords to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC Form for product complaints.

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

> Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
>
> Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
>
> Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

M reasonable possibility '—¥t'‘xµt ,•—’~•“'v—○xκ'',~t ,',,~x‘x't ‘x'yt v,,’5x○•wx–vx5t –w8—‘' arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

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

The investigator will also consult the IB in their assessment.

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

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

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

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

Follow-up of AEs and SAEs

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

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

10.3.5. Reporting of SAEs

SAE reporting via paper form

The primary mechanism for reporting an SAE will be the SAE paper form.

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the medical monitor.

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 ’“—’—‘ ’'•–’„‘×v„•—’.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Investigator safety reports will be prepared for SUSARs according to local regulatory requirements and sponsor policy. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and

then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Consistent with the EU CTR (536/2014), the sponsor has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs. h “—'t –'•–○x’„•zt „—‘ ’'‘x“—‘„'–y an SAE, the sponsor will evaluate the data, including confirmation of relatedness and assessment of expectedness. The sponsor will submit any qualifying reports to the EudraVigilance database within the required time frame. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and will be forwarded to investigators as necessary.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they have a congenital anomaly such as Müllerian agenesis are infertile due to surgical sterilization, or are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note, or aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a FSH >40 mIU/mL, or 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women **should not** be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Females

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

	I
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, and not plan a pregnancy during the study	use periodic abstinence methods ○ calendar ○ ovulation ○ symptothermal, or ○ postovulation declare abstinence just for the duration of a trial, or use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Contraception	Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These methods of contraception must be used for the duration of the study and for 230 days after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	female sterilization[a] (including fallopian tube ligation, hysteroscopic sterilization) combination oral contraceptive pill progestin-only contraceptive pill (mini-pill) implanted contraceptives injectable contraceptives contraceptive patch (only women <198 pounds or 90 kg) total abstinence vasectomy (for men in clinical trials and for female "t ‘„•v•"t –„ ’'"t ‘„–x''if only sexual partner) fallopian tube implants (if confirmed by hysterosalpingogram) combined contraceptive vaginal ring, or intrauterine devices
Effective contraception	male or female condoms with spermicide diaphragms with spermicide or cervical sponges barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: Male and female condoms should not be used in combination.
Ineffective forms of contraception whether used alone or in any combination	spermicide alone periodic abstinence fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) withdrawal postcoital douche, or lactational amenorrhea

[a] Hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a WNOCBP.

Males

The table below describes contraception guidance for men.

Participant Population	Contraception Guidance
All men...	should refrain from sperm donation for the duration of the study and for 230 days after the last dose of the study intervention.
Men with partner(s) who are WOCBP...	must remain abstinent (if this is their preferred and usual lifestyle), or use condoms and use at least 1 additional highly effective method of contraception for the duration of the study and for 230 days after the last dose of the study intervention.
Men with partner(s) who are pregnant	must remain abstinent (if this is their preferred and usual lifestyle), or use condoms for the duration of the study and for 230 days after the last dose of the study intervention.
Men in exclusively same-sex relationships, as their preferred and usual lifestyle.	are not required to use contraception.

Examples of different methods of contraception: same as those listed in the subsection on female contraception

Approved on 23 Apr 2025 GMT

10.5. Appendix 5: Genetics

Use and 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 study intervention or RMS and related diseases. CCI [redacted] Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3541860 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.

Sample retention is described in Appendix 1, Section 10.1.12.

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

10.6.1. Hepatic Evaluation Testing

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

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

The local laboratory must be qualified in accordance with applicable local regulations.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[a]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	HDV IgM antibody
Direct bilirubin	**Hepatitis E virus (HEV) testing:**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine aminotransferase (ALT)	HEV IgM antibody
Aspartate aminotransferase (AST)	HEV RNA[a]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)**[b]
Hepatic Coagulation Panel	**Anti-actin antibody**[c]
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[a]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[a]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody

Urine Chemistry	**Microbiology Culture:**
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV DNA[a]	
EBV antibody	

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

b Not required if anti-actin antibody is tested.

c Not required if anti-smooth muscle antibody (ASMA) is tested.

10.6.2. Close Hepatic Monitoring

Laboratory tests, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur.

If a participant with baseline results of...	**develops the following elevations:**
ALT or AST <1.5 times ULN	MXg'—'Mf g' 3 times ULN
ALP <1.5 times ULN	MXc' 2 times ULN
TBL <1.5 times ULN	gNX' 2 times ULN
MXg'—'Mf g' : 7 5 times ULN	MXg'—'Mf g' 2 times baseline
MXc' : 7 5 times ULN	MXc' 2 times baseline
gNX' : 7 5 times ULN	gNX' : 7 5 times baseline

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 : ',,—'<',,•.. x'' ● xx≥µκ5ut 'xw'—',,~x'"t ',,•v•"t –,, ''vµ•–•vt l condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the "t ',,•v•"t –,, ''vµ•–•vt µv—w•,,•—'t –w'laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

10.6.3. Comprehensive Hepatic Evaluation

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

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 times ULN	MXg'—‘'Mf g' 3 times ULN with hepatic signs or symptoms[a], or MXg'—‘'Mf g' 5 times ULN
ALP <1.5 times ULN	MXc' 3 times ULN
TBL <1.5 times ULN	gNX' 2 times ULN
MXg'—‘'Mf g' : 7 5 times ULN	MXg'—‘'Mf g' 2 times baseline with hepatic signs or symptoms[a], or MXg'—‘'Mf g' 3 times baseline
MXc' : 7 5 times ULN	MXc' 2 times baseline
gNX' : 7 5 times ULN	gNX' 2 times baseline

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

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

Nt ’xw—',~x'“t ,•x–,, ’'~•’,,—κ't –w•–•,•t µ‘x’ ×µ,’ 5y×‘ther 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, ×‘•–x',,–β•v–µ z κ'’v‘xx–5j •µ — ’'disease, blood alcohol levels, urinary ethyl glucuronide, and uµ—w“~—’“~t ,•wκµx,~t —µ7Nt ’xw—',~x'v•‘v×…’,‡ –vx’'t –w,~x'•–○x’,•zt ,—‘ ’'t ’’x’’ .. x–,'—y,~x' “t ‘,•v•“t –,, ’'vµ•–•vt µv—w•,•—5,~x'•–○x’,•zt ,—‘'’~—×µw—’•wx‘'‘xyx‘‘•–z',~x'“t ‘,•v•“t –,'y—‘'t' hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

10.6.4. Additional Hepatic Data Collection (Hepatic Safety CRF) in Study Participants Who Have Abnormal Liver Tests during the Study

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

1. Qux○t ,,•—'–y'’x‘×…!MXg',,–' Atimes'h Xa '—'; '–‘'…–‘x'v—’xv×,,•○x'uμ—w',,x’,,’5•y' ut’xμ–x'MXg'H: 7A',,•..x''h Xa
   U–'“t‘,,•v•“t–,,''●•,,~'ut’xμ–x'MXg' : 75 times h Xa 5',,~x',,~‘x’~—μw'•''MXg' 3 times baseline on 2 or more consecutive tests
2. Qux○t ,,xw'g NX',,–' ; times'h Xa 5•y'ut’xμ–x'g NX'H: 7A',,•..x''h Xa '
   U–'“t‘,,•v•“t–,,''●•,,~'ut’xμ–x'g NX' : 7A',,•..x''h Xa 5',,~x',,~‘x’~—μw'’~—×μw'ux'g NX' ;' ,,•..x''ut’xμ–x
3. Qux○t ,,•—'–y'’x‘×…!MXc',,–' ; times'h Xa '—'; '–‘'…–‘x'v—’xv×,,•○x'uμ—w',,x’,,’5•y' ut’xμ–x'MXc'H: 7A',,•..x''h Xa
   U–'“t‘,,•v•“t–,,''●•,,~'ut’xμ–x'MXc' : 7A',,•..x''h Xa 5',,~x',,~‘x’~—μw'•''MXc' ;',,•..x'' ut’xμ–x'—'; '–‘'…–‘x'v—’xv×,,•○x'uμ—w',,x’,,’
4. Tx“t,,•v'x○x–,,'v—’•wx‘xw',,–'ux't–'f MQ
5. P•’v—,,•–×t,,•—'–y'’,,×wx'w'×z'w×x',,–'t'~x“t,,•v'x○x–,,

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

10.7. Appendix 7: Tuberculosis Testing

This table describes recommendations for performing and interpreting TB tests. It also provides recommendations on TB retesting.

TB test type	How to perform the test	How to interpret the test	When to retest
PPD TST	1. Inject 0.1 mL of tuberculin PPD into the inner surface of the forearm. **Notes:** The injection should be made with a tuberculin syringe. The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. 2. Measure induration at the site of intradermal injection from 48 to 72 hr after intradermal injection. **Notes:** Test must be read during this window of time. Test does not need to be read at the study site but must be read by a trained medical professional, and the result must be provided to the study site before randomization. The reaction should be measured in millimeters of induration (palpable, raised, hardened area, or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).	An induration of 5 mm or more is considered positive in persons with HIV infection a recent contact with a person with TB disease fibrotic changes on chest radiograph consistent with prior TB organ transplants, or immunosuppression for other reasons, for example, taking the equivalent of >15 mg per day of prednisone for 1 month or longer, or taking TNF alpha antagonists An induration of 10 mm or more is considered positive in all other potential clinical trial participants.	2-step testing, that is, repeat TST from 1 to 3 weeks after the first TST, is recommended for certain participant groups, including those receiving immunosuppressant treatment having a history of temporally remote increased risk of TB infection, or for whom the first test is negative, and retesting is recommended per local public health and/or professional medical society recommendations.

TB test type	How to perform the test	How to interpret the test	When to retest
IGRA for *M tuberculosis*	Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.	Results are provided by the laboratory assaying the test.	The investigator may discuss retesting with „~x'’“—’–‘ ’'wx’•z–t ,xw’..xw•vt µ…—•„–'' if the investigator suspects a false-positive IGRA result in a participant with no increased risk of TB infection during lifetime, and there is no evidence of prior or current TB on physical examination and/or on chest X-ray interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and with documented chest X-ray report).

Abbreviations: IGRA = interferon gamma release assay; PPD = purified protein derivative; TB = tuberculosis; TNF = tumor necrosis factor; TST = tuberculin skin test.

10.8. Appendix 8: Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

This table lists examples of infections that may be considered opportunistic in the context of biologic therapy. This table is provided to aid the investigator in recognizing infections that may be considered opportunistic. This list is not exhaustive. For data analysis, infections will be categorized by Lilly as opportunistic according to the article by Winthrop et al. (2015).

Bacterial	
Bartonellosis (disseminated disease only)	Tuberculosis
Campylobacteriosis (invasive disease only)	Non-tuberculous mycobacterial disease
Legionellosis	Salmonellosis (invasive disease only)
Listeriosis (invasive disease only)	Shigellosis (invasive disease only)
Nocardiosis	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral	
BK virus disease, including polyomavirus-associated nephropathy	
Cytomegalovirus disease	
Hepatitis B virus reactivation	
Hepatitis C virus progression	
Herpes simplex (invasive disease only)	
Herpes zoster (any form)	
Posttransplant lymphoproliferative disorder (Epstein-Barr virus)	
Progressive multifocal leukoencephalopathy, John Cunningham virus	
Fungal	
Aspergillosis (invasive disease only)	
Blastomycosis	
Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual)	
Coccidioidomycosis	
Cryptococcosis	
Histoplasmosis	
Paracoccidioides infections	
Penicilliosis	
Pneumocystosis	
Sporotrichosis	
Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*	
Parasitic	
Leishmaniasis (visceral only)	
Strongyloidiasis (hyperinfection syndrome or disseminated disease)	
Microsporidiosis	
Toxoplasmosis	
Trypanosoma cruzi •–yxv„•—'lO~t z t ’ 'w•’xt ’x'“‘–z‘x’’•—2 lw•’’x..•–t„xw w•’xt ’x'—µκ2	
Cryptosporidiosis (chronic disease only)	

Source: Based on Winthrop et al. (2015).



Approved on 23 Apr 2025 GMT

10.10. Appendix 10: Provisions for Changes in Study Conduct during Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

Ʊ't –'xβvx“„•—t µv•‘v×…’,‡–vxƽt y„x'' ‘xvx•○•–z',„~x'’“—’—‘ ’'● ‘•„„x–'t ““‘–○t µß’•„x’'..ŧ κ' implement changes if permitted by local regulations.

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

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section e x…–„x'i •’•„’
- a change in the method of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.

Mobile healthcare:

Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing specified per the written guidance. However, central laboratory testing must be retained for PK, biomarker, and immunogenicity sampling. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies, including participant diaries

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

asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit

asking the participant ''designee to go to the site and receive study supplies on a “t ‘„•v•“t –„ ’'ux~t µy

arranging delivery of study supplies, and

working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location, such as an infusion center.

These requirements must be met before action is taken:

> Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including ○x‘•y•vt „•—'–y‘“t ‘„•v•“t –„ ’'‘xvx•“„'–y‘’„×wκ'’×““‘µ•x’7
> When delivering supplies to a location other than the study site (for example, pa‘„•v•“t –„ ’'~—. x), the investigator or sponsor, or both, should ensure oversight of the shipping process to ensure accountability and product quality, that is, storage conditions maintained and intact packaging upon receipt.
> Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirement must be met:

> Only authorized study personnel may supply, prepare, or administer study intervention.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the •–○x’„•zt „—‘’ source documentation and should be transferred to the site in a secure and timely manner.

10.11. Appendix 11: Abbreviations and Definitions

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AIPW	augmented inverse propensity weighted [estimator]
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HCV	antibodies to HCV
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an auxiliary medicinal product
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
BCG	Bacillus Calmette-Guerin
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received

Term	Definition
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CK	creatine kinase
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of this role may be performed by a physician, clinical research scientist, global safety physician, or other medical officer
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system
compliance	adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed (or computerized) tomography
CTA	Clinical Trial Agreement
CTR	Clinical Trial Regulation
data monitoring committee	A data monitoring committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study
DNA	deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders. 5th ed.
ECG	electrocardiogram
ED	early discontinuation visit
EDC	electronic data capture

Term	Definition
EDSS	Expanded Disability Status Scale
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives
ERB	Ethics (or ethical) review board. An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human participants involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial participants.
EU	European Union
FS	functional system
FSH	follicle-stimulating hormone
CCI	[redacted]
GCP	good clinical practice
GdE	gadolinium-enhancing
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IAC	internal assessment committee
IB	Investigator's Brochure
ICEs	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee; see "ERB"

Term	Definition
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon gamma release assay
IMP	•–○x’„•zt „•—t µ‥xw•v•–t µ“‘–w×v,¦l’xx't µ̨—' •–○x’„•zt „•—t µ“‘–w×v,, 2 A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial
Informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the part•v•“t –,, ’'wxv•’ •—',,—'“t ‘,•v•“t ,x7U-y—‘‥xwv—’x–,,'•''w–v×‥x–,,xẇuκ' means of a written, signed, and dated informed consent form
INFSR	infusion-site reaction
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 zt •–'y×‘,,~x‘'•–y—‘‥t „•—'t u–×,,¦,,~x't ×,,~—‘•-xẇy—‘‥7f xx't µ̨—' Ψ c
IRB	•–’,,•,,×,,•—t µ‘x○•x● 'u–t-‘wG xx' Qe N
IRR	infusion-related reaction
IV	intravenous, or intravenously
IWRS	interactive web-response system
LLN	lower limit of normal
LTBI	latent tuberculosis infection
mAb	monoclonal antibody
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities

Term	Definition
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, these may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling, for example, Summary of Product Characteristics, IB, local label, protocol, or • shared use of cartridges or prefilled pens, or both
misuse	use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MS	multiple sclerosis
NB	negative binomial
CCI	[redacted]
NIMP	Non-investigational Medicinal Product See "AxMP." A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment
NOAEL	no-observed-adverse-effect level
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PCR	polymerase chain reaction
PD	pharmacodynamics
CCI	[redacted]

Term	Definition
CCI	[redacted]
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
CCI	[redacted]
PT-INR	prothrombin time, international normalized ratio
CCI	[redacted]
CCI	[redacted]
QTc	corrected QT interval
QTL	quality tolerance limit
RMS	relapsing multiple sclerosis
RNA	ribonucleic acid
CCI	[redacted]
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous, or subcutaneously
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
SIB	suicidal ideation and behavior
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
T1 lesion	hypointense lesion (black hole), where the brain tissue is gone and cerebrospinal fluid remains
T1 contrast-enhancing lesion	lesion identified by means of the contrast leaving the blood vessels and entering the brain tissue due to a breach of the blood-brain barrier. It appears as a ring-enhancing lesion and is a new, active lesion suggestive of acute relapse

Term	Definition
T2 lesion	hyperintense lesions (white in comparison to gray matter), indicating areas of scarring (demyelination); tissue remains but the covering of the associated nerves are removed. These are old lesions (chronic)
TB	tuberculosis
TBL	total bilirubin
TE ADA	treatment-emergent anti-drug antibody
TEAE	treatment-emergent adverse event
TST	tuberculin skin test
ULN	upper limit of normal
USA	United States of America
WHO	World Health Organization
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

10.12. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [c]: (13-Dec-2024)

This amendment is considered to be non substantial.

Overall rationale for the amendment

The purpose of this amendment is to address the removal of human polyomavirus (JC virus) testing from the protocol and the update to pregnancy collection stop criteria.

The table below outlines a high-level description of changes, with a brief rationale.

Section # and Name	Description of Change	Brief Rationale
Global change, multiple sections impacted	Human polyomavirus (JC virus) testing was removed throughout the protocol.	Human polyomavirus (JC virus) is very common. Between 50% and 90% of the world's adult population would test positive for it.[1] A positive test is not an exclusion for the recruitment in the study. In addition, testing for JC virus is not part of standard of care in many territories or countries. In many of those countries the test is not available, hindering our ability to recruit patients. [1]Paz SPC, Branco L, Pereira MA de C, Spessotto C, Fragoso YD. Systematic review of the published data on the worldwide prevalence of John Cunningham virus in patients with multiple sclerosis and neuromyelitis optica. *Epidemiol Health*. 2018;40:e2018001. https://doi.org/10.4178/epih.e2018001
Section 8.3.1. Timing and Mechanism for Collecting Events	Pregnancy collection stop was changed from 120 to 230 days.	Correction

Amendment [b]: (07-Nov-2023)

This amendment is not assessed for substantiality, as it occurred prior to submission of the initial CTA in the EU.

Overall Rationale for the Amendment:

The main rationale for the amendment is to CCI [redacted] on contraception requirement window and criteria for pausing study enrollment and prompting Internal Assessment Committee review.

Minor editorial and formatting changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Objectives, Endpoints, and Estimands subsection: Revised the MRI-related measure timepoints for primary and secondary endpoints Updated the secondary endpoint for PK to read: Plasma trough concentrations of LY3541860 ~~at 24 weeks~~	CCI [redacted] to avoid redundancy
	Secondary endpoint: Changed the type of PK samples from serum to plasma	Correction
	Intervention Groups and Duration: changed the total duration of the study from "54 to 57 weeks" to "62 to 65 weeks"	
	Updated the language for primary estimand	CCI [redacted] to avoid redundancy
3. Objectives, Endpoints, and Estimands	Revised the MRI-related measure timepoints for primary, secondary, and exploratory objective Updated the secondary endpoint for PK to read: Plasma trough concentrations of LY3541860 ~~at 24 weeks~~	CCI [redacted] to avoid redundancy
	Secondary endpoint: Changed the type of PK samples from serum to plasma	Correction
	Revised the MRI-related measure timepoints and updated language for the primary and secondary estimand	CCI [redacted] to avoid redundancy
4.2. Scientific Rationale for Study Design	Duration of treatment period subsection: Revised the MRI-related measure timepoints for the primary endpoint	CCI [redacted] to avoid redundancy
5.1. Inclusion Criteria	Type of participant and disease characteristics subsection: Deleted "MRI" from criterion 3	
7.1. Discontinuation of Study Intervention	Updated the criterion for participants permanently discontinuing from study intervention related to severe or serious hypersensitivity reaction by	

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Section # and Name	Description of Change	Brief Rationale
	deleting "related to study intervention administration"	
9.1. Statistical Hypotheses	Phase 2a, Phase 2b: Revised the MRI-related measure timepoints of null hypothesis for primary objective	CCI [redacted]
9.3.1. General Considerations	Updated definition for baseline value	
9.3.2. Primary Endpoint/Estimand Analysis	Definition of primary endpoints subsection: Phase 2a, Phase 2b: Revised the MRI-related measure timepoints for primary objective Analysis of primary estimands subsection: Deleted the generalized estimating equation approach in Phase 2b analysis. Revised the missing data imputation to align with the updated primary objectives.	
9.3.3. Secondary Estimands Analysis	Deleted statement on approach and method used for primary estimand analysis	
9.4. Interim Analysis	Phase 2a: Updated the criterion for performing the first, second, and third interim analyses Phase 2b: Updated the criterion for performing the first and second interim analyses	Clarification
9.5. Sample Size Determination	Phase 2a: Updated language for sample size calculation Phase 2b: Updated the power calculation in Phase 2b	CCI [redacted]
10.1.5. Committees Structure	"Internal Assessment Committee" subsection: Updated paragraph 3 to read: "regardless of the relatedness to the study intervention ~~if judged as related to blinded study intervention by the investigator~~"	CCI [redacted]
10.1.9. Study and Site Start, Pausing, and Closure	"Pausing of enrollment to the study" subsection:	

Section # and Name	Description of Change	Brief Rationale
	Replaced language of adverse events that require pausing study enrollment from "attributed to study intervention" to "regardless of the relatedness to the study intervention"	
10.4.2. Contraception Guidance	Revised the condition for using the contraception methods to read "for 230 days after the last dose of the study intervention ~~until the completion of all the follow-up procedures~~"	CCI [redacted]
10.12. Protocol Amendment History	Added new section: Inserted date, rationale, summary of changes from Amendment (a)	To update document history

Amendment [a]: (25-Aug-2023)

This amendment is not assessed for substantiality, as it occurred prior to submission of the initial CTA in the EU.

Overall Rationale for the Amendment:

The main rationale for the amendment is to address regulatory feedback.

Minor editorial or formatting changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
Global change; multiple sections impacted	After "Human polyomavirus", added "(JC virus)"	Clarity
1.1. Synopsis	CCI [redacted]	For consistency with the relevant SoA revision
	Brief Summary: changed the total duration of the study from "54 to 57 weeks" to "62 to 65 weeks"	Per revised duration of the follow-up period
	Study Population: updated the first and last bullets in	For consistency with revised Exclusion Criteria 7 and 12

Section # and Name	Description of Change	Brief Rationale
	the second bulleted list and the table	
1.1. Synopsis and 3. Objectives, Endpoints, and Estimands	• Revised	
	○ Primary endpoints	CCI [redacted], for clarity and to use a baseline (Visit 1) scan as the reference scan to determine whether a lesion is new instead of using the scan from the previous visit 4 weeks earlier
	○ Secondary efficacy endpoints	CCI [redacted], to avoid redundancy
	○ Secondary endpoint for PK: added "at 24 weeks"	Clarity
	○ Definition of primary estimand	For consistency with the revised primary endpoints and for clarity
1.1. Synopsis, 1.2. Schema, 1.3. Schedule of Activities (SoA), 4.1.3. Follow-Up, and 4.2, Scientific Rationale for Study Design	Changed the duration of the follow-up from 8 and 16 weeks to 12 and 24 weeks	Per updated half-life for LY3541860
1.2. Schema	CCI [redacted]	Clarification and consistency with the relevant SoA revisions
1.3.1. Schedule of Activities for Phase 2a of Study J3K-MC-KIAB and 1.3.2. Schedule of Activities for Phase 2b of Study J3K-MC-KIAB	CCI [redacted]	For consistency with the relevant SoA revisions

Section # and Name	Description of Change	Brief Rationale
	Vital signs: updated the Notes.	Logical flow
	"Physical examination" row: updated the Notes to • state that the physical examination needs to be performed prior to administration of study intervention at Visits 2-10 instead of only at Visit 2	To address any concerns about emergent infections
	• clarify the guidance for assessment of signs and symptoms of TB	Clarity and logical flow
	"ECG" row: • added X's for Weeks 0 and 4	CCI
	"MRI of brain" row: added "Visit 1 MRIs need to be obtained at least 10 days before Visit 2."	Clarity
	"Lipids" row: revised the Note to read "~~Not a protocol deviation if not fasting.~~ Fasting not required."	Simplification and reduction of participant burden
	"Hepatitis B virus (HBV) screening tests" row: revised the Note to read "~~Include testing for HBsAg and anti-HBc.~~ See Section 8.2.7."	For consistency with revisions in the HCV row
	"Hepatitis C virus (HCV) screening tests" row: revised the Note to read "~~If HCV antibody test is positive, it must be followed by a NDV RNA test.~~ See Section 8.2.8."	Simplification; consistency with revisions in Section 8.2.8
	CCI	

Section # and Name	Description of Change	Brief Rationale
	CCI	To ensure the effect of the study intervention has been removed
	"Pharmacokinetics (PK) samples" row: Added an X for Visit 2, with a note stating to "Collect post dose after the completion of the infusion."	Added post-dose PK sample to measure approximate maximal exposure at the end of the infusion
	"Observe after administering study intervention" row: added X's for Weeks 8-32	CCI to address an omission
2.3.1. Risk Assessment	Second paragraph: updated to include IRRs and references for additional participant management	For consistency with the revised Section 8.3.5.1
3. Objectives, Endpoints, and Estimands	• Primary and secondary endpoints: for the description of change and brief rationale, see the "1.1. Synopsis and 3. Objectives, Endpoints, and Estimands" row at the beginning of this table.	
	CCI	Clarification

Section # and Name	Description of Change	Brief Rationale

	Primary estimand:
	• updated the definition
	• added a description for treatment, and
	• updated the descriptions of the
	  ○ endpoint
	  ○ accounting for ICEs
	  ○ population-level summary, and
	  ○ rationale for estimand
		Per revisions to the primary endpoints and for clarity and completeness

	Secondary estimand: added	For completeness
4.1.3. Follow-Up	[redacted]	Clarification
	Last sentence: added "The follow-up period will take longer than 24 weeks [redacted]	Per the relevant SoA revision
4.2. Scientific Rationale for Study Design	"Duration of follow-up period": • Changed the half-life for LY3541860 from approximately [redacted] days to approximately [redacted] days	Per current data
	• Last sentence: added "The follow-up period will take longer than 24 weeks [redacted]	For consistency with the relevant SoA revision

Section # and Name	Description of Change	Brief Rationale
4.3. Justification for Dose	Revised as follows: • First bullet: replaced ○ CCI mg to CCI mg CCI" with "CCI mg to CCI mg CCI"	Per current data
	○ "to be well tolerated" with "to have no SAEs attributed to study intervention"	Clarity
	• Second bullet:	
	○ CCI	Clarity
	○ replaced "CCI mg CCI" with "CCI mg CCI"	Per current data
	○ last sentence: added "(~100%) in blood"	
	• Third bullet: ○ second sentence: revised to read "It is ~~hypothesized~~possible that the CCI mg and CCI mg CCI doses may differentiate in terms of magnitude or duration of target engagement in tissue and hence may then differentiate in terms of efficacy." ○ added a note: "The relationship between target engagement (CD19 inhibition) and efficacy is currently not known."	Per current data and for clarity

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	• 2: ○ added "including relapsing-remitting multiple sclerosis or active secondary progressive multiple sclerosis", and ○ updated the reference	CCI [redacted]
	• 5b: updated the male contraception criteria	For consistency with changes in Appendix 4, Section 10.4
5.2. Exclusion Criteria	Updated the following exclusion criteria:	CCI [redacted]
	• 7: second bullet: revised to read "nonactive secondary progressive MS ~~with or without relapse activity~~ (~~Lublin et al. 2014~~ Klineova and Lublin 2018)"	
	• 8: updated to read "Meet criteria for neuromyelitis optica spectrum disorder"	Clarification
	• 12: revised to ○ address any notable omissions of prior/concomitant therapies ○ clarify potentially subjective descriptors of such therapies, and ○ update the washout periods per current labeling.	CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
	• 18: deleted "unless such treatment is underway".	
	• 19: revised to indicate that participants with positive HCV antibody should be excluded.	
	• 23: revised to read "hepatic (including Gilbert's syndrome)"	
	• 24: revised to o read "Have any other clinically important abnormality at screening or baseline" o exclude participants with certain levels of AST and ALT, TBL, amylase or lipase, IgG or IgM, as well as participants with a certain QTc interval	
	• 26: revised to exclude participants with any history of malignancy, except for basal cell and in situ squamous cell carcinomas of the skin that have been definitively treated.	
6.1. Study Intervention(s) and Concomitant Therapy	Added information on preparing study interventions for dosing	Clarity
	Added information on monitoring of participants after dosing	CCI [redacted]

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Section # and Name	Description of Change	Brief Rationale
7.1. Discontinuation of Study Intervention	• Second bullet: revised to read "If the investigator determines that a severe or serious systemic hypersensitivity reaction, including IRR, …"	Clarity
	• Sixth bullet: revised to read "The participant develops active TB or ~~has untreated~~ a new diagnosis of latent LTBI."	CCI [redacted]
7.1. Discontinuation of Study Intervention and 7.1.2. Temporary Discontinuation of Study Intervention	Added discontinuation criteria related to the hematology and SAEs.	To correct an omission and for consistency with revisions in Section 10.1.9
7.1.1.1. Interrupting Study Drug Based on Elevated Liver Tests, 10.6.2. Close Hepatic Monitoring, 10.6.3. Comprehensive Hepatic Evaluation, and 10.6.4. Additional Hepatic Data Collection (Hepatic Safety CRF) in Study Participants Who Have Abnormal Liver Tests during the Study	Deleted the exceptions for participants with Gilbert's syndrome	No longer applicable: participants with Gilbert's syndrome are now excluded from the study
7.1.2. Temporary Discontinuation of Study Intervention	• Renamed the section heading from "Infection-Related Criteria for Temporary Withholding" to "Temporary Discontinuation of Study Intervention". • Added subheadings for infection-related and other temporary discontinuation criteria.	For clarity and consistency with revisions in this section and Section 7.1
	• First bullet: o at the end of the sentence, added "after which, the participant may continue the study at the discretion of the investigator"	Clarification
	• deleted "(exception for LTBI, noted below)".	Per deletion of the LTBI criterion in this section

Section # and Name	Description of Change	Brief Rationale
	• Deleted the discontinuation criterion related to LTBI	For consistency with revisions in Section 7.1, CCI [redacted]
8.1.3. Exploratory Efficacy Assessments, and 8.3.3. MS Relapse	• Moved the definition of MS relapse from Section 8.3.3 to Section 8.1.3. • Added a reference to Section 8.1.3 in Section 8.3.3.	CCI [redacted] and clarity
8.2.5. Tuberculosis Testing and Monitoring	"Diagnosed LTBI": revised to say "Participants diagnosed with LTBI are excluded (Section 5.2) unless they have completed appropriate LTBI therapy."	For consistency with revised exclusion criterion 18, as well as Sections 7.1 and 7.1.2
8.2.8. Hepatitis C Testing	Updated to indicate that the participant will be excluded from the study if either anti-HCV antibody or HCV RNA are positive.	CCI [redacted] for consistency with revisions to exclusion criterion #19
8.3.5.1. Hypersensitivity Reactions, Including Infusion-Related Reactions	• First sentence: added "including IRRs"	Clarity and consistency with the section heading
	• Throughout the section: clarified and added information for managing hypersensitivity reactions and IRRs	CCI [redacted]
8.3.5.3, Infusion Site Reactions	Second paragraph: revised as follows: • ISR → INFSR • "injection site pain" → "infusion site pain" • "degree and area of erythema, …" → "severity and area of erythema, …"	Clarity, accuracy, and consistency with the CRF name
8.4. Pharmacokinetics and 9.3.5. Pharmacokinetic/Pharmacodynamics Analysis	Changed the type of PK samples from serum to plasma.	Correction
8.7. Biomarkers	Changed "Serum and plasma" samples" to "Blood samples"	Correction

Section # and Name	Description of Change	Brief Rationale
8.8. Immunogenicity Assessments	Replaced "serum concentration" with "plasma concentration"	Correction
9.1. Statistical Hypotheses	Replaced "primary endpoint" with "primary objective"	Correction
9.3.2. Primary Endpoint/Estimand Analysis	CCI	For consistency with the revised primary objective
		For consistency of the estimator with the estimand
		CCI
9.3.3. Secondary Estimands Analysis		For clarity and consistency with the revised method for the primary estimand imputation
10.1.5. Committees Structure	• Updated the description of the IAC, and • Added the description of the internal safety review team.	CCI
10.1.9. Study and Site Start, Pausing, and Closure	• Added the study pausing criteria • Updated the section heading to include "Pausing"	CCI

Section # and Name	Description of Change	Brief Rationale
10.1.12. Sample Retention	CCI [redacted]	For flexibility
10.2. Clinical Laboratory Tests	• Clinical Chemistry panel: added lipase	CCI [redacted]
	• TB, HIV, and Hepatitis Serology: updated the comments for T-SPOT®.TB and TST to indicate that T-SPOT®.TB may be done locally and TST will be done locally	Corrections
	CCI [redacted]	
10.4.2. Contraception Guidance	Updated the definitions and contraception guidance for female participants	Per revised Lilly guidance and per study design
	Added contraception criteria for male participants	CCI [redacted]

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