Protocol J2X-MC-PYAG (b)

A Randomized, Placebo-Controlled, Participant- and Investigator-Blind, Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of LY3819253 Administered Subcutaneously to Healthy Participants

NCT04537910

Approval Date: 14-Oct-2020

Title Page

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Protocol Number: J2X-MC-PYAG

Amendment Number: b

Compound: LY3819253

Study Phase: 1

Short Title: A Randomized, Placebo-Controlled, Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of LY3819253 Administered Subcutaneously to Healthy Participants

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number:

IND: 150440

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

Approval Date: 14-Oct-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	17-Aug-2020
Protocol amendment (a)	02-Sep-2020

Amendment (b)

Overall Rationale for the Amendment:

This protocol is being amended to remove the requirement that the optional Cohort 3 must enroll at least 9 participants.

Section # and Name	Description of Change	Brief Rationale
• Section 1.1, Synopsis • Section 4.1.1, Screening and Enrollment • Section 9.2, Sample Size Determination	Specified that only Cohorts 1 and 2 have an intended minimum number of participants with evaluable data.	Optional Cohort 3 does not feature a safety review for purposes of moving to a subsequent cohort, and therefore does not have the same requirement for minimum participant numbers.
• Section 1.2 Schema	Added a note to the schema to clarify that the LY:PBO ratio for Cohort 3 is an intention only.	As above.
• Section 6.1.1, Injection volumes and formulation concentrations	Added a note to clarify that the number and volume of injections will be adjusted if any dose levels are modified.	Mistakenly omitted from earlier versions of the protocol.
• Section 10.3.3, Recording and Follow-Up of AE and/or SAE	Removed reference to the Division of AIDS (DAIDS) table for grading AEs and SAEs.	The DAIDS table will not be used for this study.
• Section 11, References	Removed DAIDS reference.	As above.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Placebo-Controlled, Participant- and Investigator-Blind, Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of LY3819253 Administered Subcutaneously to Healthy Participants

Short Title: A Randomized, Placebo-Controlled, Phase 1 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of LY3819253 Administered Subcutaneously to Healthy Participants

Rationale: The clinical program for LY3819253 so far has involved IV dosing of LY3819253.

Study PYAG will investigate SC dosing of LY3819253. Single SC doses of LY3819253, 350 mg and 700 mg, will be administered to establish the PK, safety, and tolerability profiles in healthy participants.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the PK of single SC doses of LY3819253 in healthy participants	AUC(0-∞)
Secondary	
To describe safety and tolerability following single SC doses of LY3819253 in healthy participants	Incidence of spontaneously reported AEs, TEAEs, and SAEs; vital signs; clinical laboratory results
Exploratory	
To assess ISRs following single SC doses of LY3819253 in healthy participants	Characterization and measurement of incidence and severity of ISRs, including injection site pain, using data collected from the ISR assessment, and the exploratory tool (Scarletred)
To determine the immunogenicity of LY3819253 following single SC doses in healthy participants	Incidence of TEADA

Abbreviations: AE = adverse event; AUC(0-∞) = area under the concentration versus time curve from time 0 to infinity; ISR = injection site reaction; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TEADA = treatment-emergent antidrug antibodies; TEAE = treatment-emergent adverse event.

Overall Design

This is a single-site study in healthy participants who will receive a single SC dose of LY3819253. The study will be participant- and investigator-blinded, randomized, and placebo controlled.

Disclosure Statement: This is a PK and safety study to test LY3819253 and placebo in up to 3 dose cohorts.

Number of Participants:

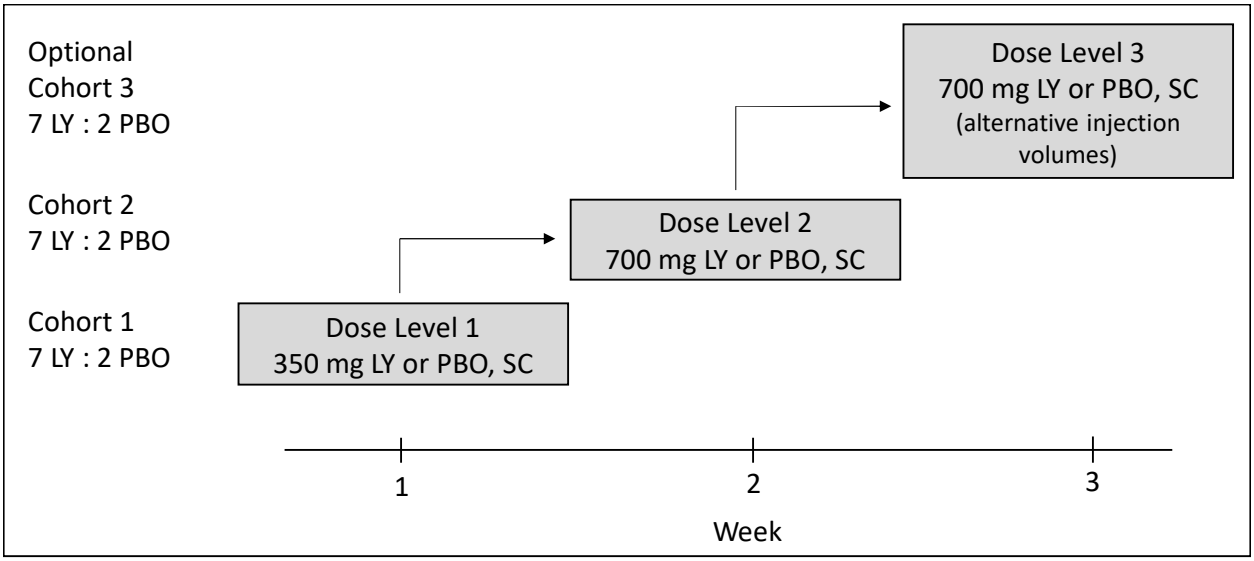
A maximum of 36 participants will be enrolled to study intervention, with the intention that at least 6 participants randomized to LY3819253 have sufficient evaluable data in each of Cohorts 1 and 2.

Intervention Groups and Duration:

This is a single-dose study with an estimated duration for each participant of up to 16 weeks from screening through follow-up.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: LY = LY3819253; PBO = placebo; SC = subcutaneous.

Note: The LY:PBO ratio for the optional Cohort 3 is an intention and may change subject to enrollment numbers. The planned dose for Cohort 3 may change based on data review during the study.

1.3. Schedule of Activities (SoA)

Procedure / Assessments	Screening	Treatment Period								Follow-up Visits				Comment
Visit Number	**V1**	**V2**								**V3**	**V4**	**V5**	**V6/ ED**	
Week(s)		**0**								**2**	**4**	**8**	**12**	
Study Day	**-14 to –1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15** ±2d	**29** ±3d	**60** ±3d	**85** ±3d	
Informed consent (written)	X													
Review/ confirm I/E criteria	X	X												After screening, ensure participants continue to meet I/E criteria.
Medical history including pre-existing conditions	X													
Weight/height	X												X	Height at screening only.
Urinalysis	X								X					
COVID-19 clinical screening	X	X								X	X	X	X	Symptoms and recent contact (see Section 5.2 for a description of symptoms and close contact). At designated timepoints and as needed during the study.
SARS-CoV-2 serology		X								X	X	X	X	Serology results are not needed before dosing.

Procedure / Assessments	**Screening**	**Treatment Period**								**Follow-up Visits**				**Comment**
Visit Number	**V1**	**V2**								**V3**	**V4**	**V5**	**V6/ ED**	
Week(s)		**0**								**2**	**4**	**8**	**12**	
Study Day	**-14 to –1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15** ±2d	**29** ±3d	**60** ±3d	**85** ±3d	
SARS-CoV-2 point-of-care test	X	X												Additional point-of-care tests may be conducted at the investigator's discretion. See Section 8.3.7.
Naso-pharyngeal swab			X											Can be before or after LY3819253 administration. For research purposes. See Section 8.3.7.
Nasal swab				X										For research purposes. This swab may be taken if a point-of-care test is done during the study, as described in Section 8.3.7.
Admission to study site		X												
Discharge from study site									X					
Physical examination Medical assessment	X	X	Predose			X			X	As needed			X	Full PE/MA at screening and Visit 6/ED. Symptom-directed PE/MA at all other indicated time points and as deemed necessary by the investigator or designee.

Procedure / Assessments	**Screening**	**Treatment Period**								**Follow-up Visits**				**Comment**
Visit Number	**V1**	**V2**								**V3**	**V4**	**V5**	**V6/ ED**	
Week(s)		**0**								**2**	**4**	**8**	**12**	
Study Day	**-14 to –1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15** ±2d	**29** ±3d	**60** ±3d	**85** ±3d	
Vital signs: blood pressure, body temperature, pulse rate[a]	X	X	Predose	24 h (±2 h)		X			X	X	X	X	X	Vital signs should be taken following at least 5-min rest in a supine position. Vital signs may be taken any time prior to dosing. If screening takes place on Day -1, there is no need to take vital signs twice on Day -1.
Single 12-lead ECG	X													
Concomitant medications review	X	X								X	X	X	X	
AE review	X	X	Predose	X	X	X	X	X	X	X	X	X	X	AEs to be reviewed only after participant has signed the study ICF.
HIV, hepatitis B/C serology	X													

Procedure / Assessments	**Screening**	**Treatment Period**								**Follow-up Visits**				**Comment**
Visit Number	**V1**	**V2**								**V3**	**V4**	**V5**	**V6/ ED**	
Week(s)		**0**								**2**	**4**	**8**	**12**	
Study Day	**-14 to –1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15** ±2d	**29** ±3d	**60** ±3d	**85** ±3d	
Pregnancy test (women only)[b]	X	X											X	Serum pregnancy test at screening, urine test at other timepoints. Day -1 urine test refers to test at admission; this is not needed if admissions is on the same day as screening. Postdose urine test(s) can be performed at the judgment of the investigator, if pregnancy is suspected.
Clinical laboratory tests[a]	X	X							X	X	X	X	X	Fasting is not required for these tests. If screening takes place on Day -1, there is no need to conduct these tests twice on Day -1.
Breath or urine ethanol screen		X												Ethanol screen may be repeated at other time points at the discretion of the investigator.
Urine drug screen	X	X												Day -1 urine test refers to test at admission; this is not needed if admission occurs on the same day as screening. Drug screen may be repeated at other time points at the discretion of the investigator.

Procedure / Assessments	**Screening**	**Treatment Period**								**Follow-up Visits**				**Comment**
Visit Number	**V1**	**V2**								**V3**	**V4**	**V5**	**V6/ ED**	
Week(s)		**0**								**2**	**4**	**8**	**12**	
Study Day	**-14 to –1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15** ±2d	**29** ±3d	**60** ±3d	**85** ±3d	
SC LY3819253 or placebo dosing			X											
LY3819253 PK sampling[a]			X	X	X	X	X	X	X	X	X	X	X	Day 1 collection should be taken up to 4h postdose ±4h. The exact time of draw must be recorded. For Day 2 onwards, PK samples may be taken at any time after vital signs.
Injection site assessments			Predose; 1min ±1min, 10min ±2min, 30min ±5min, 240min ± 10min	24h ±4h	X	X	X	X	X	X	X	X	X	Timepoints include ISR assessment, VAS, if pain is reported, and the exploratory Scarletred tool. Scarletred timing is flexible and not confined to the windows shown, except for predose. See Section 8.2.5 for detail.
Immunogen-icity			Predose							X	X	X	X	
Serum sample for exploratory biomarkers[a]			Predose		X					X	X	X	X	
Pharmaco-genetics sample[a]			Predose											For storage only.

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease-2019; ECG = electrocardiogram; ED = early discontinuation; h = hours; HIV = human immunodeficiency viruses; I/E = inclusion/exclusion; ICF = informed consent form; MA = medical assessment; ISR = injection site reaction; min = minutes; PE = physical examination; PK = pharmacokinetics; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous; V = visit; VAS = visual analog scale.

[a] When conducted on the same day, the order of procedures should be vital signs, ECG, and then blood sampling.

[b] For women who are considered to be postmenopausal, follicle-stimulating hormone should be drawn to confirm postmenopausal status if necessary, according to Appendix 4 (Section 10.4).

2. Introduction

2.1. Study Rationale

The clinical program for LY3819253 so far has involved IV dosing of LY3819253.

Study PYAG, will investigate SC dosing of LY3819253. Single SC doses of LY3819253, 350 mg and 700 mg, will be administered to establish the PK, safety, and tolerability profiles in healthy participants.

2.2. Background

The efficient community spread of SARS-CoV-2 has resulted in the current pandemic of COVID-19. There are no approved therapies to date for the treatment of COVID-19; Remdesivir is available under an emergency use authorization in the US (Gilead Sciences 2020).

SARS-CoV-2 gains entry to cells through binding of the spike protein to angiotensin-converting enzyme 2 receptors on cells (Hoffmann et al. 2020). LY3819253 is a neutralizing immunoglobulin G1 mAb to the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, and to neutralize the virus.

2.2.1. Summary Information from LY3819253 Program to Date

Additional information can be found in the IB.

2.2.1.1. Safety

The following blinded summaries of safety are as of 24 July 2020.

LY3819253 has been administered to humans in 2 clinical studies, Study PYAA and Study PYAB.

No SAEs or deaths have been recorded to date in either study.

Study PYAA

The first 3 cohorts of Study PYAA each consisted of 8 hospitalized participants with moderate or severe COVID-19 who were randomized to receive either a single IV dose of LY3819253 or placebo at a ratio of 6:2. The dose range was 700 mg to 7000 mg.

Sixteen out of 24 participants dosed with LY3819253 (across all doses) or placebo experienced at least 1 TEAE. Most TEAEs reported were mild to moderate severity. There have been no dose-limiting safety issues identified.

No AEs of infusion-related reaction have been reported.

Study PYAB

Enrollment is open for 700-mg (or placebo), 2800-mg, and 7000-mg cohorts. The treatment-group assignment for each participant remains blinded since the study is ongoing.

Eighty-eight participants have been administered LY3819253 or placebo. There have been 4 infusion reactions reported to date. Based on conversations with the site, these occurred within

approximately 30 minutes after the infusion was started, and were considered related to study treatment.

2.2.1.2. Pharmacokinetics

Preliminary data in a limited number of subjects suggest the PK profile of LY3819253 is consistent with the PK model-predicted profile and dose proportional following a single IV dose of 700 mg up to 7000 mg. Pharmacokinetic model-estimated IV clearance and half-life approximately 0.3 L/day and 2 to 4 weeks, respectively.

2.3. Benefit/Risk Assessment

Anticipated risk is considered low and is based on the known mechanism of action for human derived neutralizing antibodies in acute viral disease states. LY3819253 consists of a highly specific mAb directed at foreign (non-human) epitope(s). The complementarity determining regions of the mAb were derived from B lymphocytes of a convalescent SARS-CoV-2-infected patient; and, thus, have undergone natural positive and negative selection pressures in vivo, unlike humanized antibodies generated in mice. Therefore, off-target binding and tissue cross-reactivity are considered unlikely.

Nonclinical safety studies conducted to date using the IV route of administration have not demonstrated safety concerns. Toxicity studies supporting LY3819253 clinical trials consist of a tissue cross reactivity study, a 21-day rat toxicity study (IV administration), and an evaluation of ADE in vitro and in African green monkeys. Tissue cross-reactivity data did not suggest off-target binding of clinical relevance and supports use of the rat as the nonclinical safety model. The treatment phase of the 21-day repeat-dose toxicity study in rats, including histopathology evaluation, is complete and did not demonstrate adverse findings. Lastly, no evidence for ADE was observed in vitro or in nonhuman primates.

The maximum planned dose of LY3819253 in this study is 700 mg SC. This is lower than the maximum dose delivered IV in previous studies.

A theoretical risk is that LY3819253 may cause ADE of viral replication. This is based on responses observed to some mAb therapies used in other unrelated viral diseases. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronavirus infections, and has not been reported to date with SARS-CoV-2. Additionally, limited experience with the use of convalescent serum as a treatment for patients with severe COVID-19 disease has not indicated safety concerns (Duan et al. 2020; Shen et al. 2020).

Additional manageable risks associated with most therapeutic monoclonal antibodies are the potential for hypersensitivity and cytokine release reactions. In addition, there is a potential for ISRs. Study participants will be in-house for the first 7 days after dosing, which will enable close monitoring for hypersensitivity reactions and ISRs post-injection.

Given the totality of data on LY3819253 and the well-established safety profile of other therapeutic monoclonal antibodies, the overall benefit/risk assessment of this study is considered favorable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3819253 may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the PK of single SC doses of LY3819253 in healthy participants	AUC(0-∞)
Secondary	
To describe safety and tolerability following single SC doses of LY3819253 in healthy participants	Incidence of spontaneously reported AEs, TEAEs, and SAEs; vital signs; clinical laboratory results
Exploratory	
To assess ISRs following single SC doses of LY3819253 in healthy participants	Characterization and measurement of incidence and severity of ISRs (including injection site pain) using data collected from the ISR assessment, as well as the exploratory tool (Scarletred).
To determine the immunogenicity of LY3819253 following single SC doses in healthy participants.	Incidence of TEADA.

Abbreviations: AE = adverse event; AUC(0-∞) = area under the concentration versus time curve from time 0 to infinity; ISR = injection site reaction; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TEADA = treatment-emergent antidrug antibodies; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

This is a single-site study in healthy participants who will receive a single SC dose of LY3819253. The study will be participant- and investigator-blinded, randomized, and placebo controlled.

4.1.1. Screening and enrollment

Up to 3 cohorts may be enrolled. In Cohorts 1 and 2, there will be at least 9 participants per cohort (7 LY3819253:2 placebo), with the intention that at least 6 participants randomized to LY3819253 have sufficient evaluable data in each cohort.

For the optional Cohort 3, up to 9 participants will be enrolled and the cohort may be closed when at least 5 participants have been randomized to LY3819253. The number of participants and the ratio of LY3819253 to placebo may change based on enrollment numbers. However, the number assigned to LY3819253 will not exceed 7, and the number assigned to placebo will not exceed 2.

Participants will be screened within 14 days prior to Day 1 of dosing for each cohort. Participants will be admitted to the CRU as part of an inpatient visit on Day -1 and will be sequentially enrolled and then randomized to treatment.

4.1.2. Inpatient stay

Participants will be admitted to the study site on Day -1. They will remain inpatient until discharge on Day 7 after study procedures are complete.

Dosing

Dosing will occur on Day 1. Intended doses of LY3819253 are as follows:

- Cohort 1: 350 mg
- Cohort 2: 700 mg
- Cohort 3 (optional): 700 mg (alternative injection volumes)

See Section 6.1 for detail of injection volumes.

Participants will undergo PK sampling and safety assessment after dosing.

For Cohorts 1 and 2, a safety review will be conducted to determine whether it is appropriate to proceed with dosing of the next cohort. This safety review will be conducted based on data from at least 4 participants, after at least 4 days after dosing.

Sentinel dosing

Cohort 1 will include sentinel dosing. The first 2 participants will be randomized and dosed (1 LY3819253:1 placebo).

The investigator and the Lilly sponsor team are responsible for determining if safety and tolerability is acceptable to continue with dosing subsequent participants.

Tolerability as measured by ISRs and their severity is anticipated to be the main safety consideration for this assessment. While no serious systemic reactions have been seen with LY3819253 to date, participants will be closely monitored.

If the investigator and Lilly sponsor team determine that safety and tolerability is acceptable, the remaining participants in the cohort will be dosed on the next day.

Cohort 2 and the optional Cohort 3 will not include sentinel dosing.

Postdose sampling

On Days 1 through 7, participants will undergo PK sampling and safety assessment as shown in the SoA (Section 1.3).

4.1.3. Outpatient follow-up

Follow-up visits will be conducted through Day 85, as shown in the SoA (Section 1.3).

In the event a participant has suspected or confirmed SARS-CoV-2 infection, follow-up visits may be conducted at the participant's home.

4.2. Scientific Rationale for Study Design

This is the first study to evaluate a new formulation via SC route of administration in humans. This study will be conducted with healthy participants, rather than patients with COVID-19, because the important biopharmaceutic questions related to the new SC route of administration, such as PK and tolerability, will be more efficiently investigated in the healthy human population.

The 4-day safety review together with in-patient status after dosing is sufficient to detect an acute adverse systemic response that would preclude dose escalation.

Placebo will be used as a comparator to allow interpretation of safety and tolerability data following administration of LY3819253.

4.3. Justification for Dose

Previous studies have evaluated LY3819253 IV doses in a range of 700 mg to 7000 mg and shown to be safe and well tolerated.

For Study PYAG, the planned doses of LY3819253 350 mg and 700 mg have been chosen to evaluate PK following this new SC route of administration.

The calculated human AUC(0-∞) following a single IV dose at 700 mg was 54000 hr*µg/mL which is 14-fold lower than the AUC at the no-observed-adverse-effect level in the 21-day rat IV toxicology study [AUC(0-168hr) in rats at 500 mg/kg = 755000 hr*µg/mL].

The starting dose of 350 mg dose is expected to result in lower plasma concentrations (maximum drug concentration [C_{max}] and area under the concentration versus time curve [AUC]) tested with IV dosing in previous studies with LY3819253. The concentrations following 350-mg and 700-mg SC dosing are expected to be quantifiable for pharmacokinetic evaluation, including a model-based estimate of bioavailability.

4.4. End of Study Definition

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

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. are aged 18 to 60 years at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. are overtly healthy as determined by medical evaluation including medical history and physical examination
3. have safety laboratory test results within the reference range for the population at the study site, or results with acceptable deviations that are judged to be not clinically significant by the investigator
4. have venous access sufficient to allow for blood sampling as described in this protocol (SoA, Section 1.3)
5. are reliable and willing to make themselves available for the duration of the study
6. are willing to follow study procedures, including having nasal or nasopharyngeal swabs collected as described in this protocol (SoA, Section 1.3).

Weight

7. have a BMI within the range ≥18.5 to <35 kg/m^2.

Sex

8. are male or female
    a. male participants must agree to adhere to contraception restrictions
    b. female participants must be of non-childbearing potential

Contraception requirements and definition of non-childbearing potential are detailed in Appendix 4 (Section 10.4).

Informed Consent

9. are capable of giving signed informed consent as described in Appendix 1 (Section 10.1), 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 the following criteria apply:

Medical Conditions

10. have current SARS-CoV-2 infection confirmed by nasal or nasal pharyngeal swab results at screening or Day -1.

11. have had prior SARS-CoV-2 infection within 6 weeks before screening, confirmed by either previous nucleic acid-based test, or previous serology
12. have suspected current SARS-CoV-2 infection, in the opinion of the investigator, based on either or both of the following:
    a. a recent exposure to SARS-CoV-2, defined as:
       - living in the same household as a person with SARS-CoV-2;
       - having had direct physical contact with a person with SARS-CoV-2 (for example, shaking hands);
       - having unprotected direct contact with infectious secretions of a person with SARS-CoV-2 (for example, being coughed on or touching used paper tissues with a bare hand);
       - having had face-to-face contact with a person with SARS-CoV-2, within 2 meters and for more than 15 minutes
    b. signs or symptoms that, in the opinion of the investigator, are suggestive of infection (for example, fever, dry cough, shortness of breath, hypoxia, etc.)
13. have a history or presence of cardiovascular (including hypertension), respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric, or neurological disorders that, in the opinion of the investigator, are capable of
    a. significantly altering the absorption, metabolism, or elimination of drugs
    b. constituting a risk while taking the investigational product, or
    c. interfering with the interpretation of data
14. have clinically significant abnormal ECG results constituting a risk while taking the investigational product, as determined by the investigator
15. have an abnormal blood pressure as determined by the investigator. In case blood pressure appears to be abnormally high during the screening period, it is possible to repeat the measure(s) 1 time in a quiet room to avoid an exclusion due to the white coat effect
16. have significant allergies to humanized mAbs
17. have any of the following that are clinically significant:
    a. multiple or severe drug allergies
    b. intolerance to topical corticosteroids, or
    c. severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
18. have known allergies to LY3819253, related compounds, or any components of the formulation
19. have had lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
20. have had breast cancer within the past 10 years
21. show evidence of HIV infection and/or positive human HIV antibodies
22. show evidence of current hepatitis C (that is, test positive for anti-hepatitis C antibody with confirmed presence of HCV RNA)

Note: Patients with a previous diagnosis of hepatitis C who received antiviral therapy and achieved a sustained virological response may be eligible for inclusion in the study, provided that they have no detectable HCV RNA on the screening HCV polymerase chain reaction test for this protocol. A sustained virological response is defined as an undetectable HCV RNA level 24 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.
Patients who have spontaneously cleared HCV infection, defined as (1) a positive HCV antibody test and (2) a negative HCV RNA test, with no history of HCV antibody (anti-HCV) treatment, may be eligible for inclusion in the study, provided that they have no detectable HCV RNA at screening for this study.

23. have history of hepatitis B infection, or show evidence of current hepatitis B:
    a. test positive for hepatitis B surface antigen, and/or
    b. test positive for hepatitis B core antibody and negative for hepatitis B surface antibody

Prior/Concomitant Therapy

24. have received treatment with biologic agents (such as mAbs, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing
25. have previously completed or withdrawn from this study and have previously received the investigational product
26. intend to use over-the-counter medication in the 7 days prior to dose administration or prescription medication in the 14 days prior to dose administration, with the exception of hormone replacement therapy, thyroid replacement medications, vitamin and mineral supplements and occasional use of acetaminophen. Note that acetaminophen is NOT allowed within 24 hours before dosing.

Prior/Concurrent Clinical Study Experience

27. are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
28. have participated in a clinical study involving an investigational product, with last dose within the past 30 days or 5 half-lives, whichever is longer, prior to dosing

Other Exclusions

29. are pregnant or breast feeding
30. have donated blood of more than 500 mL within the previous 3 months of study screening, or intend to donate blood during the course of the study
31. have an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), or are unwilling to stop alcohol consumption from 48 hours prior to admission to and while resident at the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)
32. currently smoke in excess of 10 cigarettes per day or are unwilling to abide by CRU smoking restrictions

33. regularly use known drugs of abuse and/or show positive findings on drug screening unless they were prescribed by a physician (for example, benzodiazepines).
34. are Lilly employees or are employees of a third-party organization involved with the study that requires exclusion of its employees are study site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
35. have tattoos or scars over the abdomen, or other factors (for example, rash or excessive folds of skin) that, in the investigator's opinion, would interfere with injection site assessments
36. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

5.3. Lifestyle Considerations

Reproductive and contraceptive guidance is provided in Appendix 4 (Section 10.4).

5.3.1. Meals and Dietary Restrictions

Participants will be required to fast for at least 2 hours before being given a dose of LY3819253 (see SoA, Section 1.3). Per oral intake, should be limited to clear liquids for 4 hours prior to dosing. Standard meals will be administered while participants are resident at the study site.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants must abide by the CRU restriction policy regarding consumption of alcohol and tobacco.

5.3.3. Activity

Participants should follow all site procedures and local guidelines for measures intended to prevent Covid-19 infection.

Participants should not engage in strenuous physical exercise or activities from 48 hours prior to dosing until discharge from the study or completion of all study procedures. When certain study procedures are in progress at the site, participants may be required to remain supine or sitting.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently enrolled in the study.

Individuals who fulfill eligibility criteria, but are not randomized within the 14-day screening window, may still enroll in the study provided randomization occurs within 28 days of the first screening visit, and provided that they repeat site procedures to confirm Covid-19 status. These subjects do not need to be documented as screen failures. Subjects who are eligible, but are not enrolled within 28 days of their initial screening visit, will need to follow re-screen procedures described below.

For the purposes of assessing eligibility, screening clinical laboratory tests may be repeated if the result is considered likely due to a technical or handling error.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a transient minor illness or concomitant medication may be re-screened if and when they later meet eligibility criteria.

Re-screened participants should be assigned a new screening number. When re-screening, all screening tests and procedures should be repeated (except safety laboratory analyses, if randomization is to occur within 28 days of the first screening tests). Individuals may be re-screened once, and must sign a new ICF.

6. Study Intervention

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

The SC injection site(s) will be peri-umbilical.

The study intervention will be given in the CRU by qualified CRU personnel as designated by the investigator. Study injections should be given by a limited number of personnel for consistency.

The site of administration of each injection will be recorded; when there is more than 1 injection, the same site will not be used, but another quadrant will be used.

6.1. Study Interventions Administered

Intervention	**LY3819253**	**Placebo**
Type	Biologic	Not applicable
Dose Formulation	solution	0.9% sodium chloride solution
Unit Dose Strength(s)	262.5 mg/2.1 mL vial (125 mg/mL)	Placebo
Planned Dosage Level(s)	Cohort 1: 350 mg Cohort 2: 700 mg Cohort 3: 700 mg	Not applicable
Route of Administration	SC injection	SC injection
Use	experimental	placebo
IMP and NIMP	IMP	IMP
Sourcing	From Lilly	Commercially available 0.9% sodium chloride solution
Packaging and Labeling	Study Intervention will be provided in glass vials and will be labeled appropriately	Commercially available 0.9% sodium chloride solution will be used as a placebo for this study

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product; SC = subcutaneous.

6.1.1. Injection volumes and formulation concentrations

Injection volumes are as follows:

Cohort (LY3819253 dose)	Number of injections and volumes
Cohort 1 (350 mg)	2x 1.4 mL
Cohort 2 (700 mg)	1x 1.4 mL + 2x 2.1 mL
Optional Cohort 3 (700 mg)	2x 1.9 mL + 1x 1.8 mL*

* Doses may be adjusted based on data review during the study, as described in Section 6.6. In this event, the number or volume of injections, or both, will be adjusted accordingly.

The LY3819253 formulation concentration will be 125 mg/mL in all cases.

6.1.2. In the Event of a Retrospective Positive Sterility Finding from Prepared Study Intervention

If a positive sterility finding occurs in the terminally sterile filtered study intervention, the participants who were dosed from the impacted batch should be contacted immediately and undergo a full physical examination including, but not limited to, blood pressure, pulse rate, and body temperature.

A blood sample should be collected for culture and assayed for inflammatory markers such as C-reactive protein and elevations in white blood cell counts.

If the signs and symptoms indicated a participant has a possible infection, they will be clinically managed, treated, and followed up until resolution. Any AEs will be recorded as appropriate.

6.2. Preparation/Handling/Storage/Accountability

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

To protect blinding, the interventions must be prepared by unblinded site personnel qualified to prepare study intervention who are not involved in any other study-related procedures. Instructions for preparation will be provided by the sponsor.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization tables for allocation of either LY3819253 or placebo will be prepared by the statistician or their designee.

This study will be participant- and investigator-blind.

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

Emergency codes will be available to the investigator. A code, which reveals the treatment group for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

If an investigator, site personnel performing assessments, or participant is unblinded during dosing, the participant must be withdrawn from further study intervention. If any amount of study intervention was administered, follow procedures according to the SoA, as described in Section 7.1.

Upon completion of the study, all codes must be returned to Lilly or its designee.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of dosing in the clinic will be recorded in the source documents and in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study intervention.

6.5. Concomitant Therapy

All concomitant medications, whether prescription or over the counter, used at baseline and/or during the course of the trial, must be recorded on the Concomitant Medication eCRF. Participants will be instructed to consult the investigator or other appropriate study personnel at the study site before taking any new medications or supplements during the study.

In general, concomitant medication should be avoided. Use of chronic, stable doses of hormone replacement therapy, thyroid replacement medications, or vitamin and mineral supplements is allowed.

Acetaminophen (1 g, maximum 3 g/24 hours) may be administered at the discretion of the investigator for treatment of headache, etc. However, acetaminophen may not be given within 24 hours before dosing.

If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the participant may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP.

Any medication used during the course of the study must be documented.

All vaccines are prohibited until study completion.

6.6. Dose Modification

Depending on the results of a given trial-level safety review, the dose of the subsequent cohort(s) may be adjusted. Because these adjustments to dose levels are allowable changes permitted by the protocol, they would not require a protocol amendment.

6.6.1. Dose-Escalation Criteria

Data will be evaluated on an ongoing basis.

After at least 4 participants assigned to LY3819253 have completed Day 4 in a given cohort, all safety data up to this cutoff date will be reviewed to determine whether the next cohort can be randomized after agreement between Lilly's medical monitor and the investigator. Safety and tolerability data will be the primary criteria guiding dose escalation.

The investigator and the Lilly sponsor team are responsible for determining any dose decisions. The investigator(s) will remain blinded and the Lilly sponsor team will be unblinded during these reviews. All available data from previous cohorts will be reviewed.

If temporary stopping criteria are met (Section 6.6.3), dosing will be temporarily halted and no further participants will be dosed until a full safety review of the study has taken place.

6.6.2. Access to Data during the Study

A limited number of unblinded Lilly study team personnel will have access to safety and/or PK data during the study.

6.6.3. Temporary Stopping Criteria

Dosing will be temporarily halted, and no further participants will be dosed until safety data available at that point have been reviewed:

- pending discussion between the investigator and sponsor, if 3 or more participants develop AEs that are considered to be related to study treatment;
- if 1 or more participants develop AEs that are considered to be related to study treatment and that are serious (SAEs) or graded as severe.

This table describes the location of AE-related information in this protocol.

Topic	Location
Definition of AEs	Section 10.3.1
Assessment of Intensity/Severity	Section 10.3.3

Changes to the planned dosing schedule must be appropriately documented and communicated with the study personnel and the IRB/IEC before dosing continues.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

These sections describe reasons for a participant's

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

Discontinuation of the trial as a whole is handled as part of regulatory, ethical, and trial oversight considerations in Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow-up should be performed as outlined in

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

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

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

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 or designee 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

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, and neurological systems. Height and weight will also be measured and recorded at screening.

Investigators should pay special attention to clinical signs related to COVID-19.

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3). Additional vital signs may be measured during each study period at the investigator's judgment. Blood pressure and pulse rate should be measured after at least 5 minutes supine.

Orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, supine vital signs only will be recorded.

Additional vital signs may be measured during each study period, if warranted.

8.2.3. Electrocardiograms

A single, local, 12-lead ECG will be obtained as shown in the SoA, using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and corrected QT intervals. Additional ECG readings may occur at investigator discretion.

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

8.2.5. Injection Site Reaction Assessment

Injection site assessments using the ISR CRF, VAS if required (see below), and an exploratory tool (Scarletred) will be performed at times specified in the SoA (Section 1.3).

Injection site pain assessments are part of the solicited and spontaneous ISR assessments. The baseline assessment, and all positive responses of pain from then on, will require an additional assessment using the Pain VAS.

As there are multiple injections for each dose, ISR assessments will be done for each injection.

Manifestations of a local ISR may include erythema, induration, pain, pruritus, and edema. Injection site findings will be captured on the eCRF.

Injection site reactions, if recorded as a result of the prespecified (or solicited) assessment, will be recorded as AEs only if they qualify as SAEs.

If a spontaneous (or unsolicited) ISR is reported by a participant or investigator, the ISR CRF will be used to capture additional information about this reaction (for example, degree and area of erythema) at additional visits until resolution of the event.

The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually "no pain" and "worst imaginable pain." The participant will be asked to rate any pain at the injection site on a scale of 0 to 100 on the line, as soon as possible following each injection.

In addition, the exploratory tool (Scarletred) will be used to acquire exploratory ISR data at each of the time points where the ISR data is being collected by administration of the ISR CRF. Failure to take this assessment at any of the indicated time points will not result in a protocol deviation.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant.

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

Discontinuation information is in Section 7.

Detailed AE definitions and procedures are in Section 10.3.

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

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

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

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

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

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation (Day 85). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until at least 5 months after the last dose.

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

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

8.3.6. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional details describing each symptom should be provided to the sponsor in the Hypersensitivity/Anaphylactic/Infusion-Related Reaction CRF.

Sites should have appropriately trained medical personnel and appropriate medical equipment available when study participants are receiving intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidance (Lieberman et al. 2015; Simons et al. 2015).

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

8.3.7. SARS-CoV-2 Infection

Site procedures for participant management will be followed in the event of a suspected SARS-CoV-2 infection during the study.

A nasopharyngeal swab will be taken on Day 1 and shipped to the sponsor. This is for research purposes, such as viral sequencing.

In addition, SARS-CoV-2 point-of-care tests may be performed at specific timepoints during the study at the discretion of the investigator. Every time such a point-of-care test is performed post

baseline, an additional nasal swab sample may be collected in parallel, for research purposes such as viral sequencing. This research swab sample will be shipped to the sponsor only if the point-of-care test is positive. If the point-of-care test is negative, the research swab sample should be discarded.

8.3.8. Product Complaints

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

The sponsor collects product complaints on study interventions used in clinical studies to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study intervention so that the situation can be assessed.

NOTE: Any AEs or SAEs that are associated with a product complaint will follow the processes outlined in Section 8.3.3 and Section 10.3, Appendix 3, of the protocol.

Time Period for Detecting Product Complaints

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

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

Prompt Reporting of Product Complaints to Sponsor

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

The Product Complaint Form will be sent to the sponsor by a method designated by the sponsor.

Follow-up of Product Complaints

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

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

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

8.4. Treatment of Overdose

For the purposes of this study, an overdose of LY3819253 is considered any dose higher than the dose assigned through randomization. In case of suspected overdose, participants should be monitored for any signs or symptoms of adverse reactions or effects, and supportive care should be provided as necessary.

8.5. Pharmacokinetics

Venous blood samples will be collected as specified in the SoA for determination of serum concentrations of LY3819253 used to evaluate the PK for LY3819253.

A maximum of 5 samples 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 Lilly.

Site personnel will record

- the date and time (24-hour clock time) of investigational drug administration, and
- the date and time (24-hour clock time) of each PK sample.

It is essential that the times are recorded accurately.

8.5.1. Bioanalytical

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3819253 will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated subjects are not planned.

Sample retention is described in Appendix 1, Section 10.1.10. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

8.6. Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.7. Genetics

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

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

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

8.8. Biomarkers

Serum samples for exploratory biomarker research will be collected at the time specified in the SoA where local regulations allow.

Samples will be stored and analysis may be performed on biomarkers thought to play a role in immune system-related responses to viral infection or administration of LY3819253 including, but not limited to, immune pathways or serum analytes to evaluate their association with LY3819253 administration.

Samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to the intervention target (spike protein), pathways associated with disease, and/or the mechanism of action of the study intervention.

Swab samples taken during the study may be used for research purposes, such as viral sequencing.

Sample retention is described in Section 10.1.10.

8.9. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA, predose venous blood samples will be collected to determine antibody production against LY3819253. The actual date and time (24-hour clock time) of each sample collection will be recorded. To aid interpretation of these results, the immunogenicity sampling timepoints all coincide with a PK sampling timepoint.

Sample collection, handling, and use

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

Immunogenicity will be assessed using a validated assay designed to detect ADAs in the presence of LY3819253 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3819253.

Sample retention

Sample retention is described in Section 10.1.10.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

Formal statistical hypothesis testing is not planned. Therefore, adjustments for multiple testing do not apply.

9.2. Sample Size Determination

A maximum of 36 participants will be enrolled to study intervention with the intention that at least 6 participants randomized to LY3819253 have sufficient evaluable data in each of Cohorts 1 and 2.

This would mean at least 12 participants with evaluable data if Cohorts 1 and 2 only are enrolled. If the optional Cohort 3 is used, the total number of participants in the study with evaluable data will depend on enrollment numbers for that cohort.

The sample size is not powered on the basis of statistical hypothesis testing. However, based on an assumption of 40% CV for between subject variability in a PK parameter of interest, 6 subjects on active treatment per cohort may provide approximately 70% chance to ensure that a PK parameter's 90% confidence interval falls within (0.7, 1.43) over the corresponding geometric mean, such as AUC(0-∞).

A participant will be considered evaluable when the participant completes up to 29 days of study procedures. When a participant does not complete up to 29 days of study procedures, the sponsor will be consulted if the participant will need to be replaced.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF
Enrolled/Intent-to-Treat	All participants assigned to treatment, regardless of whether they received study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.
Safety	All participants randomly assigned to study intervention and who received study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All treated participants who received study intervention and have sufficient evaluable PK samples.

Abbreviations: ICF = informed consent form; PK = pharmacokinetic.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of sponsor or its designee.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, unless otherwise stated, and all confidence intervals will be given at a 2-sided 90% level.

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

The SAP will be finalized prior to 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.

9.4.1. General Considerations

Statistical analyses will be performed using SAS® Version 9.4 or higher.

For continuous measures, summary statistics will include sample size, mean, standard deviation, minimum, median, and maximum. For categorical measures, summary statistics will include the sample size, frequency count, and percentage.

For all safety analyses, baseline will be defined as the last evaluable value before dosing.

9.4.2. Primary Endpoint: Pharmacokinetics

Pharmacokinetic parameter estimates for LY3819253 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be AUC(0-∞) of LY3819253 following SC administration. Other noncompartmental parameters, such as half-life, t_{max}, apparent clearance, and volume of distribution following SC administration may be reported.

In addition to noncompartmental analysis, the data may be combined with data from other studies to be analyzed using non-linear mixed-effect modelling of the PK data. This model will enable estimation of mean and variability (variances) of LY3819253 PK parameters, including bioavailability, following SC administration and to investigate potential covariates explaining that variability.

9.4.3. Secondary Endpoint: Safety

9.4.3.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Adverse events reported to occur prior to randomization will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

All SAEs will be reported.

9.4.3.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital sign measurements. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.4.4. Exploratory Endpoint: Injection Site Reaction Assessments

Injection site reactions will be listed and may be summarized by dose if data warrant.

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

9.6. Data Monitoring Committee (DMC)

Not applicable.

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.

The investigator will be responsible for the following:

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

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

10.1.2. Informed Consent Process

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

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

The 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 and, if applicable, the individual designated to witness a verbal consent, must also sign the ICF.

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

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

10.1.3. Data Protection

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

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

The participant must be informed that 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 data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

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

10.1.5. Data Quality Assurance

Investigator responsibilities

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

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

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

Data monitoring and management

The Monitoring Plan includes

- 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
- requirements
- handling of noncompliance issues, and
- monitoring techniques.

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

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

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement 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.

The sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and by 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.

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

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

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

10.1.6. Source Documents

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

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

The definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. Study and Site Start and Closure

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

Site Closure

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 enough notice is given in advance of the intended termination.

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

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator, or
- discontinuation of further study intervention development.

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

10.1.8. 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 if the results are deemed to be of significant medical importance.

10.1.9. Investigator Information

Physicians with a specialty in infectious disease, critical care, or pulmonary disease may participate as investigators.

10.1.10. Long-Term Sample Retention

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

This table describes the retention period for potential sample types.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacogenetics sample	Sponsor or designee	up to 15 years
Exploratory Biomarker Samples	Sponsor or designee	up to 15 years
PK sample	Sponsor or designee	up to 2 years
Immunogenicity (ADA) sample	Sponsor or designee	up to 15 years

10.2. Appendix 2: Clinical Laboratory Tests

- Clinical laboratory tests will be performed according to the SoA. Additional details are provided in the following table for specific laboratory tests.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing will be performed according to the SoA.
- The following table describes when the local or central laboratory will be used.
- If the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.
- Laboratory results that could unblind the study will not be reported to study sites or other blinded personnel.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Investigators must document their review of each laboratory safety report.

Clinical Laboratory Tests	Comments
Hematology	Assayed by local laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Leukocytes (WBCs - white blood cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC)	
Clinical Chemistry	Assayed by local laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	Record on Day -1 and repeat if significantly abnormal value
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Blood urea nitrogen (BUN)	
Creatinine	

Clinical Laboratory Tests	Comments
Uric acid	Record on Day -1 and repeat if significantly abnormal value
Total protein	
Albumin	
Calcium	
Phosphorus	
Random glucose	
Calculations	Completed locally
Hepatitis B surface antigen	
Hepatitis B surface antibody	
Hepatitis B core antibody (HBcAb)	
Hepatitis C antibody	
HIV	
SARS-Cov-2 viral infection determination	Local laboratory
SARS-Cov-2 point of care	
SARS-Cov-2 nasal or nasopharyngeal sample for research purposes	Day 1 sample assayed by Lilly-designated laboratory. Subsequent samples sent to Lilly-designated laboratory for analysis only if the SARS-Cov-2 point of care test performed in parallel is positive
SARS-Cov-2 serology	Assayed by Lilly-designated laboratory.
Urinalysis	Assayed by local laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Microscopy	If dipstick test is abnormal.
Hormones (female)	Assayed by local laboratory.
Serum pregnancy	
Urine pregnancy	
Ethanol/drug screening	Assayed by local laboratory.
Urine or breath ethanol screen	
Urine drug screen	
Pharmacokinetic (PK) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the study sites.
Pharmacogenetic sample	Assayed by Lilly-designated laboratory. Results will not be provided to the study sites.
Exploratory Biomarker Serum Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the study sites.

Abbreviations: HIV = human immunodeficiency virus; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	15		
SARS-CoV-2 serology	10	5	50
Pharmacokinetics	4	12	48
Immunogenicity	10	5	50
Blood discard for cannula patency	1	5	5
Pharmacogenetics	10	1	10
Serum for exploratory biomarkers	10	6	60
Total			268
Total for clinical purposes (rounded up to nearest 10 mL)			270

[a] Additional samples may be drawn if needed for safety purposes.

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition

• Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.
• The following study-specific clinical events related to COVID-19 are exempt from AE reporting unless the investigator deems the event to be related to the administration of intervention:
  o Hypoxemia due to COVID-19 requiring supplemental oxygen;
  o Hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices;

- Respiratory failure due to COVID-19 requiring invasive mechanical ventilation or ECMO
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease under study, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, such as endoscopy or appendectomy. The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

Please note: If an event is not an AE per definition above, then it cannot be an SAE.

An SAE is defined as any AE that:

a. Results in death

b. Is immediately life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for >"23 hour observation" and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording

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

The investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the AE/SAE CRF page.

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

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

Assessment of Intensity/Severity

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

Mild: Mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated.

Moderate: Moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated.

Severe: Severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.

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

Assessment of Causality

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

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

The investigator will use clinical judgment to determine the relationship.

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

The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

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

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

The investigator may change their opinion of causality after consideration of follow-up information and send a SAE follow-up report with the updated causality assessment.

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

Follow-up of AEs and SAEs

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

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

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

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

10.3.4. Reporting of SAEs

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

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

10.4.1. Women

Only women of non-childbearing potential may participate in this study.

Definitions:

Woman of Childbearing Potential

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

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

Woman Not of Childbearing Potential

Women in the following categories are not considered woman of childbearing potential

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

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

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

3. Postmenopausal female is defined as, women with
    - 12 months of amenorrhea for women >55 years, with no need for follicle-stimulating hormone
    - 12 months of amenorrhea for women >40 years with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that induced amenorrhea)

10.4.2. Men

Men, regardless of their fertility status, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective method of contraception (less than 1% failure rate) or effective method of contraception with nonpregnant women of childbearing potential partners for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 140 days after the last dose.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure to the fetus, predicted to be 140 days after the last dose.

Acceptable Methods of Contraception for Female Partners of Male Participants

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

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

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

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

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

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

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy.

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

Female participants who become pregnant

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

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

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

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

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

10.5. Appendix 5: Genetics

Sample collection information is found in Appendix 2, Section 10.2.

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 may be used for research related to SARS-CoV-2 and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3819253 or SARS-CoV-2. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome as appropriate.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to LY3819253 or study interventions of this class to understand study disease or related conditions.

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

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

The samples will be retained at a facility selected by the sponsor or its designee while research on SARS-CoV-2 continues, but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events

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

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

Clinical Lab Tests for Hypersensitivity Events

Hypersensitivity Tests	**Notes** Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
LY3819253 anti-drug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3819253 concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. Urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Collect a follow-up urine sample after approximately 4 weeks. **Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, collect a urine sample for N-methylhistamine testing.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **NOTE:** The basophil activation test is an in vitro cell based assay that only requires a serum sample. It is a surrogate assay for drug specific IgE, but is not specific for IgE.
Complement (C3, C3a, and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Abbreviations: IgE = immunoglobulin E; PK = pharmacokinetic.

10.7. Appendix 7: Abbreviations

Term	Definition
ADE	antibody-dependent enhancement
AE	adverse event
AUC	area under the curve
AUC(0-∞)	AUC(0-∞) area under the concentration versus time curve from zero to infinity
CFR	Code of Federal Regulations
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.
COVID-19	coronavirus disease-2019
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
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.
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Term	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ISR	injection site reaction
IV	intravenous(ly)
mAb	monoclonal antibody
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
PK	pharmacokinetics
PYAA	J2W-MC-PYAA
PYAB	J2W-MC-PYAB
PYAG	J2X-MC-PYAG
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
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.
SoA	Schedule of Activities

Term	Definition
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time of maximum observed drug concentration
VAS	visual analog scale

10.8. Appendix 8: Protocol Amendment History

Amendment (a)

Overall Rationale for the Amendment:

Following feedback from the U.S. Food and Drug Administration (FDA), typographical errors have been corrected. Additional changes described below have been made for clarity for clinical site activities.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Physical Examination/Medical Assessment • Corrected "Visit 7/ED" to "Visit **6**/ED" Injection Site Assessments • Simplified language in Comments column to denote ISR assessement, pain VAS and Scarletred for all timepoints, and added clarification regarding predose Scarletred timing.	There is no Visit 7 per the Schedule of Activities. Typographical correction. Scarletred will be assessed during the predose activities.
Section 5.2. Exclusion Criteria	Updated Criterion 12.a to correct for typo: "within 2 minutes" should be "within 2 **meters**."	FDA feedback. Typographical correction.
Section 6.1. Study Interventions Administered	LY3819253 unit dose and strength updated to 262.5 mg/2.1 mL vial (125 mg/mL).	Clarification added for vial fill volume (2.1 mL) and drug product concentration (125mg/mL).
Section 6.1.1. Injection Volumes and Formulation Concentrations	Updated Cohort 3 injection volumes to reflect syringe accuracy specification: "3x 1.86 mL" updated to "2x 1.9 mL + 1x 1.8 mL."	Due to limitations with syringe gradations, accurate measurement of 0.06 mL with a 3-cc syringe is not possible. Therefore, the injection volume was rounded to 1 decimal to enable accurate volume for dosing.
Section 10.7. Appendix 7, Abbreviations	Added FDA to list of abbreviations.	FDA used on this page.

11. References

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