Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2029849

This supplement contains the following items:

Title Page

Protocol Title:

A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3819253 in Participants with Mild to Moderate COVID-19 Illness

Protocol Number: J2W-MC-PYAB

Amendment Number: This is the initial protocol

Compound: LY3819253

Study Phase: 2

Short Title: A randomized, double-blind, placebo-controlled, Phase 2 study to evaluate LY3819253 in participants with mild to moderate COVID-19 illness

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 150440

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

Medical Monitor Name and Contact Information will be provided separately

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3819253 in Participants with Mild to Moderate COVID-19 Illness

Rationale:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which in critical cases results in progressive pulmonary failure, complications with acute respiratory distress syndrome (ARDS), and death. There is an urgent need for effective therapeutics to modify disease outcomes.

LY3819253 is a neutralizing IgG1 monoclonal antibody (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, potentially treating even established COVID-19 by providing a specific potent, neutralizing antibody to SARS-CoV-2.

This study aims to evaluate the impact of LY3819253 on viral clearance and clinical outcomes in patients with COVID-19 illness. The data from this study will inform decisions for the clinical development of LY3819253.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load
Secondary	
Characterize the effect of LY3819253 compared to placebo on safety	• Safety assessments such as AEs and SAEs
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
Characterize the effect of LY3819253 compared to placebo on symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22 • Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22

Characterize the effect of LY3819253 compared to placebo on symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 15 and 22) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed at Day 29
Characterize the pharmacokinetics of LY3819253	• LY3819253 mean concentration on Day 29
Characterize the effect of LY3819253 compared to placebo on overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 o COVID-19 related hospitalization (defined as ≥24 hours of acute care) o a COVID-19 related emergency room visit, or o death

Abbreviations: AE = adverse event; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Overall Design:

This is a Phase 2, randomized, double-blind, placebo-controlled, single-dose study in participants with mild to moderate COVID-19 illness.

Design Outline

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures.

The investigator will review symptoms, risk factors and other non-invasive inclusion and exclusion criteria prior to any invasive procedures. If the participant is eligible after this review, then the site will perform the invasive procedures to confirm eligibility.

Double-blind Treatment and Assessment Period

Participants will be randomized to placebo or LY3819253. As dose levels in Study J2W-MC-PYAA (PYAA) are determined to be safe, these dose levels may be introduced in Study PYAB. This table describes the planned treatment arms.

Treatment arms	LY3819253
1	placebo
2	700 mg
3	2800 mg
4	7000 mg

An optional LY3819253 treatment arm may be added based on interim analysis results.

This is the general sequence of events during the treatment and assessment period:

- Complete baseline procedures and sample collection
- Participants are randomized to LY3819253 or placebo
- Participants receive a single IV infusion of study intervention, and
- Complete all safety monitoring and post-infusion sample collection.

This table describes the visit types for this study.

Study Day	Visit Type
1	site
2, 4, 5, and 6	telephone
3, 7 – 29	may be conducted as outpatient clinic or home visits
Early discontinuation and follow-up	may be conducted as outpatient clinic or home visits

If a participant is hospitalized, procedures and assessments will continue per the SoA.

This table describes discharge from hospital scenarios if an outpatient is subsequently hospitalized.

Discharge from hospital (Outpatients Subsequently Hospitalized)

If hospital discharge…	Then…
Occurs prior to Day 29	participants will be asked to complete the remaining study assessments at the timepoints indicated in the SoA. NOTE: Strategies to manage infection risks and reduce the burden of return visits should be used by sites, such as home visits.
Occurs on the same day as a study assessment visit	assessments do not need to be repeated if the study assessments occurred within 8 hours of discharge and there has been no change in clinical status and the information is available to the site.
Does not occur at or prior to Day 29	assessments will continue to occur weekly up to Day 60 or until hospital discharge, whichever is sooner.

Post-treatment follow-up

Post-treatment follow-up assessments will be conducted at Day 60 and Day 85 to assess clinical status and for adverse events. Strategies to manage infection risks and reduce the burden of return visits may be used by sites, such as home visits.

Disclosure Statement: This is a treatment study that is participant and investigator blinded.

Number of Participants:

A sample size of approximately 100 participants per treatment arm.

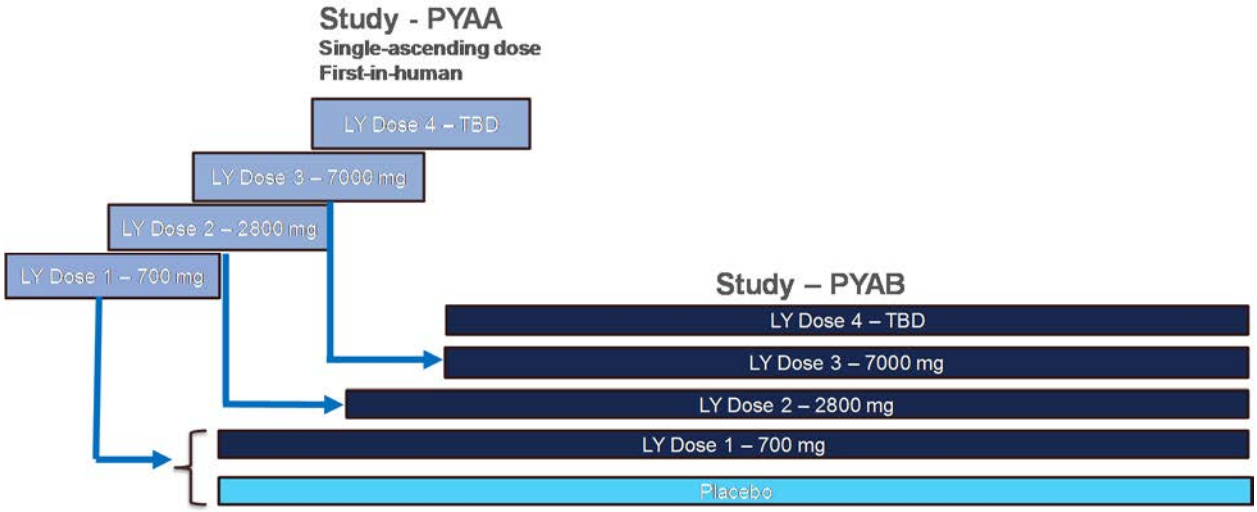
Intervention Groups and Duration:

There are 4 planned intervention groups including placebo, LY3819253 700 mg, 2800 mg and 7000 mg, with the option for a fifth LY3819253 dose arm that will not exceed 7000 mg.

Participants will receive a single IV infusion, assessments occur to Day 29 and follow-up to Day 85.

Data Monitoring Committee: Yes, there will be an assessment committee.

1.2. Schema



Abbreviations: LY = Lilly study intervention; PYAA = J2W-MC-PYAA; PYAB = J2W-MC-PYAB; TBD = to be determined.
NOTE: PYAB LY Dose 4 is optional and determined by interim analysis.
Maximum dose will not exceed 7000 mg.

Figure 1. Single-dose study J2W-MC-PYAB schema

1.3. Schedule of Activities (SoA)

Assessments obtained previously as part of routine clinical care may be used as the baseline assessment if they were done no more than 48 hours before randomization. Visits may be conducted as a telephone call, outpatient clinic or home visit, as long as the protocol SoA is followed.

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Procedures																	
Informed Consent	X																
Inclusion and exclusion criteria review	X																
Demographics	X																Including age, gender, race, ethnicity
Preexisting conditions and medical history	X																Obtained from interview or available information, and including timing of exposure and onset of symptoms suggestive of SARS-CoV-2 infection
Height		X															
Weight		X															
Prior treatments of special interest within the last 30 days	X																NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or other investigational treatments.

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Tobacco use	X																
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3.
Physical Evaluation or Clinical Assessments																	
Physical examination	X																
Symptom-directed physical exam				X								X	X				As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations.
Vital signs		X		X		X	X	X	X	X	X	X	X	X	X	X	Documentation of hospital-based exam is acceptable. Includes: body temperature, pulse rate, BP, respiratory rate, SpO2, and supplemental oxygen flow rate, FiO2 if known, and method of delivery, if applicable. Record SpO2 while participant is at rest. **Screening visit only**: SpO2 while breathing room air. **Day 1** timing:

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
																	• immediately before the infusion, • every 30 minutes during the infusion, as possible • 30 minutes after infusion. During infusion, only record pulse rate, BP and SpO2. Automation may be used. **All other study days:** once daily.
Hospitalization events			Daily										X	X	X	X	Record if the following events occur: • Emergency room visits • hospitalized • ICU admittance, • Extended care facility admittance, and • discharge
Clinical status and concomitant procedures if participant is hospitalized			Daily if hospitalized										X	X			Documentation from hospital records is acceptable. Includes: consciousness status (ACVPU), limitation on activities due to COVID-19, and requirements for • Ongoing hospital medical care • Supplemental oxygen

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
																	• Non-invasive ventilation or high flow oxygen device • Mechanical ventilation • ECMO, or • Additional organ support (e.g. pressors, renal replacement).
Laboratory Tests and Sample Collection																	
Hematology		X		X				X				X	X				Day 1: before IV infusion All other days: sample may occur at any time during the day No samples needed if participant is hospitalized Lilly-designated central laboratory
Clinical Chemistry		X		X				X				X	X				Day 1: before IV infusion All other days: sample may occur at any time during the day No samples needed if participant is hospitalized Lilly-designated central laboratory

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
• C-reactive protein (CRP); high - sensitivity • Ferritin • D-dimer • Procalcitonin • Troponin		X		X				X				X	X				Day 1: before IV infusion All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory
Documentation of positive SARS-CoV-2 viral infection	X																Sample for first positive test must be collected within 3 days prior to start of infusion.. Local laboratory and/or Point-of-Care testing.
Urine or serum pregnancy	X														X	X	Only for WOCBP (Section 10.4 Appendix 4) Local laboratory
Pharmacokinetic (PK) sample		X						X				X	X		X	X	Day 1: before IV infusion and anytime just prior to the end of infusion. All other scheduled samples may occur at any time during the day. No samples needed if participant is hospitalized. Lilly-designated central laboratory

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Immunogenicity (ADA) sample		X						X				X	X		X	X	Day 1: collect before IV infusion. All other scheduled and unscheduled immunogenicity samples should be collected with a time-matched PK sample. No samples needed if participant is hospitalized Lilly-designated central laboratory
Pharmacodynamic (PD) NP swab		X		X		X	X	X	X	X	X	X	X				Swab is taken from both nostrils. Day 1: swab before IV infusion. No samples needed if participant is hospitalized Lilly-designated central laboratory
Exploratory biomarker samples		X		X				X				X	X				Day 1: before IV infusion. No samples needed if participant is hospitalized Lilly-designated central laboratory
Pharmacogenetics sample		X															Lilly-designated central laboratory
Randomization and Dosing																	
Randomization		X															

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Administer study intervention (IV infusion)		X															Study intervention must be administered within 3 days from the time of first positive SARS-CoV-2 test sample collection. For participants that receive dialysis on the same day as the IV infusion, complete dialysis first followed by the IV infusion. Participants will be monitored for at least 2 hours after completion of the infusion.
Participant Questionnaire																	
Symptoms and overall clinical status			Daily on Days 2-29 for outpatients only										X		X		

Abbreviations: ACVPU = alert, consciousness, verbal, pain, unresponsive scale; ADA = anti-drug antibody; BP = blood pressure; ECMO = extracorporeal membrane oxygenation; ED = early discontinuation visit; FiO2 = fraction of inspired oxygen in the air; ICU = intensive care unit; IV = intravenous; NP = nasopharyngeal; NSAIDS = non-steroidal anti-inflammatory drugs; SpO2 = saturation of peripheral oxygen; WOCBP = women of child-bearing potential.

2. Introduction

The efficient community spread of SARS-CoV-2 has resulted in the current pandemic of COVID-19, which in severe and critical cases results in progressive pulmonary infection, complicated by respiratory failure, with a high prevalence of acute respiratory distress syndrome. Although several therapies have been explored in severe COVID-19, none have improved survival, including antivirals, glucocorticoids, and immunoglobulins (Liu et al 2020).

The SARS-CoV-2 gains entry to cells through binding of the spike (S) protein to ACE2 receptors on cells (Hoffmann 2020). Eli Lilly and Company has a partnership with AbCellera Biologics Inc. (AbCellera; Vancouver, Canada) to develop neutralizing IgG1 monoclonal antibodies (mAbs) to the Spike (S) protein of SARS-CoV-2 as a potential treatment for COVID-19. Candidate antibody gene sequences have been selected from a recently recovered COVID-19 United States patient's serum using AbCellera's core platform screening technologies.

LY3819253 is a neutralizing IgG1 monoclonal antibody (mAb) to the spike protein of SARS-CoV-2, predicted to have a half-life of 19 days. It is designed to block viral attachment and entry into human cells, and to neutralize the virus, potentially treating even established COVID-19 by providing a specific potent, neutralizing antibody to SARS-CoV-2. The blocking of viral entry into respiratory cells and viral replication, and viral neutralization is expected to mitigate the severity of disease in patients in whom ongoing viral spread and replication is the primary driver of COVID-19 pathophysiology. The decrease in viral replication may also shorten a patient's extent and duration of viral shedding and transmission, positively impacting public health.

2.1. Study Rationale

This study aims to evaluate the impact of LY3819253 on viral clearance and clinical outcomes in patients with mild to moderate COVID-19 illness. The data from this study will inform decisions for the clinical development of LY3819253.

2.2. Background

Nonclinical information for LY3819253 is described in the Investigator's Brochure (IB).

LY3819253 has not been administered to humans. Lilly is evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3819253 in participants hospitalized for COVID-19, in a randomized, placebo-controlled, double-blind, single ascending dose, Phase 1, first in human study (Study J2W-MC-PYAA [PYAA]). Study PYAA will start prior to this study and will inform the dose levels administered in Study PYAB.

2.3. Benefit/Risk Assessment

Information on the safety and tolerability of LY3819253 in humans will come from Study PYAA. All available study data will be reviewed before that dose is administered in Study PYAB.

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 is a highly specific

mAb directed at foreign (non-human) epitope(s). The complementarity determining regions (CDRs) of the mAb were derived from B lymphocytes of a convalescent naturally 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.

A theoretical risk is that LY3819253 may cause antibody-dependent enhancement (ADE) of viral replication. This is based on responses observed to some monoclonal antibody therapies used in other unrelated viral diseases. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronaviral infections, such as SARS and MERS, 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, 2020). LY3819253 will be administered to patients at sufficiently high dose levels to neutralize SARS-CoV-2 and avoid sub-neutralizing concentrations in the presence of virus that are typically associated with ADE.

Additional manageable risks associated with most therapeutic monoclonal antibodies are the potential for infusion-related hypersensitivity and cytokine release reactions. The single infusion in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made and/or the infusion stopped, if indicated. Additional information regarding infusion reaction management options is in Section 6.1.1.

Given the data on LY3819253 and the well described safety profile of other therapeutic mAbs, and the lack of disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment this study is considered favorable.

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load
Secondary	
Characterize the effect of LY3819253 compared to placebo on safety	• Safety assessments such as AEs and SAEs
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
Characterize the effect of LY3819253 compared to placebo on symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22 • Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22
Characterize the effect of LY3819253 compared to placebo on symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 15 and 22) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed at Day 29
Characterize the pharmacokinetics of LY3819253	• LY3819253 mean concentration on Day 29
Characterize the effect of LY3819253 compared to placebo on overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 o COVID-19 related hospitalization (defined as ≥24 hours of acute care) o a COVID-19 related emergency room visit, or o death

Objectives	Endpoints
Exploratory	
Characterize emergence of viral resistance to LY3819253	• Comparison from baseline to Day 29
Characterize the effect of LY3819253 compared to placebo on SpO2 over time	• SpO2 AUC assessed at Day 29
Characterize the effect of LY3819253 compared to placebo on symptom severity	• Symptom severity as assessed by mean AUC at Day 29 of symptom questionnaire

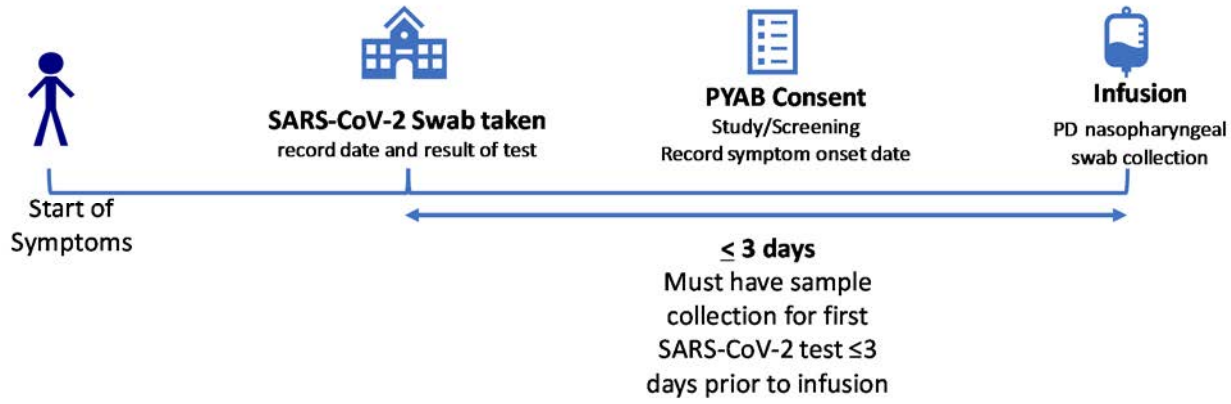
Abbreviations: AE = adverse event; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = saturation of peripheral oxygen.

4. Study Design

4.1. Overall Design

This is a Phase 2, placebo-controlled, double-blind, randomized single-dose study in participants with mild to moderate COVID-19 illness.

4.1.1. Design Outline



Abbreviations: PD = pharmacodynamic; PYAB = Study J2W-MC-PYAB.

Figure 2. Overview of participant flow from time of SARS-CoV-2 symptoms to IV infusion.

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures. The participant may enter the study with a previous positive SARS-CoV-2 viral test result from an external testing facility. This test result must be the first time the patient has tested positive for SARS-CoV-2.

The investigator will review symptoms, risk factors and other non-invasive inclusion and exclusion criteria prior to any invasive procedures. If the participant is eligible after this review, then the site will perform the invasive procedures to confirm eligibility.

Double-blind Treatment and Assessment Period

Participants will be randomized to placebo or LY3819253. As dose levels in Study J2W-MC-PYAA (PYAA) are determined to be safe, these dose levels may be introduced in Study PYAB. This table describes the planned treatment arms.

Treatment arms	LY3819253
1	placebo
2	700 mg
3	2800 mg
4	7000 mg

An optional LY3819253 treatment arm may be added based on interim analysis results.

This is the general sequence of events during the treatment and assessment period:

- Complete baseline procedures and sample collection
- Participants are randomized to LY3819253 or placebo
- Participants receive a single IV infusion of study intervention, and
- Complete all safety monitoring and post-infusion sample collection.

This table describes the visit types for this study.

Study Day	Visit Type
1	site
2, 4, 5, and 6	telephone
3, 7 – 29	may be conducted as outpatient clinic or home visits
Early discontinuation and follow-up	may be conducted as outpatient clinic or home visits

If a participant is hospitalized, procedures and assessments will continue per the SoA.

This table describes discharge from hospital scenarios if an outpatient is subsequently hospitalized.

If hospital discharge…	Then…
Occurs prior to Day 29	participants will be asked to complete the remaining study assessments at the timepoints indicated in the SoA. NOTE: Strategies to manage infection risks and reduce the burden of return visits should be used by sites, such as home visits.
Occurs on the same day as a study assessment visit	assessments do not need to be repeated if the study assessments occurred within 8 hours of discharge and there has been no change in clinical status and the information is available to the site.
Does not occur at or prior to Day 29	assessments will continue to occur weekly up to Day 60 or until hospital discharge, whichever is sooner.

Post-treatment follow-up

Post-treatment follow-up assessments will be conducted at Day 60 and Day 85 to assess clinical status and for adverse events. Strategies to manage infection risks and reduce the burden of return visits may be used by sites, such as home visits.

4.2. Scientific Rationale for Study Design

Overall Design

This study is designed to evaluate the efficacy of LY3819253 in a range of doses that will inform the clinical drug development plan for LY3819253.

The follow-up at Day 85 adequately covers the duration for immune response.

Participant Characteristics

The participant population are those infected with SARS-CoV-2 that have developed symptoms consistent with COVID-19. There is historical evidence that patients infected with upper respiratory viruses who are treated early in their disease course have better responses to anti-viral

therapies (Aoki et.al., 2003). This hypothesis will be tested with a focused subgroup analysis on participants who received intervention within 8 days of symptom onset and a virology endpoint (see Section 3).

The population of participants with mild to moderate COVID-19 illness was chosen to evaluate if effective antiviral antibody therapy may prevent progression to the severe form of COVID-19 illness by treating this population early in their disease course and prior to respiratory compromise and failure.

Interim Reviews

The interim safety and efficacy reviews will inform the clinical drug development plan for LY3819253.

4.3. Justification for Dose

The dose levels of LY3819253 administered in this study are informed by Study PYAA. As dose information from Study PYAA are determined to be safe, these dose levels may be added to the study.

The doses are determined based on these key variables:

- projected human PK of the mAb, including lung tissue distribution
- in vitro binding potency to the viral targets
- neutralization of virus cell entry and replication, and
- antibody-viral dynamic modeling and simulation.

The projected human half-life is expected to be in the 2-4 weeks range.

The starting dose of 700 mg in Study PYAA is expected to have a sustained concentration above the *in vitro* IC90 of viral cell-entry neutralization for at least 28 days. The maximum dose of 7000 mg is selected due to uncertainty in model predicted PK concentrations, viral load reduction and consideration of infusion volume in participants. The dose will not exceed 7000 mg in this study.

The dose levels are fixed, not body weight based. Given the planned dose levels, the predicted impact of body weight on therapeutic response will be minimal.

4.4. End of Study Definition

A participant is considered to have completed the study if they have 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 in the trial globally.

5. Study Population

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

Due to the criticality of participant health, verbal interview of the potential participant, or their legal representative or family member, may be the source for disease characteristics and medical history, unless otherwise specified within the eligibility criteria.

5.1. Inclusion Criteria

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

Age

1. Are ≥18 years of age at the time of randomization

Disease Characteristics

2. Are currently not hospitalized
3. Have one or more mild or moderate COVID-19 symptoms (FDA resource page [WWW])
    i. Fever
    ii. Cough
    iii. Sore throat
    iv. Malaise
    v. Headache
    vi. Muscle pain
    vii. Gastrointestinal symptoms, or
    viii. Shortness of breath with exertion
4. Must have sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of the infusion

Sex

5. Are men or non-pregnant women
   Reproductive and Contraceptive agreements and guidance is provided in Section 10.4, Appendix 4. Contraceptive use by men or women should be consistent with local regulations for those participating in clinical studies.

Study Procedures

6. Understand and agree to comply with planned study procedures
7. Agree to the collection of nasopharyngeal swabs and venous blood

Informed Consent

8. The participant or legally authorized representative give signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

9. Have SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA resource page, WWW)
10. Require mechanical ventilation or anticipated impending need for mechanical ventilation
11. Have known allergies to any of the components used in the formulation of the interventions
12. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
13. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
14. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
15. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.

Other Exclusions

16. Have a history of a positive SARS-CoV-2 serology test
17. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
18. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
19. Have received treatment with a SARS-CoV-2 specific monoclonal antibody
20. Have a history of convalescent COVID-19 plasma treatment
21. Have participated in a previous SARS-CoV-2 vaccine study
22. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
23. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
24. Are pregnant or breast feeding
25. Are investigator site personnel directly affiliated with this study.

5.3. Lifestyle Considerations

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

Each participant will receive a single IV infusion of either placebo or LY3819253.

Study intervention must be administered within 3 days of the first positive SARS-CoV-2 test sample collection.

Intervention Name	Placebo	LY3819253	LY3819253	LY3819253
Dose Formulation	0.9% sodium chloride solution	Solution	solution	solution
Dosage Level(s) (mg)	Not applicable	700	2800	7000
Use	placebo	experimental		
IMP and NIMP	IMP	IMP		
Sourcing	Commercially available 0.9% sodium chloride solution	From Lilly		
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately		

Abbreviations: IMP = investigational medicinal product; IV = intravenous.

An optional 4th LY3819253 dose level may be tested based on interim analysis results. The dose levels for this optional treatment arm will not exceed 7000 mg and may include 175 mg.

Infusion information may be found in the pharmacy manual.

The infusion rate may be reduced as deemed necessary if an infusion reaction is observed (Section 6.1.1.2). Participants will be monitored for at least 2 hours after completion of the infusion.

The site must have resuscitation equipment, emergency drugs and appropriately training staff available during the infusion and for at least 2 hours after the completion of the infusion.

6.1.1. Special Treatment Considerations

6.1.1.1. Premedication for Infusions

Premedication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication.

The investigators and sponsor may decide to use premedication if the frequency of infusion reactions among participants warrants it.

If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants.

The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation.

Any premedications given will be documented as a concomitant therapy.

6.1.1.2. Management of Infusion Reactions

All participants should be monitored closely, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Infusion-related reactions severity will be assessed and reported using the Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

This table describes the severity of reactions according to DAIDS.

Parameter	Mild	Moderate	Severe	Severe and Potentially Life-threatening
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized Urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Cytokine Release Syndrome[a]	Mild signs and symptoms AND Therapy, that is, antibody infusion interruption not indicated	Therapy (that is, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

[a] = A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

Source: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (July 2017).

Site Needs

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

Management of Infusion Reactions

Investigators should determine the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms.

If a participant permanently discontinues from study intervention, they should complete AE monitoring and other procedures as stated in the SoA.

6.1.2. Temporary Stopping Criteria

The Assessment Committee (AC) members individually will review unblinded safety data and meet as described in the AC Charter. The Assessment Committee (AC) will conduct a full safety review before determining if enrollment should be stopped and/or other study parameters should be modified. (see Section 9.6).

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

Topic	Location
DAIDS table describing severity of reactions	Section 6.1.1.2
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.

6.2. 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 an 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

All participants will be centrally randomized to study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Participants will be stratified by duration since symptom onset to randomization (≤8 days versus >8 days).

All eligible participants will be randomized, initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made in an effort to achieve an equal allocation across the treatment arms at the end of enrollment. See Section 9.5 for details.

Blinding

This is a blinded study. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study.

This table describes general procedures for unblinding.

Unblinding (IWRS)	• Emergency unblinding for adverse events may be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS • In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted • Participant safety must always be the first consideration in making such a determination. However, the investigator should make all attempts to contact the Medical Monitor in advance of unblinding • If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance • The date and reason that the blind was broken must be recorded in the source documentation and case report form.

Abbreviations: IWRS = interactive web-response system.

If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion stopped. If any amount of study intervention was administered, follow procedures according to the SoA.

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 will be recorded in the source documents and recorded 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 staff other than the person administering the study intervention.

6.5. Concomitant Therapy

Prior Treatment for Indication

Any prior therapy, such as antivirals, antibiotics, or anti-malarials used as treatment prior to signing informed consent should be recorded.

Therapy prior to enrollment with antivirals including lopinavir/ritonavir, remdesivir, or other therapeutic agents (e.g. corticosteroids) are permitted.

Convalescent COVID-19 plasma treatment is not allowed prior to enrollment.

Concomitant Therapy

Participants should be treated according to standard of care, even as it evolves, and medications may be part of the treatment paradigm. Therefore, remdesivir may be initiated as standard of

care for participants hospitalized with severe disease (if available through the FDA Emergency Use Authorizations) outside of local standard of care per written policies or guidelines.

If the local standard of care per written policies or guidelines (that is, not just an individual clinician decision) includes lopinavir/ritonavir, chloroquine, hydroxychloroquine or other investigational agents, then initiating these during the study is permitted, but may require additional safety monitoring by the site.

Convalescent COVID-19 plasma treatment is not allowed.

Any medication, investigational agent, or vaccine, including over the counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- Reason for use
- Dates of administration including start and end dates, and
- Dosage information including dose and frequency for concomitant therapy of special interest.

Acetaminophen and corticosteroid use are permitted at any time during the study.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the sponsor if required.

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

6.6. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum dose will not exceed 7000 mg or the maximum tolerated dose from PYAA.

6.7. Intervention after the End of the Study

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the trial as a whole are handled as part of regulatory, ethical, and trial oversight considerations in Section 10.1.9.,Appendix 1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If the IV infusion is definitively discontinued, the participant will remain in the study for follow-up and any further evaluations that need to be completed as described in the SoA.

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
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study 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, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study intervention unless there are extenuating circumstances that make it medically necessary for the participant to continue study intervention.

If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently

enrolled participant to continue in the study with or without treatment with investigational product.

Safety follow up is as outlined in

- Section 1.3 (Schedule of Activities)
- 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 they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Protocol waivers or exemptions are not allowed.

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

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

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

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

8.1. Efficacy Assessments

Hospitalization events (Section 8.2.4), procedures of special interest (Section 8.2.5), vital signs (Section 8.2.2) and symptomology (Section 8.1.1) will be used to characterize the effect of LY3819253 compared to placebo on clinical status from baseline to Days 7, 15 and 29.

8.1.1. Symptoms and Overall Clinical Status Participant Questionnaire

Participants will rate their overall clinical status and severity of symptoms associated with COVID-19 by a daily questionnaire. This questionnaire is for outpatients only.

Participants will complete three questions about their overall clinical status daily, including

- severity of symptoms
- general physical health, and
- change in overall health.

The questionnaire contains these symptoms

- cough
- shortness of breath
- feeling feverish
- fatigue
- body aches and pain
- sore throat
- chills
- headache
- loss of appetite, and
- changes in taste and smell.

Each symptom will be scored daily by the participant as experienced during the past 24 hours.

Rating	Score
None or absent	0
Mild	1
Moderate	2
Severe	3

Participants will rate changes in taste and smell with a yes/no response.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will be performed at the screening visit. This examination excludes pelvic, rectal, and breast examinations unless clinically indicated.

A symptom-directed physical examination will be performed at other visits, as specified in the SoA and as clinically indicated.

Investigators should pay special attention to clinical signs related to COVID-19, to ongoing medical conditions and to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will be measured as specified in the SoA and as clinically indicated. Vital signs include

- Body temperature
- Blood pressure
- Pulse rate
- Respiration rate
- Saturation of peripheral oxygen, and
- Supplemental oxygen flow rate, FiO2 if known, and method of delivery, if applicable.

Additional vital signs may be measured during the study if warranted, as determined by the investigator.

8.2.3. Clinical Laboratory Assessments

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

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the dose of study intervention should be repeated until the

values return to normal or baseline or are no longer considered clinically significant by the investigator or sponsor.

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

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.

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

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), report in the AE section of the CRF.

Pregnancy Testing

Women of childbearing potential (WOCBP) must undergo pregnancy testing according to the SoA. Participants who are pregnant will be discontinued from the study.

8.2.4. Hospitalization events

If a participant is admitted to the hospital, the participant will remain in the study and follow the procedures outlined in the SoA. Hospitalization is defined as ≥24 hours of acute care.

The date of hospitalization events will be recorded in the CRF and includes

- hospitalization
- emergency room visit
- ICU admittance
- Extended care facility admittance, and
- Discharge.

8.2.5. Procedures of Special Interest

The participants' clinical status and concurrent procedures of special interest will be recorded in the CRF and include consciousness status using alert, consciousness, verbal, pain, unresponsive scale (ACVPU), limitation on activities due to COVID-19, and requirements for

- ongoing hospital medical care
- supplemental oxygen
- non-invasive ventilation or a high flow oxygen device
- mechanical ventilation
- ECMO, or
- additional organ support (e.g. pressors, renal replacement).

8.2.6. Respiratory Support

Once enrolled in the study, participants may be managed with high-flow nasal cannula, noninvasive positive pressure ventilation or any other form respiratory support as needed per investigator discretion.

8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the participant, or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

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

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 informed consent form (ICF) until participation in study has ended.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event 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 timeframe if it is considered reasonably possibly related to study procedures.

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

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

8.3.2. 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.

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it 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 will be collected for 90 days after dosing.

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, and 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 infusion-related reaction/hypersensitivity CRF.

If symptoms and/or signs occur during or within 6 hours after infusion of LY3819253 and are believed to be hypersensitivity or due to cytokine release, then investigators are encouraged to report the event as infusion-related immediate hypersensitivity reaction or cytokine release-associated infusion reaction, respectively.

Sites should have appropriately trained medical staff 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 the local standard of care.

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.

In case of skin lesions or rash consistent with vasculitis, efforts should be made to perform the following as soon as possible

- dermatology consultation
- skin biopsy, and
- photographs of lesions of interest, including skin biopsy site.

8.3.7. Infusion-related Reactions

As with other mAbs, infusion-related reactions may occur during or following LY3819253 administration. If an infusion-related reaction occurs, additional data describing each symptom and sign should be provided to the sponsor in the CRF.

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

Topic	Location
Special treatment considerations	Section 6.1.1
Premedication for infusions	Section 6.1.1.1
Management of infusion reactions	Section 6.1.1.2
DAIDS table describing severity	Section 6.1.1.2
Treatment guidelines for infusion-related reactions	Section 6.1.1.2

Symptoms occurring during or after infusion of study intervention may also be defined according to AE categories such as acute allergic reaction or cytokine release syndrome (refer to DAIDS).

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.

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

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

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

Time Period for Detecting Product Complaints

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

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to an intervention provided for the study, 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

There is no known antidote for LY3819253 overdose.

In the event of an overdose, the investigator should

1. Contact the sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities
3. Provide supportive care as necessary, and
4. Document the quantity of the excess dose in the CRF.

Decisions regarding infusion interruptions or modifications will be made by the investigator, in consultation with the sponsor, based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

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

A maximum of 3 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 administration (start and end of infusion), 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 participants are not planned.

Sample retention is described in Appendix 1, Section 10.1.12. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

8.6. Pharmacodynamics

The SARS-CoV-2 viral RNA level and viral clearance will be evaluated by nasopharyngeal swabs. See Section 10.2 Clinical Laboratory Tests, and Section 1.3, the SoA for sample collection information.

Sample retention is described in Appendix 1, Section 10.1.12. Remaining samples may be used for additional exploratory studies to better understand LY3819253 and the disease, which may include sequencing and/or culture of the virus for future studies.

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 , the SoA for sample collection information.

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

8.8. Biomarkers

Blood samples will be collected from all participants for analysis of immune system-related markers. Serum, whole blood for cellular and/or epigenetic analysis, and whole blood RNA 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 including, but not limited to, immune pathways, cellular composition, serum analytes, or epigenetic biomarkers, to evaluate their association with observed clinical responses to LY3819253 and the disease state.

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the intervention target (S protein), the COVID-19 disease state, pathways associated with disease, and/or the mechanism of action of the study intervention.

Sample retention is described in Section 10.1.12.

8.9. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA, 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.

Sample collection, handling, and use

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

Immunogenicity may be assessed by 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 Appendix 1, Section 10.1.12.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

9.2. Sample Size Determination

The initial planned sample size is approximately 400 participants equally allocated across four treatment arms. Up to 100 additional participants may be introduced either for a new dose level or an addition to an existing treatment arm based on planned interim analyses. See Section 9.5 for interim analysis details.

Participants will be stratified by duration since symptom onset category (≤8 days versus >8 days).

A viral dynamic model was used to simulate viral loads over time for participants treated with LY3819253 and placebo. This simulated population and Monte Carlo methods were used to estimate statistical power associated with the comparison of Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load between LY3819253 and placebo. The mean log change from baseline to Day 11 for LY3819253 and placebo in the simulated population were approximately -4.38 and -3.48 (standard deviation 1.9), respectively, representing an average of 87% viral load reduction.

Given these assumptions, an assumed sample size of 100 participants per arm provides approximately 91% power to test superiority of an LY3819253 vs placebo in effect on viral load, as measured by change from baseline to Day 11 (± 4 days), at the two-sided 0.05 alpha level.

Periodic adjustments to the allocation ratio of participants will be informed by planned interim analyses. See Section 9.5 for details.

9.3. Populations for Analyses

This table defines the populations for analysis.

Population	Description
Entered	All participants who sign the informed consent form
Efficacy	All randomized participants who received study intervention and provided at least one post-baseline measure for the relevant endpoint. Participants will be analyzed according to the intervention to which they were randomized. (Intention to treat).
Safety	All participants randomly assigned and who received study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic	All randomized participants who received study intervention and have evaluable PK sample. Participants will be analyzed according to the intervention they received.

9.4. Statistical Analyses

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

Unless otherwise specified, treatment effects will be conducted using 2-sided tests at an alpha level of 0.05. No adjustment for multiplicity will be performed in this study.

Details of the handling of dropouts or missing data will be fully described in the statistical analysis plan (SAP).

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. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to the first final database lock (i.e., first unblinding of the sponsor), 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 secondary endpoints.

9.4.1. General Considerations

This table describes the general statistical methods that may be used in this study.

Method	**Analysis**
Descriptive Statistics	number of participants, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures
Kaplan-Meier curves and summary statistics	Treatment comparisons of time-to-event based endpoints
Logistic regression analysis	Treatment comparisons of binary variables with treatment and randomization stratification variables in the model.
Nonparametric (for example, Mann-Whitney or van Elteren tests)	Treatment comparison of ordinal, nominal and non-normally distributed continuous variables.

Additional statistical methodology, sensitivity analyses accounting for missing data, and adjustments for covariates, if any, will be described in the SAP.

9.4.2. Primary Endpoints

Primary endpoint is the change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load. Statistical hypothesis testing for the primary endpoint will be conducted using a mixed model repeated measure (MMRM) analysis method at the two-sided 0.05 level. Full details will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Safety

Safety analyses will be conducted using the safety population described above.

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 intervention as perceived by the investigator. Adverse events reported prior to randomization will be distinguished from those reported as new or increased in severity during the study post-randomization.

Safety parameters that will be assessed include, but are not limited to, safety laboratory parameters, and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.4.3.2. Additional Secondary Endpoints

Endpoints will include

- Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤8 days of symptoms prior to randomization
- Time to symptom resolution
    - symptoms are scored as absent
- Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22
- Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22
- Time to symptom improvement
    - symptoms scored as moderate or severe at baseline are scored as mild or absent, AND
    - symptoms scored as mild or absent at baseline are scored as absent.
- Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22
- SARS-CoV-2 viral load and viral clearance including:
    - Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 15, and 22)
    - Time to SARS-CoV-2 clearance
    - SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed at Day 29
- Proportion (percentage) of participants who experience these events by Day 29
    - COVID-19 related hospitalization (defined as ≥ 24 hours of acute care)
    - a COVID-19 related emergency room visit, or
    - death.

Full details of the analyses will be in the SAP.

9.4.3.3. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on data from all participants who receive intervention and have evaluable PK.

The PK data may be analyzed using a population modeling approach via a nonlinear mixed-effects modeling (NONMEM) program, if deemed necessary.

9.4.4. Exploratory Analyses

Full details of the planned exploratory analyses will be described in the SAP.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety, pharmacodynamic, or population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

9.4.5. Immunogenicity Analyses

If data from validated immunogenicity assays are available, treatment-emergent anti-drug antibodies (TE-ADAs) may be assessed.

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADA and who are TE-ADA positive (TE-ADA+) to LY3819253 will be tabulated.

The distribution of titers and frequency of neutralizing antibodies (if assessed) for the TE-ADA+ participants may also be tabulated.

The relationship between the presence of antibodies and PK parameters, efficacy response or safety to LY3819253 may also be assessed. Additional details may be provided in the SAP.

9.4.6. Subgroup Analyses

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

Subgroup analyses will be conducted for the primary endpoint. Subgroups may include

- time of symptom onset to study consent
- baseline severity of COVID-19
- age
- sex
- race
- ethnicity, and
- geographic region.

Treatment group differences will be evaluated within each category of the subgroup regardless of whether the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided, that is, no inferential testing.

Definitions for the levels of the subgroup variables, the analysis methodology, and any additional subgroup analyses will be defined in the SAP.

9.5. Interim Analyses

The ongoing study may be modified based on planned interim analyses. Based on the observed data at the time of the interim analyses, the study may

- suspend enrollment to an LY3819253 treatment arm (or arms) demonstrating lack of efficacy, and/or
- initiate/expand enrollment to an additional/existing LY3819253 treatment arm (or arms).

The modifications proposed are done so to ensure participants are being exposed to treatment with an acceptable risk-benefit profile during the ongoing trial. Additionally, the potential modifications will provide information to more fully characterize the dose response profile.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by Assessment Committee (AC) members. Details of the unblinded safety reviews, including the frequency and approximate timing, are specified in the AC charter.

The approximate timing, decision criteria, and statistical methods associated with each possible modification to the ongoing trial will be fully described in the SAP and AC Charter and finalized prior to the first study unblinding.

Periodic adjustments to the allocation ratio may be made to achieve an equal allocation treatment arms at the conclusion of enrollment.

Only the AC is authorized to evaluate unblinded interim analyses and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.6. Data Monitoring Committee (DMC)

The sponsor will form an AC to analyze the interim study data. To minimize any bias introduced into the analysis of the study results, analysis plans will be finalized and approved prior to the interim analyses.

The primary goal of the AC is to review the interim results regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

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

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

10.1.2. Financial Disclosure

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

10.1.3. 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 (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

Due to strict respiratory isolation policies, limited access to COVID-19 patient rooms, and SARS-CoV-2 transmissibility via droplet-contaminated paper, verbal consent and alternative methods of obtaining consent (for example, by phone) will be allowed if approved by the IRB.

If a signed paper copy of the ICF is allowed by site/institution policy, then the process of how it will be obtained and stored will need to be determined.

Any variation from the standard consent process due to isolation and infection control should be sent to the IRB for approval prior to enrollment. The site will document the process in their regulatory files and demonstrate that the process has IRB concurrence or approval.

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.

10.1.4. Data Protection

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

The participant must be informed that 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.

10.1.5. Committees Structure

The AC will consist of members internal and external to the sponsor. The membership will include, at a minimum, a chair external to Lilly, a statistician and two physicians. The AC members will not have data entry/validation responsibilities or direct contact with the site(s) or testing facilities.

10.1.6. Dissemination of Clinical Study Data

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

10.1.7. Data Quality Assurance

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 (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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 and 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 (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents. 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.

If on-site monitoring activities cannot occur, alternative measures will be used. Examples of alternative measures are use of technology for off-site monitoring or providing pseudonymized

copies of source documents to the monitor electronically. The remote source data verification will be focused on critical efficacy data and important safety data.

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 (CTA) unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

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 Sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

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

Data reported on the CRF 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 10.1.7.

10.1.9. Study and Site Start and Closure

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

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.

10.1.10. Publication Policy

In accordance with the sponsor’s publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.11. Investigator Information

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

10.1.12. Long-Term Sample Retention

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

This table describes the retention period for potential sample types.

Sample Type	Custodian	Retention Period After Last Participant Visit
Pharmacodynamic Samples	Sponsor or designee	up to 7 years
Pharmacogenetics sample	Sponsor or designee	up to 7 years
Exploratory Biomarker Samples	Sponsor or designee	up to 7 years
Immunogenicity (ADA) sample	Sponsor or designee	up to 7 years
Pharmacokinetic (PK) sample	Sponsor or designee	up to 2 years

10.2. Appendix 2: Clinical Laboratory Tests

Clinical laboratory tests will be performed according to the SoA.

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

Central and local laboratories will be used. The table below describes when the local or central laboratory will be used.

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

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

Pregnancy testing will be performed according to the SoA.

Investigators must document their review of each laboratory safety report.

Refer to Section 10.6 for recommended laboratory testing for hypersensitivity events.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - Red Blood Cells)	
Mean cell volume	
Mean cell hemoglobin	
Leukocytes (WBCs - White Blood Cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell Morphology (RBC and WBC)	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Amylase	
Lipase	
Lactate dehydrogenase (LDH)	
Calculations	
eGFR	Calculated by CKD-EPI equation. Results will not be provided to the investigative sites.

Clinical Laboratory Tests	Comments
SARS-CoV-2 viral infection determination	Local laboratory and/or Point-of-Care testing
SARS-CoV-2 Test Panel	Assayed by Lilly-designated laboratory.
C-reactive protein (CRP); high-sensitivity	
Ferritin	
D-dimer	
Procalcitonin	
Troponin	
Hormones (female)	
Urine Pregnancy	Local laboratory
Serum Pregnancy	Local laboratory
Pharmacokinetic Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Pharmacodynamic sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
SARS-CoV-2 nasopharyngeal swab	
Pharmacogenetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory Biomarker Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
RNA (PAXGene)	
Whole Blood (EDTA)	
Whole Blood (EDTA) Epigenetics	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3819253 antibodies	
Anti-LY3819253 antibodies neutralization	

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

10.3.1. Definition of AE

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

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

Events NOT Meeting the AE Definition

• The following study-specific clinical events related to COVID-19 are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug:
  ○ Hypoxemia due to COVID-19 requiring supplemental oxygen;
  ○ 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, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories, which together with serious (i.e., SAE) criteria on the AE CRF ("results in death" and "life-threatening"), are aligned with the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 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 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 an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in site training documents.

SAE Reporting via Paper CRF

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

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

Women

Woman of Childbearing Potential (WOCBP)

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

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

Woman not of Childbearing Potential (WOCBP)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with either
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy, or
    c. Documented bilateral oophorectomy.

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

Note: Determination 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:
    a. 12 months of amenorrhea for women >55, with no need for FSH
    b. 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that induced amenorrhea)

Participation in the Study

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

Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at the screening visit.

Women of child-bearing potential who are completely abstinent or in a same sex relationship, as part of their preferred and usual lifestyle, must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.

All other women of child-bearing potential must agree to use two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study.

Abstinence or contraception must continue for 90 days after the last dose of intervention.

Acceptable Methods of Contraception

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

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

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

Not Acceptable Methods of Contraception

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

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

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

Men

Men, regardless of their fertility status, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective method of contraception (less than 1% failure rate) or effective method of contraception with non-pregnant women of child bearing 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 90 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 90 days after the last dose.

Acceptable Methods of Contraception

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

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

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

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

Other Guidance

Men should refrain from sperm donation 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 90 days after the last dose.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

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

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

Female Participants who become pregnant

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

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

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

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

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

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study and will follow the standard discontinuation process.

10.5. Appendix 5: Genetics

Sample collection information is found in Appendix 2, Section 10.2 (Clinical Laboratory Tests).

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples 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 one or more candidate genes or the analysis of genetic markers throughout the genome as appropriate.

The samples may be analyzed as part of a multi-study 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 (CSR) or in a separate study summary.

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

The samples will be retained at a facility selected by the sponsor or its designee while research on SARS-CoV-2 continues but no longer than 7 years or other period as per local requirements.

10.6. Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events.

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

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

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: ADA = anti-drug antibody; IgE = immunoglobulin E; PK = pharmacokinetic.

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

Close Hepatic Monitoring

This table describes when close hepatic monitoring should occur.

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

The laboratory tests listed in Appendix 2, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine whether it is increasing or decreasing.

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

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

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

Comprehensive Hepatic Evaluation

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

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

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

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

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

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

Additional Hepatic Data Collection (Hepatic Safety CRF)

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants who either have a hepatic event considered to be an SAE or meet 1 or more of these conditions:

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

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

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

Hepatic Evaluation Testing

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

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

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

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin

Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [b]	Anti-actin antibody [c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

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

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

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

10.8. Appendix 8: Abbreviations

Term	Definition
AC	assessment committee
ADA	anti-drug antibody
ADE	antibody-dependent enhancement
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
CIOMS	Council for International Organizations of Medical Sciences
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 an intervention.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
DMC	data monitoring committee
ECG	electrocardiogram
FiO2	fraction of inspired oxygen in the aire
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.
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product

Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
intervention	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.
IWRS	interactive web-response system
NP	nasopharyngeal
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/PD	pharmacokinetics/pharmacodynamics
SAE	serious adverse event
SAP	statistical analysis plan
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.
SpO2	saturation of peripheral oxygen

11. References

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Approver: PPD

Approval Date & Time: 30-May-2020 03:11:33 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 30-May-2020 17:35:31 GMT

Signature meaning: Approved

Title Page

Protocol Title:

A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness

Protocol Number: J2W-MC-PYAB

Amendment Number: b

Compound(s): LY3819253, LY3832479

Study Phase: 2

Short Title: A randomized, double-blind, placebo-controlled, Phase 2 study to evaluate LY3819253 and LY3832479 in participants with mild to moderate COVID-19 illness

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 150440

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

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

Amendment b

Overall Rationale for the Amendment:

A new treatment is added to this study with the combination of LY3819253 and LY3832479.

Section # and Name	Description of Change	Brief Rationale
Title Page	Change in study title	Updated text for the addition of LY3832479
1.1 Synopsis	Updated text to match the body of the protocol. • Rationale • Objectives and endpoints table • Design Outline • Number of participants • Intervention Groups and Duration - moved treatment group table here and updated content.	Updated text for the addition of LY3832479 and new combination treatment arm. Moved information to more appropriate section.
1.2 Schema	Updated Schema and removed footnote that was no longer correct	Addition of new combination treatment arm
1.3 Schedule of Activities	Visit 3 visit window changed to +1	To avoid the possibility of too many blood draws for the participant
1.3 Schedule of Activities	Added assessment on Day 85 for participant questionnaire and instructions for Day 1	Needed to meet clinical status endpoint
2.0 Introduction	Updated text	For the addition of LY3832479
2.1 Study Rationale	Updated text	For the addition of LY3832479
2.2 Background	Updated text	For the addition of LY3832479
2.3 Benefit/Risk Assessment	Updated text	For the addition of LY3832479and availability of new data
3 Objectives and Endpoints	Objectives were restructured to add text for the combination with LY3832479	For the addition of LY3832479
3 Objectives and Endpoints	Changed SARS-CoV-2 viral load area under the concentration-time curve to area under the response-time curve	Correction
3 Objectives and Endpoints	Updated PK objective and endpoints	For the addition of LY3832479

Section # and Name	Description of Change	Brief Rationale
4.1.1 Design outline	Updated text, moved text around and updated the treatment table	Moved text for better flow of information. Updated text and table for the addition of the new combination treatment.
4.2 Scientific Rationale for Study Design	Updated text	Addition of new combination treatment
4.3 Justification for Dose	Text was rearranged and added for LY3819253. New text added for LY3832479.	Addition of new combination treatment and availability of new data for LY3819253
6.1 Study Intervention(s) Administered	Text was rearranged for LY3819253. New text added for LY3832479.	For the addition of LY3832479
6.3 Measures to Minimize Bias: Randomization and Blinding	Added new text for additional placebo participants	Addition of new combination treatment and optional treatment arms
6.6 Dose Modification	New text added for LY3832479	For the addition of LY3832479
8.1 Efficacy Assessments	Updated text	Addition of new combination treatment arm
8.1 Efficacy Assessments	Added Day 11	Per objective endpoints
8.2.2 Vital Signs	Added clarifying text before table and text in table	Clarifying the collection timepoints because the infusion times may vary
8.3.6 Hypersensitivity Reactions	Removed LY3189253-specific text	For the addition of LY3832479
8.3.7 Infusion-related Reactions	Removed LY3189253-specific text	For the addition of LY3832479
8.4 Treatment of Overdose	Updated text	For the addition of LY3832479
8.5 Pharmacokinetics	Updated text	For the addition of LY3832479
8.5.1 Bioanalytical	Updated text	For the addition of LY3832479
8.6 Pharmacodynamics	Updated text	For the addition of LY3832479
8.8 Biomarkers	Updated text	For the addition of LY3832479
8.9 Immunogenicity Assessments	Updated text	For the addition of LY3832479
9.2 Sample Size Determination	Updated text	Addition of new treatment arms
9.4.3.3 Pharmacokinetic Analyses	Updated text	Details of the analyses added.
9.4.4 Exploratory Analyses	Updated text	Clarifications provided
9.4.5 Immunogenicity Analyses	Updated text	For the addition of LY3832479
9.5 Interim Analyses	Updated text	For the addition of the new treatment arms
10.1.7. Data Quality Assurance, Data Capture System	Added text for symptom assessment direct entry into EDC	To provide flexibility for data entry into the EDC

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2 Clinical Laboratory Tests	Removed eGFR calculation	Not needed.
10.2 Appendix 2 Clinical Laboratory Tests	Updated pharmacokinetic and immunogenicity samples	For the addition of LY3832479
10.5 Appendix 5 Genetics	Updated text	For the addition of LY3832479
10.6 Appendix 6 Recommended Laboratory Testing for Hypersensitivity Events	Updated table	For the addition of LY3832479
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness

Rationale:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the pandemic spread of coronavirus disease 2019 (COVID-19), which in critical cases results in progressive pulmonary failure, complications with acute respiratory distress syndrome (ARDS), and death. There is an urgent need for effective therapeutics to modify disease outcomes.

LY3819253 and LY3832479 are neutralizing IgG1 monoclonal antibodies (mAb) to the spike protein of SARS-CoV-2. They are designed to block viral attachment and entry into human cells, and to neutralize the virus, potentially treating even established COVID-19 by providing a combination of specific, potent, neutralizing antibodies to SARS-CoV-2.

This study aims to evaluate the impact of LY3819253 and LY3832479 on viral clearance and clinical outcomes in participants with COVID-19 illness. The data from this study will inform decisions for the clinical development of LY3819253 and LY3832479.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on SARS-CoV-2 viral load and viral clearance	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load
Secondary The secondary objectives are to characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on…	
• safety	• Safety assessments such as AEs and SAEs
• SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
• symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22

	• Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22
• SARS-CoV-2 viral load and viral clearance	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15 and 22) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 29, 60 and 85 o COVID-19 related hospitalization (defined as ≥24 hours of acute care) o a COVID-19 related emergency room visit, or o death
Additional Secondary	
Characterize the pharmacokinetics of LY3819253 and LY3819253 in combination with LY3832479	• Mean concentration of LY3819253 and LY3819253 in the presence of LY3832479 on Day 29 • Mean concentration of LY3832479 in the presence of LY3819253 on Day 29

Abbreviations: AE = adverse event; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Overall Design:

This is a Phase 2, randomized, double-blind, placebo-controlled, single-dose study in participants with mild to moderate COVID-19 illness.

Design Outline

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures.

The investigator will review symptoms, risk factors and other non-invasive inclusion and exclusion criteria prior to any invasive procedures. If the participant is eligible after this review, then the site will perform the invasive procedures to confirm eligibility.

Double-blind Treatment and Assessment Period

This is the general sequence of events during the treatment and assessment period:

- Complete baseline procedures and sample collection
- Participants are randomized to an intervention group
- Participants receive study intervention, and
- Complete all safety monitoring and post-infusion sample collection.

This table describes the visit types for this study.

Study Day	**Visit Type**
1	site
2, 4, 5, and 6	telephone
3, 7 – 29	may be conducted as outpatient clinic or home visits
Early discontinuation and follow-up	may be conducted as outpatient clinic or home visits

If a participant is hospitalized, procedures and assessments will continue per the SoA.

This table describes discharge from hospital scenarios if an outpatient is subsequently hospitalized.

Discharge from hospital (Outpatients Subsequently Hospitalized)

If hospital discharge…	**Then…**
Occurs prior to Day 29	participants will be asked to complete the remaining study assessments at the timepoints indicated in the SoA. NOTE: Strategies to manage infection risks and reduce the burden of return visits should be used by sites, such as home visits.
Occurs on the same day as a study assessment visit	assessments do not need to be repeated if the study assessments occurred within 8 hours of discharge and there has been no change in clinical status and the information is available to the site.
Does not occur at or prior to Day 29	assessments will continue to occur weekly up to Day 60 or until hospital discharge, whichever is sooner.

Post-treatment follow-up

Post-treatment follow-up assessments will be conducted at Day 60 and Day 85 to assess clinical status and for adverse events. Strategies to manage infection risks and reduce the burden of return visits may be used by sites, such as home visits.

Disclosure Statement: This is a treatment study that is participant and investigator blinded.

Number of Participants:

Approximately 500 participants equally allocated across five treatment arms. Up to 350 additional participants may be introduced either for a new dose level or to increase the size of an existing treatment arm based on planned interim analyses or at the discretion of the sponsor.

Intervention Groups and Duration:

This table describes the planned treatment arms.

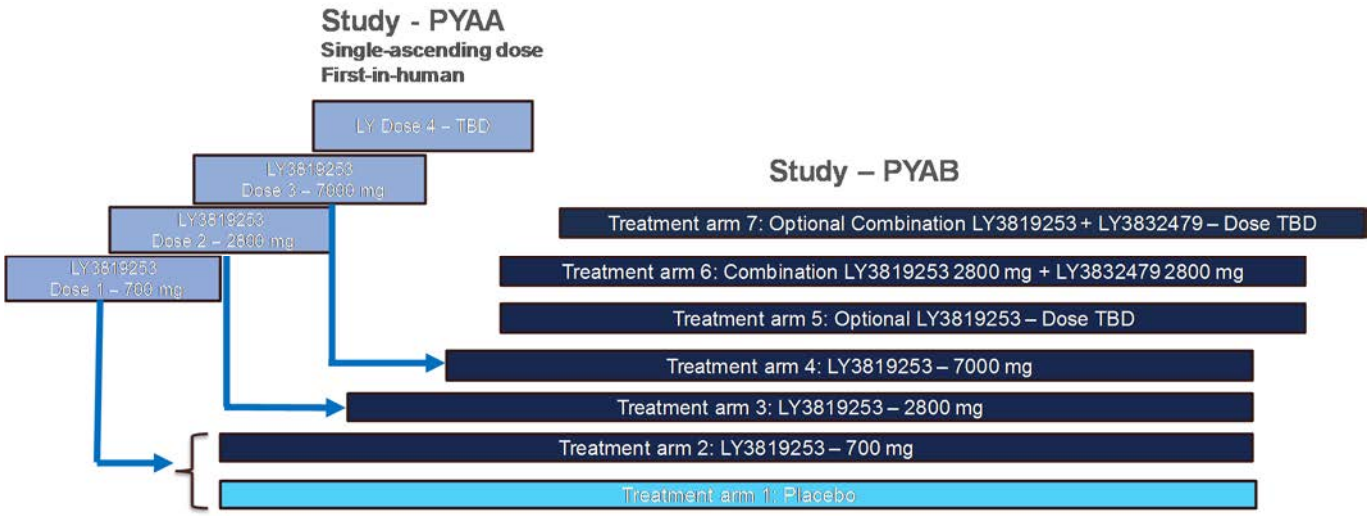
Treatment arms	Dose	Intervention
1	---	placebo
2	700 mg	LY3819253
3	2800 mg	LY3819253
4	7000 mg	LY3819253
Optional 5	To Be Determined	LY3819253
6	2800 mg + 2800 mg	LY3819253+LY3832479
Optional 7	To Be Determined	LY3819253+LY3832479

The optional LY3819253 treatment arm 5 may be added based on interim analysis results. The optional combination treatment arm 7 may be initiated at the discretion of the sponsor.

Participants will receive a single IV infusion, assessments occur to Day 29 and follow-up to Day 85.

Data Monitoring Committee: Yes, there will be an assessment committee.

1.2. Schema



Abbreviations: LY = Lilly study intervention; PYAA = J2W-MC-PYAA; PYAB = J2W-MC-PYAB; TBD = to be determined.

Figure 1. Study J2W-MC-PYAB schema

1.3. Schedule of Activities (SoA)

Assessments obtained previously as part of routine clinical care may be used as the baseline assessment if they were done no more than 48 hours before randomization. Visits may be conducted as a telephone call, outpatient clinic or home visit, as long as the protocol SoA is followed.

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Procedures																	
Informed Consent	X																
Inclusion and exclusion criteria review	X																
Demographics	X																Including age, gender, race, ethnicity
Preexisting conditions and medical history	X																Obtained from interview or available information.

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
																	Includes: timing of exposure and onset of symptoms suggestive of SARS-CoV-2 infection, and risk factors and comorbidities associated with severe COVID-19 illness, such as living in a nursing home or long-term care facility.
Height		X															
Weight		X															
Prior treatments of special interest within the last 30 days	X																NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or other investigational treatments.
Tobacco use	X																
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3.

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Physical Evaluation or Clinical Assessments																	
Physical examination	X																
Symptom-directed physical exam				X								X	X				As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations.
Vital signs	X	X		X		X	X	X	X	X	X	X	X	X	X	X	Documentation of hospital-based exam is acceptable. Includes: body temperature, pulse rate, BP, respiratory rate, SpO2, and supplemental oxygen flow rate, FiO2 if known, and method of delivery, if applicable. Record SpO2 while participant is at rest. **Screening visit only**: SpO2 while breathing room air. Data not collected on CRF.

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
																	Day 1 timing: • immediately before the infusion • every 15 minutes during the infusion, as possible, and • every 30 minutes for 2 hours after the infusion. During infusion, only record pulse rate, BP and SpO2. Automation may be used. See Section 8.2.2 for data collected on CRF. **All other study days:** once daily.
Hospitalization events		Daily											X	X	X	X	Record if the following events occur: • Emergency room visits • hospitalized • ICU admittance, • Extended care facility admittance, and • discharge

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Clinical status and concomitant procedures if participant is hospitalized			Daily if hospitalized										X	X			Documentation from hospital records is acceptable. Includes: consciousness status (ACVPU), limitation on activities due to COVID-19, and requirements for • Ongoing hospital medical care • Supplemental oxygen • Non-invasive ventilation or high flow oxygen device • Mechanical ventilation • ECMO, or • Additional organ support (e.g. pressors, renal replacement).
Laboratory Tests and Sample Collection																	

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Hematology		X		X				X				X	X				Day 1: before IV infusion All other days: sample may occur at any time during the day No samples needed if participant is hospitalized Lilly-designated central laboratory
Clinical Chemistry		X		X				X				X	X				Day 1: before IV infusion All other days: sample may occur at any time during the day No samples needed if participant is hospitalized Lilly-designated central laboratory
• C-reactive protein (CRP); high - sensitivity • Ferritin • D-dimer • Procalcitonin • Troponin		X		X				X				X	X				Day 1: before IV infusion All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Documentation of positive SARS-CoV-2 viral infection	X																Sample for first positive test must be collected within 3 days prior to start of infusion. Local laboratory and/or Point-of-Care testing.
Urine or serum pregnancy	X														X	X	Only for WOCBP (Section 10.4 Appendix 4) Local laboratory
Pharmacokinetic (PK) sample		X						X				X	X		X	X	Day 1: before IV infusion and anytime just prior to the end of infusion. All other scheduled samples may occur at any time during the day. No samples needed if participant is hospitalized. Lilly-designated central laboratory

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Immunogenicity (ADA) sample		X						X				X	X		X	X	Day 1: collect before IV infusion. All other scheduled and unscheduled immunogenicity samples should be collected with a time-matched PK sample. No samples needed if participant is hospitalized Lilly-designated central laboratory
Pharmacodynamic (PD) NP swab		X		X		X	X	X	X	X	X	X	X				Swab is taken from both nostrils. Day 1: swab before IV infusion. No samples needed if participant is hospitalized Lilly-designated central laboratory
Exploratory biomarker samples		X		X				X				X	X				Day 1: before IV infusion. No samples needed if participant is hospitalized Lilly-designated central laboratory
Pharmacogenetics sample		X															Lilly-designated central laboratory

Study J2W-MC-PYAB	**Screen**	**Double-blind treatment and assessments**											**ED**	**Follow-up if inpatient in hospital on Day 29**	**Post-treatment follow-up**		**Comments**
Study Day		**1**	**2***	**3**	**4-6 ***	**7**	**11**	**15**	**18**	**22**	**25**	**29**		Every 7 days until discharge or Day 60	**60**	**85**	Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
Randomization and Dosing																	
Randomization		X															
Administer study intervention (IV infusion)		X															Study intervention must be administered within 3 days from the time of first positive SARS-CoV-2 test sample collection. For participants that receive dialysis on the same day as the IV infusion, complete dialysis first followed by the IV infusion. Participants will be monitored for at least 2 hours after completion of the infusion.
Participant Questionnaire																	
Symptoms and overall clinical status		Daily on Days 1-29 for outpatients only											X		X	X	Day1: assess prior to dosing

Abbreviations: ACVPU = alert, consciousness, verbal, pain, unresponsive scale; ADA = anti-drug antibody; BP = blood pressure; ECMO = extracorporeal membrane oxygenation; ED = early discontinuation visit; FiO2 = fraction of inspired oxygen in the air; ICU = intensive care unit; IV = intravenous; NP = nasopharyngeal; NSAIDS = non-steroidal anti-inflammatory drugs; SpO2 = saturation of peripheral oxygen; WOCBP = women of child-bearing potential.

2. Introduction

The efficient community spread of SARS-CoV-2 has resulted in the current pandemic of COVID-19, which in severe and critical cases results in progressive pulmonary infection, complicated by respiratory failure, with a high prevalence of acute respiratory distress syndrome. Although several therapies have been explored in severe COVID-19, none have improved survival, including antivirals, glucocorticoids, and immunoglobulins (Liu et al 2020).

The SARS-CoV-2 gains entry to cells through binding of the spike (S) protein to ACE2 receptors on cells (Hoffmann 2020). Eli Lilly and Company has a partnership with AbCellera Biologics Inc. (AbCellera; Vancouver, Canada) to develop neutralizing IgG1 monoclonal antibodies (mAbs) to the Spike (S) protein of SARS-CoV-2 as a potential treatment for COVID-19. Candidate antibody gene sequences have been selected from a recently recovered COVID-19 United States patient's serum using AbCellera's core platform screening technologies.

LY3819253 and LY3832479 are neutralizing IgG1 monoclonal antibodies (mAb) to the spike protein of SARS-CoV-2. They are designed to block viral attachment and entry into human cells, and to neutralize the virus, potentially treating even established COVID-19 by providing a combination of specific, potent, neutralizing antibodies to SARS-CoV-2. The blocking of viral entry into respiratory cells and viral replication, and viral neutralization is expected to mitigate the severity of disease in patients in whom ongoing viral spread and replication is the primary driver of COVID-19 pathophysiology. The decrease in viral replication may also shorten a patient's extent and duration of viral shedding and transmission, positively impacting public health.

2.1. Study Rationale

This study aims to evaluate the impact of LY3819253 and LY3819253 in combination with LY3832479 on viral clearance and clinical outcomes in participants with mild to moderate COVID-19 illness. The data from this study will inform decisions for the clinical development of these neutralizing IgG1mAbs.

2.2. Background

Nonclinical information for LY3819253 and LY3832479 are described in each respective Investigator's Brochure (IB).

Lilly is evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3819253 in participants hospitalized for COVID-19, in a randomized, placebo-controlled, double-blind, single ascending dose, Phase 1, first in human study (Study J2W-MC-PYAA [PYAA]). Study PYAA started prior to this study and informed the dose levels administered in Study PYAB.

Lilly is evaluating the safety, tolerability, PK, and immunogenicity of LY3832479 in healthy participants, in a randomized, placebo-controlled, single dose, Phase 1 study (Study J2Z-MC-PGAA [PGAA]) under IND 150707. Concurrent with Study PGAA, LY3832479 is also under development in China in an ongoing Phase 1 clinical study in healthy participants, Study JS016-001-I. Both studies have started prior to this amendment.

2.3. Benefit/Risk Assessment

Information on the safety and tolerability of LY3819253 in humans will come from Study PYAA. All available study data will be reviewed before that dose is administered in Study PYAB.

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 and LY3832479 consist of highly specific mAbs directed at foreign (non-human) epitope(s). The complementarity determining regions (CDRs) of the mAbs were derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient and, thus, have undergone natural positive and negative selection pressures *in vivo*, unlike humanized antibodies generated in mice. No clinically relevant off-target binding has been observed in tissue cross reactivity studies of membrane targets in human tissues. Therefore, off-target binding and tissue cross-reactivity are considered unlikely.

A theoretical risk is that these interventions may cause antibody-dependent enhancement (ADE) of viral replication. This is based on responses observed to some monoclonal antibody therapies used in other unrelated viral diseases. To address this risk, LY3819253 and LY3832479 have been assessed with *in vitro* cell culture models and, for LY3819253, an *in vivo* nonhuman primate model.

The risk of clinical ADE for either intervention or in combination is considered low due to

- the structural features of LY3832479, which is engineered to suppress its binding to Fc receptors and C1qm
- the absence of ADE from in vitro studies, and
- the absence of ADE from in vivo nonhuman primate studies for LY3189253.

LY3819253 will also be administered to participants at sufficiently high dose levels to neutralize SARS-CoV-2 and avoid sub-neutralizing concentrations in the presence of virus that are typically associated with ADE.

Additional manageable risks associated with most therapeutic monoclonal antibodies are the potential for infusion-related hypersensitivity and cytokine release reactions. The infusions in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made and/or the infusion stopped, if indicated. Additional information regarding infusion reaction management options is in Section 6.1.1.

Given the data on LY3819253 and LY3832479, the well described safety profile of other therapeutic mAbs, and the lack of disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment this study is considered favorable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3819253 and LY3832479 may be found in each respective IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on SARS-CoV-2 viral load and viral clearance	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load
Secondary The secondary objectives are to characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on…	
• safety	• Safety assessments such as AEs and SAEs
• SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
• symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22 • Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22
• SARS-CoV-2 viral load and viral clearance	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15 and 22) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 29, 60 and 85 o COVID-19 related hospitalization (defined as ≥24 hours of acute care) o a COVID-19 related emergency room visit, or o death
Additional Secondary	

Objectives	Endpoints
Characterize the pharmacokinetics of LY3819253 and LY3819253 in combination with LY3832479	• Mean concentration of LY3819253 and LY3819253 in the presence of LY3832479 on Day 29 • Mean concentration of LY3832479 in presence of LY3819253 on Day 29
Exploratory The exploratory objectives are to characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on…	
• SpO2 over time	• SpO2 AUC assessed through Day 29
• symptom severity	• Symptom severity as assessed by mean AUC through Day 29 of symptom questionnaire
• overall improvement using the NIAID ordinal scale	• Comparison of the mean worst daily NIAID ordinal eight-point scale values at Days 7, 11, 15 and 22
Additional Exploratory	
Characterize emergence of viral resistance to LY3819253 and LY3819253 in combination with LY3832479	• Comparison from baseline to the last evaluable time point up to Day 29

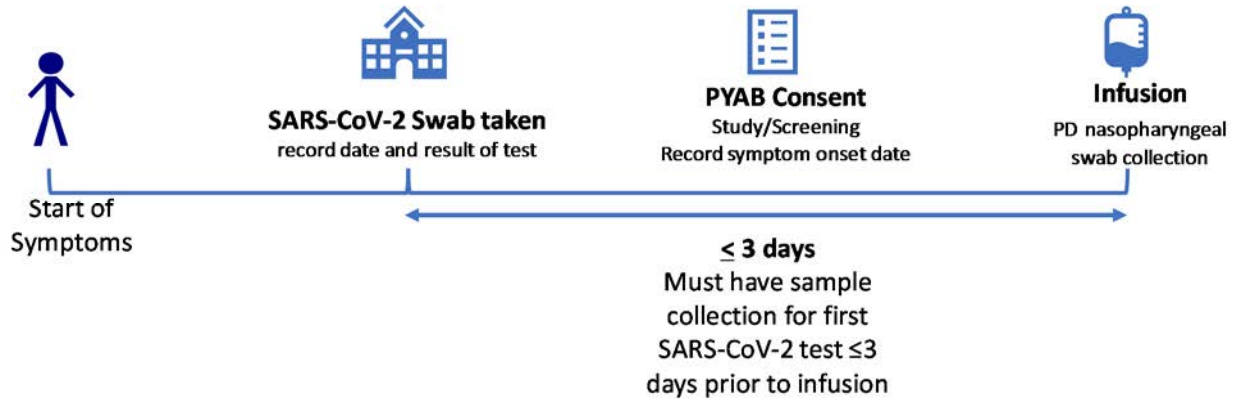
Abbreviations: AE = adverse event; NIAID = National Institute of Allergy and Infectious Diseases; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = saturation of peripheral oxygen.

4. Study Design

4.1. Overall Design

This is a Phase 2, placebo-controlled, double-blind, randomized single-dose study in participants with mild to moderate COVID-19 illness.

4.1.1. Design Outline



Abbreviations: PD = pharmacodynamic; PYAB = Study J2W-MC-PYAB.

Figure 2. Overview of participant flow from time of SARS-CoV-2 symptoms to IV infusion.

Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures. The participant may enter the study with a previous positive SARS-CoV-2 viral test result from an external testing facility. This test result must be the first time the patient has tested positive for SARS-CoV-2.

The investigator will review symptoms, risk factors and other non-invasive inclusion and exclusion criteria prior to any invasive procedures. If the participant is eligible after this review, then the site will perform the invasive procedures to confirm eligibility.

Double-blind Treatment and Assessment Period

This is the general sequence of events during the treatment and assessment period:

- Complete baseline procedures and sample collection
- Participants are randomized to an intervention group
- Participants receive study intervention, and
- Complete all safety monitoring and post-infusion sample collection.

This table describes the planned treatment arms.

Treatment arms	Dose	Intervention
1	---	placebo
2	700 mg	LY3819253
3	2800 mg	LY3819253
4	7000 mg	LY3819253
Optional 5	To Be Determined	LY3819253
6	2800 mg + 2800 mg	LY3819253+LY3832479
Optional 7	To Be Determined	LY3819253+LY3832479

As LY3819253 dose levels in Study J2W-MC-PYAA (PYAA) are determined to be safe, treatment arms 2 -4 may be introduced in Study PYAB.

An optional LY3819253-only treatment arm 5 may be added based on interim analysis results. An optional combination treatment arm 7 may be initiated at the discretion of the sponsor.

This table describes the visit types for this study.

Study Day	Visit Type
1	site
2, 4, 5, and 6	telephone
3, 7 – 29	may be conducted as outpatient clinic or home visits
Early discontinuation and follow-up	may be conducted as outpatient clinic or home visits

If a participant is hospitalized, procedures and assessments will continue per the SoA.

This table describes discharge from hospital scenarios if an outpatient is subsequently hospitalized.

If hospital discharge…	Then…
Occurs prior to Day 29	participants will be asked to complete the remaining study assessments at the timepoints indicated in the SoA. NOTE: Strategies to manage infection risks and reduce the burden of return visits should be used by sites, such as home visits.
Occurs on the same day as a study assessment visit	assessments do not need to be repeated if the study assessments occurred within 8 hours of discharge and there has been no change in clinical status and the information is available to the site.
Does not occur at or prior to Day 29	assessments will continue to occur weekly up to Day 60 or until hospital discharge, whichever is sooner.

Post-treatment follow-up

Post-treatment follow-up assessments will be conducted at Day 60 and Day 85 to assess clinical status and for adverse events. Strategies to manage infection risks and reduce the burden of return visits may be used by sites, such as home visits.

4.2. Scientific Rationale for Study Design

Overall Design

This study is designed to evaluate the efficacy of LY3819253 in a range of doses that will inform the clinical drug development plan for LY3819253, and to evaluate the efficacy of the combination of LY3819253 and LY3832479.

The follow-up at Day 85 adequately covers the duration for immune response.

Participant Characteristics

The participant population are those infected with SARS-CoV-2 that have developed symptoms consistent with COVID-19. There is historical evidence that patients infected with upper respiratory viruses who are treated early in their disease course have better responses to anti-viral therapies (Aoki et.al., 2003). This hypothesis will be tested with a focused subgroup analysis on participants who received intervention within 8 days of symptom onset and a virology endpoint (see Section 3).

The population of participants with mild to moderate COVID-19 illness was chosen to evaluate if effective antiviral antibody therapy may prevent progression to the severe form of COVID-19 illness by treating this population early in their disease course and prior to respiratory compromise and failure.

Interim Reviews

The interim safety and efficacy reviews will inform the clinical drug development plan for LY3819253 and the combination of LY3819253 and LY3832479.

4.3. Justification for Dose

LY3819253

The dose levels of LY3819253 administered in this study are informed by Study PYAA. As dose information from Study PYAA are determined to be safe, these dose levels may be added to the study.

The starting dose of 700 mg LY3819253 in Study PYAA is selected based on PK and PK/PD of viral dynamics modeling to have a sustained concentration above the *in vitro* IC90 of viral cell-entry neutralization in the lung tissue for at least 28 days in 90% of the participant population. The maximum dose of 7000 mg is selected due to uncertainty in model predicted PK concentrations, viral load reduction and consideration of infusion volume in participants. The dose will not exceed 7000 mg in this study.

The projected human half-life is expected to be in the 2-4 weeks range.

LY3819253 + LY3832479

To provide coverage of the different but overlapping epitopes on SARS-CoV-2 receptor binding domain sites, the dose selection rationale for each single mAb intervention in the combination is the same as for the dose rationale for a single mAb intervention.

The dose selection of 2800 mg LY3819253 and 2800 mg LY3832479 is based on PK and PK/PD modeling to have a sustained lung concentration above the *in vitro* IC90 of viral cell-entry

neutralization (95th percentile of the estimates used) in the lung tissue for at least 28 days in greater than 90% of the participant population.

The dose levels are fixed, not body weight based. Given the planned dose levels, the predicted impact of body weight on therapeutic response will be minimal.

4.4. End of Study Definition

A participant is considered to have completed the study if they have 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 in the trial globally.

5. Study Population

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

Due to the criticality of participant health, verbal interview of the potential participant, or their legal representative or family member, may be the source for disease characteristics and medical history, unless otherwise specified within the eligibility criteria.

5.1. Inclusion Criteria

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

Age

1. Are ≥18 years of age at the time of randomization

Disease Characteristics

2. Are currently not hospitalized
3. Have one or more mild or moderate COVID-19 symptoms (FDA resource page, Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention)
    i. Fever
    ii. Cough
    iii. Sore throat
    iv. Malaise
    v. Headache
    vi. Muscle pain
    vii. Gastrointestinal symptoms, or
    viii. Shortness of breath with exertion
4. Must have sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of the infusion

Sex

5. Are men or non-pregnant women
   Reproductive and Contraceptive agreements and guidance is provided in Section 10.4, Appendix 4. Contraceptive use by men or women should be consistent with local regulations for those participating in clinical studies.

Study Procedures

6. Understand and agree to comply with planned study procedures
7. Agree to the collection of nasopharyngeal swabs and venous blood

Informed Consent

8. The participant or legally authorized representative give signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

9. Have SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA resource page, WWW)
10. Require mechanical ventilation or anticipated impending need for mechanical ventilation
11. Have known allergies to any of the components used in the formulation of the interventions
12. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
13. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
14. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
15. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.

Other Exclusions

16. Have a history of a positive SARS-CoV-2 serology test
17. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
18. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
19. Have received treatment with a SARS-CoV-2 specific monoclonal antibody
20. Have a history of convalescent COVID-19 plasma treatment
21. Have participated in a previous SARS-CoV-2 vaccine study
22. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
23. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
24. Are pregnant or breast feeding
25. Are investigator site personnel directly affiliated with this study.

5.3. Lifestyle Considerations

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

Each participant will receive a single IV infusion of either placebo, LY3819253, or a combination of LY3819253 and LY3832479.

The optional treatment arm 5 LY3819253 dose level may be tested based on interim analysis results. The dose levels for this optional treatment arm will not exceed 7000 mg and may include 175 mg. The optional treatment arm 7 for the combination may be tested at the discretion of the sponsor. The dose levels for this optional combination treatment arm will not exceed 2800 mg for LY3819253 or LY3832479.

Study intervention must be administered within 3 days of the first positive SARS-CoV-2 test sample collection.

Intervention Name	Placebo	LY3819253	LY3819253	LY3819253	LY3832479
Dose Formulation	0.9% sodium chloride solution	solution			
Dosage Level(s) (mg)	Not applicable	700	2800	7000	2800
Use	placebo	experimental			
IMP and NIMP	IMP	IMP			
Sourcing	Commercially available 0.9% sodium chloride solution	From Lilly			
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately			

Abbreviations: IMP = investigational medicinal product; IV = intravenous.

Infusion information may be found in the pharmacy manual.

The infusion rate may be reduced as deemed necessary if an infusion reaction is observed (Section 6.1.1.2). Participants will be monitored for at least 2 hours after completion of the infusion.

The site must have resuscitation equipment, emergency drugs and appropriately training staff available during the infusion and for at least 2 hours after the completion of the infusion.

6.1.1. Special Treatment Considerations

6.1.1.1. Premedication for Infusions

Premedication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication.

The investigators and sponsor may decide to use premedication if the frequency of infusion reactions among participants warrants it.

If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants.

The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation.

Any premedications given will be documented as a concomitant therapy.

6.1.1.2. Management of Infusion Reactions

All participants should be monitored closely, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Infusion-related reactions severity will be assessed and reported using the Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

This table describes the severity of reactions according to DAIDS.

Parameter	Mild	Moderate	Severe	Severe and Potentially Life-threatening
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized Urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Cytokine Release Syndrome[a]	Mild signs and symptoms AND Therapy, that is, antibody infusion interruption not indicated	Therapy (that is, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

[a] = A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

Source: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (July 2017).

Site Needs

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

Management of Infusion Reactions

Investigators should determine the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms.

If a participant permanently discontinues from study intervention, they should complete AE monitoring and other procedures as stated in the SoA.

6.1.2. Temporary Stopping Criteria

The Assessment Committee (AC) members individually will review unblinded safety data and meet as described in the AC Charter. The Assessment Committee (AC) will conduct a full safety review before determining if enrollment should be stopped and/or other study parameters should be modified. (see Section 9.6).

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

Topic	Location
DAIDS table describing severity of reactions	Section 6.1.1.2
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.

6.2. 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 an 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

All participants will be centrally randomized to study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Participants will be stratified by duration since symptom onset to randomization (≤8 days versus >8 days).

All eligible participants will be randomized, initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made in an effort to achieve an equal allocation across the treatment arms at the end of enrollment. If additional placebo participants are enrolled, then the allocation ratio may change accordingly. See Section 9.5 for details.

Blinding

This is a blinded study. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study.

This table describes general procedures for unblinding.

Unblinding (IWRS)	• Emergency unblinding for adverse events may be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS • In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted • Participant safety must always be the first consideration in making such a determination. However, the investigator should make all attempts to contact the Medical Monitor in advance of unblinding • If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance • The date and reason that the blind was broken must be recorded in the source documentation and case report form.

Abbreviations: IWRS = interactive web-response system.

If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion stopped. If any amount of study intervention was administered, follow procedures according to the SoA.

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 will be recorded in the source documents and recorded 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 staff other than the person administering the study intervention.

6.5. Concomitant Therapy

Prior Treatment for Indication

Any prior therapy, such as antivirals, antibiotics, or anti-malarials used as treatment prior to signing informed consent should be recorded.

Therapy prior to enrollment with antivirals including lopinavir/ritonavir, remdesivir, or other therapeutic agents (e.g. corticosteroids) are permitted.

Convalescent COVID-19 plasma treatment is not allowed prior to enrollment.

Concomitant Therapy

Participants should be treated according to standard of care, even as it evolves, and medications may be part of the treatment paradigm. Therefore, remdesivir may be initiated as standard of

care for participants hospitalized with severe disease (if available through the FDA Emergency Use Authorizations) outside of local standard of care per written policies or guidelines.

If the local standard of care per written policies or guidelines (that is, not just an individual clinician decision) includes lopinavir/ritonavir, chloroquine, hydroxychloroquine or other investigational agents, then initiating these during the study is permitted, but may require additional safety monitoring by the site.

Convalescent COVID-19 plasma treatment is not allowed.

Any medication, investigational agent, or vaccine, including over the counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- Reason for use
- Dates of administration including start and end dates, and
- Dosage information including dose and frequency for concomitant therapy of special interest.

Acetaminophen and corticosteroid use are permitted at any time during the study.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the sponsor if required.

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

6.6. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum dose of LY3819253 will not exceed 7000 mg or the maximum tolerated dose from PYAA.

6.7. Intervention after the End of the Study

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the trial as a whole are handled as part of regulatory, ethical, and trial oversight considerations in Section 10.1.9., Appendix 1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If the IV infusion is definitively discontinued, the participant will remain in the study for follow-up and any further evaluations that need to be completed as described in the SoA.

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

If the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study 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, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study intervention unless there are extenuating circumstances that make it medically necessary for the participant to continue study intervention.

If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently

enrolled participant to continue in the study with or without treatment with investigational product.

Safety follow up is as outlined in

- Section 1.3 (Schedule of Activities)
- 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 they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Protocol waivers or exemptions are not allowed.

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

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

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

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

8.1. Efficacy Assessments

Hospitalization events (Section 8.2.4), procedures of special interest (Section 8.2.5), vital signs (Section 8.2.2) and symptomology (Section 8.1.1) will be used to characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on clinical status from baseline to Days 7, 11, 15 and 29.

8.1.1. Symptoms and Overall Clinical Status Participant Questionnaire

Participants will rate their overall clinical status and severity of symptoms associated with COVID-19 by a daily questionnaire. This questionnaire is for outpatients only.

Participants will complete three questions about their overall clinical status daily, including

- severity of symptoms
- general physical health, and
- change in overall health.

The questionnaire contains these symptoms

- cough
- shortness of breath
- feeling feverish
- fatigue
- body aches and pain
- sore throat
- chills
- headache
- loss of appetite, and
- changes in taste and smell.

Each symptom will be scored daily by the participant as experienced during the past 24 hours.

Rating	Score
None or absent	0
Mild	1
Moderate	2
Severe	3

Participants will rate changes in taste and smell with a yes/no response.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will be performed at the screening visit. This examination excludes pelvic, rectal, and breast examinations unless clinically indicated.

A symptom-directed physical examination will be performed at other visits, as specified in the SoA and as clinically indicated.

Investigators should pay special attention to clinical signs related to COVID-19, to ongoing medical conditions and to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will be measured as specified in the SoA and as clinically indicated. Vital signs include

- Body temperature
- Blood pressure
- Pulse rate
- Respiration rate
- Saturation of peripheral oxygen, and
- Supplemental oxygen flow rate, FiO2 if known, and method of delivery, if applicable.

This table outlines Day 1 vital signs data collection on the CRF in relation to the infusion. Infusion times may vary depending on the participant.

Timepoint (minutes)	Collect data on CRF
Immediately before infusion	Yes
During Infusion, as possible	--
15	No
30	Yes
45	No
60	Yes
After Infusion – every 30 minutes for 2 hours after the end of the infusion	--
90	Yes
120	No
150	No
180	No

Additional vital signs may be measured during the study if warranted, as determined by the investigator.

8.2.3. Clinical Laboratory Assessments

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

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or sponsor.

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

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.

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

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), report in the AE section of the CRF.

Pregnancy Testing

Women of childbearing potential (WOCBP) must undergo pregnancy testing according to the SoA. Participants who are pregnant will be discontinued from the study.

8.2.4. Hospitalization events

If a participant is admitted to the hospital, the participant will remain in the study and follow the procedures outlined in the SoA. Hospitalization is defined as ≥24 hours of acute care.

The date of hospitalization events will be recorded in the CRF and includes

- hospitalization
- emergency room visit
- ICU admittance
- Extended care facility admittance, and
- Discharge.

8.2.5. Procedures of Special Interest

The participants' clinical status and concurrent procedures of special interest will be recorded in the CRF and include consciousness status using alert, consciousness, verbal, pain, unresponsive scale (ACVPU), limitation on activities due to COVID-19, and requirements for

- ongoing hospital medical care
- supplemental oxygen
- non-invasive ventilation or a high flow oxygen device
- mechanical ventilation
- ECMO, or
- additional organ support (e.g. pressors, renal replacement).

8.2.6. Respiratory Support

Once enrolled in the study, participants may be managed with high-flow nasal cannula, noninvasive positive pressure ventilation or any other form respiratory support as needed per investigator discretion.

8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the participant, or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

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

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 informed consent form (ICF) until participation in study has ended.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event 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 timeframe if it is considered reasonably possibly related to study procedures.

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

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

8.3.2. 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.

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it 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 will be collected for 90 days after dosing.

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, and 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 infusion-related reaction/hypersensitivity CRF.

If symptoms and/or signs occur during or within 6 hours after infusion and are believed to be hypersensitivity or due to cytokine release, then investigators are encouraged to report the event as infusion-related immediate hypersensitivity reaction or cytokine release-associated infusion reaction, respectively.

Sites should have appropriately trained medical staff 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 the local standard of care.

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.

In case of skin lesions or rash consistent with vasculitis, efforts should be made to perform the following as soon as possible

- dermatology consultation
- skin biopsy, and
- photographs of lesions of interest, including skin biopsy site.

8.3.7. Infusion-related Reactions

As with other mAbs, infusion-related reactions may occur during or following IV administration. If an infusion-related reaction occurs, additional data describing each symptom and sign should be provided to the sponsor in the CRF.

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

Topic	Location
Special treatment considerations	Section 6.1.1
Premedication for infusions	Section 6.1.1.1
Management of infusion reactions	Section 6.1.1.2
DAIDS table describing severity	Section 6.1.1.2
Treatment guidelines for infusion-related reactions	Section 6.1.1.2

Symptoms occurring during or after infusion of study intervention may also be defined according to AE categories such as acute allergic reaction or cytokine release syndrome (refer to DAIDS).

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.

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

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

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

Time Period for Detecting Product Complaints

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

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to an intervention provided for the study, 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

There is no known antidote for an overdose of LY3819253 or LY3819253 in combination with LY3832479.

In the event of an overdose, the investigator should

1. Contact the sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities
3. Provide supportive care as necessary, and
4. Document the quantity of the excess dose in the CRF.

Decisions regarding infusion interruptions or modifications will be made by the investigator, in consultation with the sponsor, based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Venous blood samples will be collected as specified in the SoA for determination of concentrations of LY3819253 and LY3832479 used to evaluate the PK for LY3819253 and LY3832479.

A maximum of 3 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 administration (start and end of infusion), 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 and LY3832479 will be assayed using a validated bioanalytical method. Analyses of samples collected from placebo-treated participants are not planned.

Sample retention is described in Appendix 1, Section 10.1.12. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

8.6. Pharmacodynamics

The SARS-CoV-2 viral RNA level and viral clearance will be evaluated by nasopharyngeal swabs. See Section 10.2 Clinical Laboratory Tests, and Section 1.3, the SoA for sample collection information.

Sample retention is described in Appendix 1, Section 10.1.12. Remaining samples may be used for additional exploratory studies to better understand LY3819253, LY3832479 and the disease, which may include sequencing and/or culture of the virus for future studies.

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, the SoA for sample collection information.

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

8.8. Biomarkers

Blood samples will be collected from all participants for analysis of immune system-related markers. Serum, whole blood for cellular and/or epigenetic analysis, and whole blood RNA 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 including, but not limited to, immune pathways, cellular composition, serum analytes, or epigenetic biomarkers, to evaluate their association with observed clinical responses to LY3819253, LY3832479 and the disease state.

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the intervention target (S protein), the COVID-19 disease state, pathways associated with disease, and/or the mechanism of action of the study intervention.

Sample retention is described in Section 10.1.12.

8.9. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA, venous blood samples will be collected to determine antibody production against LY3819253 or LY3832479. The actual date and time (24-hour clock time) of each sample collection will be recorded.

Sample collection, handling, and use

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

Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of LY3819253 or LY3832479 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3819253 or LY3832479.

Sample retention

Sample retention is described in Appendix 1, Section 10.1.12.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

9.2. Sample Size Determination

The initial planned sample size is approximately 500participants equally allocated across five treatment arms (treatment arms 1-4 and 6). Additional placebo participants may be enrolled to ensure up to 50 concurrent placebo controls for each treatment arm 5-7. Up to 100 additional participants may be introduced for each optional treatment arm. See Section 9.5 for interim analysis details.

Participants will be stratified by duration since symptom onset category (≤8 days versus >8 days).

A viral dynamic model was used to simulate viral loads over time for participants treated with LY3819253 and placebo. This simulated population and Monte Carlo methods were used to estimate statistical power associated with the comparison of Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load between LY3819253 and placebo. The mean log change from baseline to Day 11 for LY3819253 and placebo in the simulated population were approximately -4.38 and -3.48 (standard deviation 1.9), respectively, representing an average of 87% viral load reduction.

Given these assumptions, an assumed sample size of 100 participants per arm provides approximately 91% power to test superiority of an investigational intervention vs placebo in effect on viral load, as measured by change from baseline to Day 11 (± 4 days), at the two-sided 0.05 alpha level.

Periodic adjustments to the allocation ratio of participants will be informed by planned interim analyses. See Section 9.5 for details.

9.3. Populations for Analyses

This table defines the populations for analysis.

Population	Description
Entered	All participants who sign the informed consent form
Efficacy	All randomized participants who received study intervention and provided at least one post-baseline measure for the relevant endpoint. Participants will be analyzed according to the intervention to which they were randomized. (Intention to treat).
Safety	All participants randomly assigned and who received study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic	All randomized participants who received study intervention and have evaluable PK sample. Participants will be analyzed according to the intervention they received.

9.4. Statistical Analyses

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

Unless otherwise specified, treatment effects will be conducted using 2-sided tests at an alpha level of 0.05. No adjustment for multiplicity will be performed in this study.

Details of the handling of dropouts or missing data will be fully described in the statistical analysis plan (SAP).

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. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to the first final database lock (i.e., first unblinding of the sponsor), 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 secondary endpoints.

9.4.1. General Considerations

This table describes the general statistical methods that may be used in this study.

Method	Analysis
Descriptive Statistics	number of participants, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures
Kaplan-Meier curves and summary statistics	Treatment comparisons of time-to-event based endpoints
Logistic regression analysis	Treatment comparisons of binary variables with treatment and randomization stratification variables in the model.
Nonparametric (for example, Mann-Whitney or van Elteren tests)	Treatment comparison of ordinal, nominal and non-normally distributed continuous variables.

Additional statistical methodology, sensitivity analyses accounting for missing data, and adjustments for covariates, if any, will be described in the SAP.

9.4.2. Primary Endpoints

Primary endpoint is the change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load. Statistical hypothesis testing for the primary endpoint will be conducted using a mixed model repeated measure (MMRM) analysis method at the two-sided 0.05 level. Full details will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Safety

Safety analyses will be conducted using the safety population described above.

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 intervention as perceived by the investigator. Adverse events reported prior to randomization will be distinguished from those reported as new or increased in severity during the study post-randomization.

Safety parameters that will be assessed include, but are not limited to, safety laboratory parameters, and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.4.3.2. Additional Secondary Endpoints

Endpoints will include

- Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤8 days of symptoms prior to randomization
- Time to symptom resolution
  - symptoms are scored as absent
- Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22
- Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22
- Time to symptom improvement
  - symptoms scored as moderate or severe at baseline are scored as mild or absent, AND
  - symptoms scored as mild or absent at baseline are scored as absent.
- Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22
- SARS-CoV-2 viral load and viral clearance including:
  - Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, and 22)
  - Time to SARS-CoV-2 clearance
  - SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed through Day 29
- Proportion (percentage) of participants who experience these events by Days 29, 60 and 85
  - COVID-19 related hospitalization (defined as ≥ 24 hours of acute care)
  - a COVID-19 related emergency room visit, or
  - death.

Full details of the analyses will be in the SAP.

9.4.3.3. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on data from all participants who receive intervention and have evaluable PK.

Pharmacokinetic parameter estimates for LY3819253 and LY3832479 will be calculated using standard noncompartmental methods of analysis. A population approach using a nonlinear mixed-effects modeling (NONMEM) program may also be performed.

9.4.4. Exploratory Analyses

Full details of the planned exploratory analyses will be described in the SAP.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety, PD, or population PK and PK/PD analysis purposes.

9.4.5. Immunogenicity Analyses

If data from validated immunogenicity assays are available, treatment-emergent anti-drug antibodies (TE-ADAs) may be assessed.

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADA and who are TE-ADA positive (TE-ADA+) to LY3819253 or LY3832479 will be tabulated.

The distribution of titers and frequency of neutralizing antibodies (if assessed) for the TE-ADA+ participants may also be tabulated.

The relationship between the presence of antibodies and PK parameters, efficacy response or safety to LY3819253 or LY3832479 may also be assessed. Additional details may be provided in the SAP.

9.4.6. Subgroup Analyses

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

Subgroup analyses will be conducted for the primary endpoint. Subgroups may include

- time of symptom onset to study randomization
- baseline severity of COVID-19
- age
- sex
- race
- ethnicity
- baseline weight
- baseline body mass index
- concomitant medication, or
- high risk status for severe COVID-19 illness.

Treatment group differences will be evaluated within each category of the subgroup regardless of whether the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided, that is, no inferential testing.

Definitions for the levels of the subgroup variables, the analysis methodology, and any additional subgroup analyses will be defined in the SAP.

9.5. Interim Analyses

The ongoing study may be modified based on planned interim analyses. Based on the observed data at the time of the interim analyses, the study may

- suspend enrollment to an LY3819253 treatment arm (or arms) demonstrating lack of efficacy, and/or
- initiate/expand enrollment to an additional/existing treatment arm (or arms).

The modifications proposed are done so to ensure participants are being exposed to treatment with an acceptable risk-benefit profile during the ongoing trial. Additionally, the potential modifications will provide information to more fully characterize the dose response profile.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by Assessment Committee (AC) members. Details of the unblinded safety reviews, including the frequency and approximate timing, are specified in the AC charter.

The approximate timing, decision criteria, and statistical methods associated with each possible modification to the ongoing trial will be fully described in the SAP and AC Charter and finalized prior to the first study unblinding.

Periodic adjustments to the allocation ratio may be made to achieve an equal allocation across treatment arms at the conclusion of enrollment. If additional placebo participants are enrolled, then the allocation ratio may change accordingly.

Only the AC is authorized to evaluate unblinded interim analyses and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.6. Data Monitoring Committee (DMC)

The sponsor will form an AC to analyze the interim study data. To minimize any bias introduced into the analysis of the study results, analysis plans will be finalized and approved prior to the interim analyses.

The primary goal of the AC is to review the interim results regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

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

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

10.1.2. Financial Disclosure

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

10.1.3. 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 (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

Due to strict respiratory isolation policies, limited access to COVID-19 patient rooms, and SARS-CoV-2 transmissibility via droplet-contaminated paper, verbal consent and alternative methods of obtaining consent (for example, by phone) will be allowed if approved by the IRB.

If a signed paper copy of the ICF is allowed by site/institution policy, then the process of how it will be obtained and stored will need to be determined.

Any variation from the standard consent process due to isolation and infection control should be sent to the IRB for approval prior to enrollment. The site will document the process in their regulatory files and demonstrate that the process has IRB concurrence or approval.

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.

10.1.4. Data Protection

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

The participant must be informed that 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.

10.1.5. Committees Structure

The AC will consist of members internal and external to the sponsor. The membership will include, at a minimum, a chair external to Lilly, a statistician and two physicians. The AC members will not have data entry/validation responsibilities or direct contact with the site(s) or testing facilities.

10.1.6. Dissemination of Clinical Study Data

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

10.1.7. Data Quality Assurance

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 (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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 and 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 (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents. 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.

If on-site monitoring activities cannot occur, alternative measures will be used. Examples of alternative measures are use of technology for off-site monitoring or providing pseudonymized

copies of source documents to the monitor electronically. The remote source data verification will be focused on critical efficacy data and important safety data.

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 (CTA) unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Only symptom assessments might be directly recorded by the investigator site personnel or a delegate into the EDC. The directly entered data will serve as source documentation. The investigator will not maintain an original, separate, written or electronic record of these data. A certified copy of the respective data entry will be downloaded by the investigator for retention.

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 Sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

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

Data reported on the CRF 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 10.1.7.

10.1.9. Study and Site Start and Closure

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

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.

10.1.10. Publication Policy

In accordance with the sponsor’s publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.11. Investigator Information

Physicians with specialties, including, but not limited to infectious disease, acute or critical care, pulmonary disease, immunology, or other appropriate specialties may participate as investigators.

10.1.12. Long-Term Sample Retention

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

This table describes the retention period for potential sample types.

Sample Type	Custodian	Retention Period After Last Participant Visit
Pharmacodynamic Samples	Sponsor or designee	up to 7 years
Pharmacogenetics sample	Sponsor or designee	up to 7 years
Exploratory Biomarker Samples	Sponsor or designee	up to 7 years
Immunogenicity (ADA) sample	Sponsor or designee	up to 7 years
Pharmacokinetic (PK) sample	Sponsor or designee	up to 2 years

10.2. Appendix 2: Clinical Laboratory Tests

Clinical laboratory tests will be performed according to the SoA.

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

Central and local laboratories will be used. The table below describes when the local or central laboratory will be used.

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

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

Pregnancy testing will be performed according to the SoA.

Investigators must document their review of each laboratory safety report.

Refer to Section 10.6 for recommended laboratory testing for hypersensitivity events.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - Red Blood Cells)	
Mean cell volume	
Mean cell hemoglobin	
Leukocytes (WBCs - White Blood Cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell Morphology (RBC and WBC)	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Amylase	
Lipase	
Lactate dehydrogenase (LDH)	
SARS-CoV-2 viral infection determination	Local laboratory and/or Point-of-Care testing
SARS-CoV-2 Test Panel	Assayed by Lilly-designated laboratory.
C-reactive protein (CRP); high-sensitivity	

Clinical Laboratory Tests	Comments
Ferritin	
D-dimer	
Procalcitonin	
Troponin	
Hormones (female)	
Urine Pregnancy	Local laboratory
Serum Pregnancy	Local laboratory
Pharmacokinetic Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3819253 LY3832479	
Pharmacodynamic sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
SARS-CoV-2 nasopharyngeal swab	
Pharmacogenetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory Biomarker Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
RNA (PAXGene)	
Whole Blood (EDTA)	
Whole Blood (EDTA) Epigenetics	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-LY3819253 antibodies Anti-LY3832479 antibodies	

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

- The following study-specific clinical events related to COVID-19 are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug:
  - Hypoxemia due to COVID-19 requiring supplemental oxygen;
  - 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, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories, which together with serious (i.e., SAE) criteria on the AE CRF ("results in death" and "life-threatening"), are aligned with the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 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 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 an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in site training documents.

SAE Reporting via Paper CRF

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

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

Women

Woman of Childbearing Potential (WOCBP)

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

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

Woman not of Childbearing Potential (WOCBP)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with either
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy, or
    c. Documented bilateral oophorectomy.

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

Note: Determination 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:
    a. 12 months of amenorrhea for women >55, with no need for FSH
    b. 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that induced amenorrhea)

Participation in the Study

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

Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at the screening visit.

Women of child-bearing potential who are completely abstinent or in a same sex relationship, as part of their preferred and usual lifestyle, must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.

All other women of child-bearing potential must agree to use two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study.

Abstinence or contraception must continue for 90 days after the last dose of intervention.

Acceptable Methods of Contraception

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

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

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

Not Acceptable Methods of Contraception

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

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

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

Men

Men, regardless of their fertility status, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective method of contraception (less than 1% failure rate) or effective method of contraception with non-pregnant women of child bearing 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 90 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 90 days after the last dose.

Acceptable Methods of Contraception

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

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

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

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

Other Guidance

Men should refrain from sperm donation 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 90 days after the last dose.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

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

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

Female Participants who become pregnant

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

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

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

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

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

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study and will follow the standard discontinuation process.

10.5. Appendix 5: Genetics

Sample collection information is found in Appendix 2, Section 10.2 (Clinical Laboratory Tests).

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples 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, LY3832479 or SARS-CoV-2. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome as appropriate.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3819253, LY3832479 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 (CSR) or in a separate study summary.

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

The samples will be retained at a facility selected by the sponsor or its designee while research on SARS-CoV-2 continues but no longer than 7 years or other period as per local requirements.

10.6. Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events.

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

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

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 and LY3832479 anti-drug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3819253 and LY3832479 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: ADA = anti-drug antibody; IgE = immunoglobulin E; PK = pharmacokinetic.

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

Close Hepatic Monitoring

This table describes when close hepatic monitoring should occur.

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

The laboratory tests listed in Appendix 2, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine whether it is increasing or decreasing.

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

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

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

Comprehensive Hepatic Evaluation

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

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

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

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

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

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

Additional Hepatic Data Collection (Hepatic Safety CRF)

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants who either have a hepatic event considered to be an SAE or meet 1 or more of these conditions:

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

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

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

Hepatic Evaluation Testing

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

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

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

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin

Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [b]	Anti-actin antibody [c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

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

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

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

10.8. Appendix 8: Abbreviations

Term	Definition
AC	assessment committee
ADA	anti-drug antibody
ADE	antibody-dependent enhancement
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
CIOMS	Council for International Organizations of Medical Sciences
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 an intervention.
Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
DMC	data monitoring committee
ECG	electrocardiogram
FiO2	fraction of inspired oxygen in the aire
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.
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product

Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Intervention	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.
IWRS	interactive web-response system
NP	nasopharyngeal
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/PD	pharmacokinetics/pharmacodynamics
SAE	serious adverse event
SAP	statistical analysis plan
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.
SpO2	saturation of peripheral oxygen

10.9. Appendix 9: Protocol Amendment History

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

Amendment a

Overall Rationale for the Amendment:

This amendment addresses the United States Food and Drug Administration (FDA) feedback and provides more clarity for clinical sites.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated objectives and endpoints to match changes in Section 3.	Per FDA feedback
1.3 Schedule of Activities	Preexisting conditions and medical history – added information for risk factors and comorbidities associated with severe COVID-19 illness	Clarification of information collected
1.3 Schedule of Activities	Vital Signs – added an 'X' at screening for clarification that it would be done for inclusion/exclusion criteria, but the data will not be collected on the Case Report Form. Updated Day 1 vital sign collection times.	Per FDA feedback
1.3 Schedule of Activities	Participant questionnaire – added Day 1	Questionnaire should be completed for Days 1 – 29.
3 Objectives and Endpoints	Added Day 11 to proportion of participants that achieve SARS-CoV-2 clearance endpoint	Analysis will include Day 11.
3 Objectives and Endpoints	Added Days 60 and 85 to secondary endpoint for clinical status.	Per FDA feedback
3 Objectives and Endpoints	Exploratory endpoint for viral resistance – updated description	Clarification that assessment will be from baseline to the last evaluable timepoint up to Day 29
3 Objectives and Endpoints	Clarified for all applicable endpoints that AUC is assessed through Day 29	Clarification that AUC calculations are not for a specific day, but through Day 29
3 Objectives and Endpoints	Added an exploratory endpoint for overall improvement using the NIAID ordinal scale	For consistency across protocols
5.1 Inclusion Criteria	Added website URL for the FDA resource page	Per FDA
8.2.2 Vital Signs	Added a table to explain what data will be collected on the CRF on Day 1	Clarity for sites
9.4.3.2. Additional Secondary Endpoints	Updated according to changes in Section 3	Consistency across sections.

Section # and Name	Description of Change	Brief Rationale
9.4.6. Subgroup Analyses	Updated the subgroup analyses	New information available
10.1.11 Investigator Information	Updated description	Per feedback
Section 10.2. Clinical Laboratory Tests	Removed antibody neutralization	Assay is not available at this time
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

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1. Statistical Analysis Plan: J2W-MC-PYAB: A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3819253 in Participants with Mild to Moderate COVID-19 Illness

LY3819253 - Mild to Moderate COVID-19 Illness

This is a Phase 2, randomized, double-blind, placebo-controlled, single-dose study in participants with mild to moderate COVID-19 illness to evaluate the efficacy and safety of LY3819253.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol J2W-MC-PYAB
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 19-Jun-2020 GMT

2. Table of Contents

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to unblinding.

4. Study Objectives

4.1. Primary Objective

The primary objective of this trial is to characterize the effect of LY3819253 compared to placebo on upper respiratory tract SARS-CoV-2 (COVID-19) viral load and viral clearance among participants with mild to moderate COVID-19 illness. The primary endpoint is the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load based on nasopharyngeal swab sampling for reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. Statistical hypothesis testing for the primary endpoint will be conducted using a mixed-effects model repeated measures (MMRM) analysis method at the 2-sided 0.05 level.

4.2. Secondary Objectives

Table PYAB.4.1. Secondary Objectives of Study J2W-MC-PYAB

Objectives	Endpoints
Secondary	
Characterize the effect of LY3819253 compared to placebo on safety	• Safety assessments such as AEs and SAEs
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
Characterize the effect of LY3819253 compared to placebo on symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15, and 22 • Change in symptom score (total of ratings) from baseline to Days 7, 11, 15, and 22
Characterize the effect of LY3819253 compared to placebo on symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15, and 22
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 15, and 22) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed through Day 29

Secondary Objectives of Study J2W-MC-PYAB

Objectives	Endpoints
Characterize the pharmacokinetics of LY3819253	• LY3819253 mean concentration on Day 29
Characterize the effect of LY3819253 compared to placebo on overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 ○ COVID-19-related hospitalization (defined as ≥24 hours of acute care) ○ a COVID-19-related emergency room visit, or ○ death

Abbreviations: AE = adverse event; SAE = serious adverse event.

4.3. Exploratory Objectives

Table PYAB.4.2. Exploratory Objectives of Study J2W-MC-PYAB

Objectives	Endpoints
Exploratory	
Characterize emergence of viral resistance to LY3819253	• Comparison from baseline to the last evaluable timepoint up to Day 29
Characterize the effect of LY3819253 compared to placebo on SpO2 over time	• SpO2 AUC assessed through Day 29
Characterize the effect of LY3819253 compared to placebo on symptom severity	• Symptom severity as assessed by mean AUC through Day 29 of symptom questionnaire
Characterize the effect of LY3819253 compared to placebo on improvement on the NIAID Ordinal Scale	• Comparison of the mean worst daily NIAID ordinal scale values at Days 7, 11, 15, and 22

Abbreviation: NIAID: National Institute of Allergy and Infectious Diseases; AUC = area under the concentration-time curve.

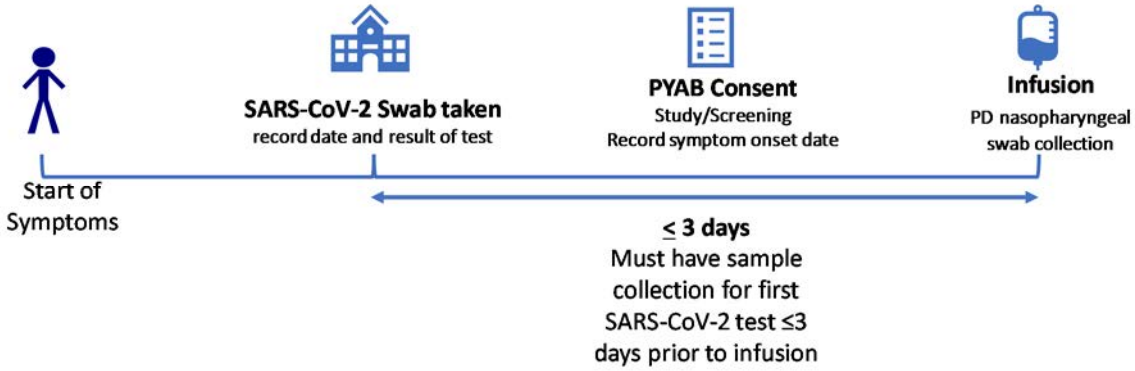
Additional exploratory objectives not previously defined in the protocol are described in Section 6.17.2.

5. Study Design

5.1. Summary of Study Design

This is a Phase 2, placebo-controlled, double-blind, randomized single-dose study in participants with mild to moderate COVID-19 illness.

5.1.1. Design Outline



Abbreviations: IV = intravenous; PD = pharmacodynamic; PYAB = Study J2W-MC-PYAB.

Figure PYAB.5.1. Overview of participant flow from time of SARS-CoV-2 symptoms to IV infusion.

5.1.2. Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures. The participant may enter the study with a previous positive SARS-CoV-2 viral test result from an external testing facility. This test result must be the first time the patient has tested positive for SARS-CoV-2.

The investigator will review symptoms, risk factors, and other noninvasive inclusion and exclusion criteria prior to any invasive procedures. If the participant is eligible after this review, then the site will perform the invasive procedures to confirm eligibility.

5.1.3. Double-blind Treatment and Assessment Period

Participants will be randomized to placebo or LY3819253. As dose levels in Study J2W-MC-PYAA (PYAA) are demonstrated to have an acceptable safety and tolerability profile through 4 days of postdose monitoring, these dose levels may be introduced in Study J2W-MC-PYAB (PYAB). Table PYAB.5.1 describes the planned treatment arms.

Table PYAB.5.1. Treatment Arms of Study J2W-MC-PYAB

Treatment arms	LY3819253
1	placebo
2	700 mg
3	2800 mg
4	7000 mg

An optional LY3819253 treatment arm may be added based on interim analysis results.

5.1.4. Posttreatment Follow-up

Posttreatment follow-up assessments will be conducted at Day 60 and Day 85 to assess clinical status and for adverse events (AEs). Strategies to manage infection risks and reduce the burden of return visits, such as home visits, may be used by sites.

5.2. Determination of Sample Size

The initial planned sample size is approximately 400 participants equally allocated across 4 treatment arms. Up to 100 additional participants may be introduced either for a new dose level or as an addition to an existing treatment arm based on planned interim analyses. See Protocol Section 9.5 for interim analysis details.

Participants will be stratified by duration since symptom onset category (≤8 days vs >8 days).

A viral dynamic model was used to simulate viral loads over time for participants treated with LY3819253 and placebo. This simulated population and Monte Carlo methods were used to estimate statistical power associated with the comparison of change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load between LY3819253 and placebo. The mean log change from baseline to Day 11 for LY3819253 and placebo in the simulated population were approximately -4.38 and -3.48 (standard deviation [SD] 1.9), respectively, representing an average of 87% viral load reduction.

Given these assumptions, an assumed sample size of 100 participants per arm provides approximately 91% power to test superiority of LY3819253 versus placebo in effect on viral load, as measured by change from baseline to Day 11 (±4 days), at the 2-sided 0.05 alpha level.

Periodic adjustments to the allocation ratio of participants will be informed by planned interim analyses. See Protocol Section 9.5 for details.

5.3. Method of Assignment to Treatment

5.3.1. Randomization

All participants will be centrally randomized to study intervention using an interactive web-response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Participants will be stratified by duration since symptom onset to randomization (≤8 days vs >8 days).

All eligible participants will be randomized initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made to achieve an equal allocation across the treatment arms at the end of enrollment. See Protocol Section 9.5 for details.

5.3.2. Blinding

This is a double-blinded study. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base lock at the conclusion of the study.

Table PYAB.5.2 describes general procedures for unblinding.

Table PYAB.5.2. Unblinding Procedures for Study J2W-MC-PYAB

Unblinding (IWRS)	• Emergency unblinding for adverse events may be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS • In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted • Participant safety must always be the first consideration in making such a determination. However, the investigator should make all attempts to contact the Medical Monitor in advance of unblinding • If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance • The date and reason that the blind was broken must be recorded in the source documentation and case report form

Abbreviation: IWRS = interactive web-response system.

If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion stopped. If any amount of study intervention was administered, follow procedures according to the Schedule of Activities (SoA).

6. A Priori Statistical Methods

6.1. General Considerations

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

All tables, figures, and listings will be created using the clinical trial database (unless otherwise noted), including data during study participation. While not reflected in a table, figure, or listing, any data collected after study participation (e.g., in the Lilly Safety System or collected through queries to the investigator) may be discussed in a clinical study report (CSR) or integrated summary document when deemed relevant.

Unless otherwise noted, displays will include columns for each treatment group, and in case of multiple doses of investigational product (IP), another column for IP doses combined will be displayed. A column that combines IP groups with placebo and/or active controls (i.e., a total column) will not be created.

Not all displays described in this statistical analysis plan (SAP) will necessarily be included in the CSR. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of, or in addition to, a static display. Any display described in this SAP and not provided would be available upon request.

All statistical analyses will be performed using SAS software Version 9.4 (or a higher version), FACTS 6.0 (or a higher version), and/or R 3.6 (or a higher version).

6.1.1. Analysis Populations

Patient populations are defined in Table PYAB.6.1 along with the analysis they will be used to conduct. The treatment groups and inferential comparisons described in Table PYAB.6.1 will be used unless otherwise specified. Also, unless otherwise specified, for all populations/analysis, participants will be analyzed according to the treatment to which they were assigned.

Table PYAB.6.1. Analysis Populations

Population	Description
Entered	**Definition:** All participants who signed informed consent. **Purpose:** Used for disposition analysis. **Treatment Groups:** None **Inferential Comparisons:** None
Efficacy	**Definition:** All randomized participants who received study intervention and provided at least 1 postbaseline measure viral load measurement. Participants will be analyzed according to the intervention to which they were randomized (Intention to treat). **Purpose:** Used for efficacy and health outcomes analyses. **Treatment Groups (Short Label):** 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), LY total, and placebo (Pbo) **Inferential Comparisons:** Each LY dose versus placebo

Analysis Populations

Population	Description
Safety	**Definition:** All participants randomly assigned and who received any amount of study intervention. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses. **Treatment Groups (Short Label):** 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), LY total, and placebo (Pbo) **Inferential Comparisons:** LY total versus placebo
Pharmacokinetic	**Definition:** All randomized participants who received study intervention and have at least 1 postdose PK sample. Participants will be analyzed according to the intervention they received. **Purpose:** Used for PK analyses. **Treatment Groups (Short Label):** 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), and placebo (Pbo) **Inferential Comparisons:** Each LY dose versus placebo

Abbreviation: PK = pharmacokinetic.

6.1.2. Definition of Study Baseline

Unless otherwise specified, for efficacy and health outcome, baseline is defined as the last nonmissing assessment recorded on, or prior to, the date of the first study drug administration at study Day 1.

Baseline for safety analysis is described in the safety section.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline values or the value at the visit is missing for a particular variable, then the change from baseline is defined as missing.

6.1.3. Study Time Intervals

To calculate the length of any time interval or time period in this study, the following formula will be used:

$$Length\ of\ interval\ (days) = End\ Date - Interval\ Start\ Date + 1$$

To convert any time length from days to weeks, the following formula will be used:

$$Length\ of\ interval\ (weeks) = Length\ of\ interval\ (days)/7$$

Only for the purpose of calculating the length of study period time intervals, the words “prior to” in Table PYAB.6.2 should be understood to mean “the day before” while the words “after” should be understood to mean “the day after.” For the purpose of determining whether a date/time lies within an interval, these words are intended to convey whether the start or end of the period is inclusive of the specified date.

Table PYAB.6.2. Definition of Study Period Time Intervals

Study Period	Interval Start Definition	Interval End Definition
Screening: All participants who sign informed consent are considered as entering the Screening Period.	Informed consent date	Prior to the start of Treatment and Assessment Period.
Treatment and Assessment Period: All participants who are randomized to the study are considered as entering the Treatment Period.	At the start of study drug administration date/time following randomization. For participants who are randomized but not dosed, the Treatment and Assessment Period starts on the date of randomization.	The minimum of treatment period discontinued date, study discontinuation date, or first Post Treatment Follow-Up visit date.
Post-Treatment Follow-Up: All participants who had a follow up visit are considered as entering follow-up period.	After the Treatment and Assessment Period ends.	The maximum of the last study visit date or study disposition date.

6.1.4. Analysis Methods

Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. SARS-CoV-2 viral load data will be evaluated in log base 10 scale. The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, Mann-Whitney, or van Elteren tests, is deemed to be more appropriate.

All hypothesis tests will be 2-sided at an alpha level of 0.05. No adjustment for multiplicity will be performed in this study.

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. Additional exploratory analyses of the data may be conducted as deemed appropriate.

Table PYAB.6.3. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Method	Analysis
Descriptive Statistics	Number of participants, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures
Kaplan-Meier curves and summary statistics, Cox proportional hazards	Treatment comparisons of time-to-event based endpoints
Logistic regression analysis	Treatment comparisons of binary variables with treatment and randomization stratification variables in the model

Tables and Figures Related to Demographics and Other Characteristics of Study Population

Nonparametric (e.g., Mann-Whitney or van Elteren tests)	Treatment comparison of ordinal, nominal, and non-normally distributed continuous variables
Mixed-effects model repeated measures (MMRM) analysis	Treatment comparisons of continuous efficacy and health outcome variables

Treatment comparisons of continuous efficacy and health outcome variables with multiple postbaseline measurements will be made using MMRM analysis. When MMRM is used, it includes: (a) treatment group, (b) stratification factor of duration since symptom onset to randomization (≤8 days vs >8 days), (c) baseline value in the model, (d) visit, and (e) the interactions of treatment-by-visit as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The first structure to yield convergence will be used for inference. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% confidence interval (CI) will also be reported. Unless otherwise specified, for MMRM, reported data from only planned visits will be used as the primary analysis.

Treatment comparisons of continuous efficacy, safety, and health outcome variables with a single postbaseline timepoint will be made using analysis of covariance (ANCOVA) with:- (a) treatment group, (b) stratification factor of duration since symptom onset to randomization (≤8 days vs >8 days), and (c) baseline value in the model. Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value-, and 95% CI, unless otherwise specified, will also be reported. Missing data imputation method for the ANCOVA model is specified in Section 6.3.

Treatment comparisons for binary endpoints will be made using logistic regression with a Firth penalized likelihood (Firth 1993). The model will include the treatment groups and duration since symptom onset to randomization category (≤8 days vs >8 days). The Firth correction can be implemented in PROC Logistic by including *'firth'* as an option in the model statement. The odds ratio and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be reported.

The Kaplan-Meier (KM) product limit method will be used for time-to-event analyses. The hazard ratio and log-rank test, stratified by duration since symptom onset to randomization (≤8 days vs >8 days), will be reported. Time for all analyses will be described in units of days.

6.2. Adjustments for Covariates

Unless otherwise specified, efficacy analyses will adjust for the baseline value of the endpoint and by the randomization stratification factor, duration since symptom onset to randomization (≤8 days vs >8 days), when modeling estimates and calculating p-values.

6.3. Handling of Dropouts or Missing Data

The SoA, outlined in the protocol, specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis but may be reported as a protocol deviation (see Section 6.15).

6.3.1. Non-Responder Imputation (NRI)

For analysis of categorical efficacy and health outcomes variables, missing data will be imputed using an NRI method. Participants will be considered nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest.

In addition, participants who were not adequately assessed to determine if they meet the clinical requirements for response at the time point of interest are also considered to have failed treatment.

6.3.2. Last Observation Carried Forward (LOCF)

A last observation analysis is performed by carrying forward the last postbaseline assessment for the continuous measures or ordinal scale measures. For participants discontinuing the study, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation.

After LOCF imputation, data from participants with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. These LOCF analyses help ensure that the maximum number of randomized participants who were assessed postbaseline will be included in the analyses.

6.3.3. Mixed-effects Model Repeated Measures (MMRM)

For continuous variables, the primary analysis will be MMRM with the missing-at-random (MAR) assumption for handling missing data. This analysis considers both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis.

6.3.4. Highest Disease States Imputation (HDSI)

For the analyses related to National Institute of Allergy and Infectious Diseases (NIAID)/World Health Organization (WHO) ordinal scales, the following imputation will be considered if applicable.

For participants whose data is missing during the hospitalization period (not yet recovered), a score of 7, which is the highest value for a hospitalization status, will be used for imputation.

For participants whose data is missing after recovery or discharged, a score of 3, the highest value for a recovery or nonhospitalized status, will be used for imputation.

6.4. Multicenter Studies

Differences between study centers will not be a feature of the statistical analyses for this study. Baseline variables and demographics may be described by site.

Individual center results may be presented, where appropriate, when the centers have sufficient numbers of participants to make such analysis potentially valuable. The possibility of qualitative or quantitative treatment-by-center interaction may be explored.

6.5. Multiple Comparisons/Multiplicity

As this is a Phase 2 (nonconfirmatory) dose-finding study; no adjustments for multiple comparisons will be made.

6.6. Participant Disposition

The treatment period disposition and study disposition will be summarized for the safety population. Disposition summaries will be by treatment group. Summaries will also include reason for discontinuation from the study tabulated by treatment group.

All participants who are randomized and discontinued from study treatment or from the study will be listed, and the timing of discontinuing (from randomization) the study will be reported. If known, a reason for their discontinuation will be given.

In addition, a graphical summary (i.e., KM plot) of time from randomization to early permanent discontinuation of study or study treatment due to AEs may be generated if there are a substantial number of such events. This graphical summary would be by treatment group and include the log-rank test results.

Table PYAB.6.4. Tables and Figures Related to Disposition

Analysis	Details
Patient Disposition	Number and percentage of participants by reason for • study discontinuation and • study treatment period discontinuation A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) No inferential statistics
Listing of study and study treatment disposition	--
Listing of participants discontinuing due to a decision-related reason (loss to follow-up, patient decision, or investigator decision)	Variables included the reason for study discontinuation, the text collected in the specify field associated with the reasons for discontinuation, and the dates of discontinuation The text in the specified field should provide information to support that the reason is unrelated to efficacy or safety
Time to early discontinuation of study treatment due to adverse events (AEs)	Presented as a figure (if necessary)

6.7. Participant Characteristics

Patient demographic variables and baseline characteristics will be summarized by treatment and overall for the efficacy populations with the baseline values. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline covariates across treatment groups will be performed. By-patient listings of basic demographic characteristics (i.e., age, sex, race, racial subgroup, ethnicity, and body weight) for the efficacy population will be provided.

Table PYAB.6.5. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Analysis	Details
Baseline Demographic Characteristics	**Variables to be included:** • Age • Age groups (<65, ≥65 and <75, ≥75 and <85, ≥85, ≥65, and ≥75 years) • Sex • Race (Amerian Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported) • Height • Weight • Body mass index, and • Days since COVID-19 symptom onset. • High-risk status for severe COVID-19 illness **Statistics to be included:** Continuous: Mean, standard deviation, min, max, median, and first quartile and third quartile Categorical: n and percent (denominator for percentages will be the number of participants with nonmissing values) A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) No inferential statistics
Medical History and Preexisting conditions	Number and percentage of participants with medical history events and preexisting conditions using MedDRA PT nested within SOC • Ordered by decreasing frequency within SOC on the LY total arm Preexisting conditions are defined as those conditions with a start date prior to the first dose of the study drug and stop dates that are at or after the informed consent date or have no stop date (i.e., are ongoing).
Listing demographics	--

Abbreviations: max = maximum; MedDRA = Medical Dictionary for Regulatory Activities; min = minimum; PT = preferred term; SOC = System Organ Class.

6.8. Treatment Compliance

As all study drug doses will be administered at the study site, treatment compliance will not be reported.

6.9. Prior Medication and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the WHO drug dictionary. Medication start and stop dates will be compared to the date of the first dose of treatment to allow medications to be classified as concomitant.

Prior medications are those medications that start and stop prior to the date of the first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment and continue into the treatment period. For all summary tables of concomitant medications, Preferred Terms of concomitant medication will be sorted by descending frequency in the LY total arm.

Table PYAB.6.6. Summary Tables Related to Concomitant Medications

Analysis	Details
Prior medications	Number and percentage of participants using Preferred Terms of prior medication • Ordered by decreasing frequency No inferential statistics
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication • Ordered by decreasing frequency No inferential statistics

6.10. Efficacy Analyses

The analysis of the of viral load lab results will utilize the following conventions:

For qualitative endpoints in the trial (viral clearance yes/no, time to viral clearance) the lab determination of "positive"/"negative" will be used. SARS-CoV-2 clearance (yes/no) is defined as 2 consecutive negative tests for the SARS-CoV-2 virus. The date of viral clearance is defined as the earliest date of the 2 consecutive negative tests.

For quantitative endpoints in the trial (change from baseline, area under the concentration-time (Ct) curve [AUC]), the Ct values will be utilized with the following considerations:

- Two Ct values will be provided on 2 different genes: N1 and N2. N1 will be used as the primary measure; N2 will only be used when the Ct value for N1 is not available.
- Ct values range between 0 and 45.
- Negative CoV-2 tests will be associated with a Ct value of 45.
- The (log base 10) viral load will be calculated from the Ct value $(45\text{-Ct})/\log_2 10$, or (45-Ct)/3.321928.

6.10.1. Primary Outcome and Methodology

Primary endpoint is the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load. Statistical hypothesis testing for the primary endpoint will be conducted using an MMRM analysis method at the 2-sided 0.05 level.

SARS-CoV-2 viral load, including changes from baseline, will be summarized and plotted by treatment and listed. Baseline is defined as the Day 1 predose assessment.

Changes from baseline to Day 11 in SARS-CoV-2 viral load data in the log base 10 scale will be statistically analyzed using a linear mixed-effect model. The model will contain log base 10 transformed baseline as a covariate, treatment, day, treatment-by-day interaction, the stratification factor duration since symptom onset to randomization category (≤8 days vs >8 days) as fixed effects. The LS means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. In addition, the geometric mean ratio to baseline and corresponding standard error for each treatment, and ratio of geometric mean ratio to baseline vs placebo, and corresponding 95% CIs will be presented. All available data will be used in the analysis. The viral load negative will be imputed as 1 before the transformation.

If Day 11 SARS-CoV-2 viral load is missing, the earliest measurement closest to the Day 11 visit, but within 4 days (Day 7-Day 15), will be used for the Day 11 value. If no measurements are available, the Day 11 viral load will treated as MAR in the analysis.

6.10.2. Additional Analyses of the Primary Outcome

6.10.2.1. Dose Response Modeling

A Bayesian model averaging approach will be used to estimate the dose-response relationship with change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load being the response variable of interest. This Bayesian model averaging approach is the Bayesian analog of the Multiple Comparisons - Modelling (MCP-MOD) methodology (Bretz et al. 2005), and the Qualification of the MCP-Mod procedure (OCP 2015) is supportive in the use of MCP-MOD or Bayesian model averaging to assist in dose selection decisions.

Bayesian model averaging is a general mixture distribution, where each mixture component is a different parametric model. Prior weights are placed on each model and the posterior model weights are updated based on how well each model fits the data. Let $\mu(d)$ represent the mean of the dose response curve at dose d, $y = \{y_1, \ldots, y_n\}$ be the observed data, and $m \in \{1, \ldots, M\}$ be an index on the M parametric models. Then the posterior of the dose response curve, $\mu(d)$, of the Bayesian model averaging model is

$$p(\mu(d) \mid y) = \sum_{m=1}^{M} p(\mu(d) \mid y, m)\, p(m \mid y)$$

$$p(m \mid y) = \frac{p(y \mid m)p(m)}{\sum_{m^*} p(y \mid m^*)p(m^*)}$$

where $p(\mu(d) \mid y, m)$ is the posterior mean dose response curve from model m, $p(m \mid y)$ is the posterior weight of model m, $p(y \mid m)$ is the marginal likelihood of the data under model m, and $p(m)$ is the prior weight assigned to model m. In cases where $p(y \mid m)$ is difficult to compute, Gould (2019) proposes using the observed data's fit to the posterior predictive

distribution as a surrogate in calculating the posterior weights; this is the approach used in this analysis.

Similar dose response methodology may be applied to additional efficacy endpoints as appropriate.

6.10.2.2. Bayesian Modeling

A Bayesian linear mixed-effect model will be fitted to evaluate the success criteria by the Lilly statistics group with the model listed below:

$$y_{ijk} = \mu + \alpha \times base + \alpha_i + \beta_k + (\alpha\beta)_{ik} + \varepsilon_{ij} + \varepsilon_{ijk}$$

Where y_{ijk}: the change from baseline in log 10 scale for treatment i, subject j at day k

μ: a constant common to all observations

α: a fixed coefficient on the covariate log base 10 baseline viral load

α_i: a parameter corresponding to treatment i

β_k: a parameter corresponding to day k

$(\alpha\beta)_{ik}$: an interaction parameter corresponding to treatment i and day k

ε_{ij}, ε_{ijk}: random error for between- and within-subject variability

prior μ, α, α_i, β_k, $(\alpha\beta)_{ik}$ ~ *N(0, 100)*

ε_{ij} ~ *N(0, σ_1)*, ε_{ijk} ~ *N(0, σ_2)*

σ_1, σ_2 ~ uniform(0, 100) or igamma(0.01,0.01)

6.10.3. Secondary Efficacy Analyses

6.10.3.1. SARS-CoV-2 Viral Load Among Participants Enrolled with ≤8 Days of Symptoms Prior to Randomization

Similar methodology, as described in Section 6.10.1, will be utilized on the subset of participants enrolled with ≤8 days of symptoms prior to randomization.

6.10.3.2. SARS-CoV-2 Viral Load AUC

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC(0-D29) will be summarized and plotted by treatment, and listed.

Additionally, AUC(0-D29) data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, log base 10 transformed baseline viral load as a covariate. The least square (LS) means and treatment differences (LY3819253 minus placebo at

each dose level) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

If deemed appropriate, the data may be log-transformed prior to analysis, and the LS means and treatment differences will be back-transformed.

A similar Bayesian model listed in Section 6.10.2, by removing the day, interaction, and within subject error term, will be applied for log base 10 transformed AUC measure analysis.

6.10.3.3. SARS-CoV-2 Clearance at Days 7, 11, 15, and 22

See Section 6.10 for more details on the definition of viral clearance.

The proportion of participants that achieve SARS-CoV-2 clearance at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that achieve SARS-Cov-2 clearance at Days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

6.10.3.4. Time to SARS-CoV-2 Clearance

See Section 6.10 for more details on the definition of viral clearance and date of viral clearance.

Time to SARS-CoV-2 clearance is defined (in days) as:

(Date when SARS-CoV-2 clearance status is first changed to "Yes" – Randomization date + 1)

If a patient has not experienced SARS-CoV-2 clearance by completion or early discontinuation of study/study treatment period, the patient will be censored at the date of their last visit during the treatment period.

Time to SARS-CoV-2 clearance will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard methodology will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to SARS-CoV-2 clearance will be presented graphically.

6.10.3.5. Symptom Resolution

Symptom resolution is defined as all symptoms (those scored 0-3) on the symptom questionnaire scored as absent.

The proportion of participants that achieve symptom resolution at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables, and listed.

In addition, the number of participants that achieve symptom resolution at Days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

6.10.3.6. Time to Symptom Resolution

Time to symptom resolution is defined (in days) as:

(First study day when symptom resolution status is changed to "Yes" – Infusion Date + 1)

If a patient has not experienced symptom resolution by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to symptom resolution will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard methodology will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to symptom resolution will be presented graphically.

6.10.3.7. Symptom Improvement

Symptom improvement is defined as a patient experiencing both:

- Symptoms on the symptom questionnaire scored as moderate or severe at baseline are subsequently scored as mild or absent, AND
- Symptoms on the symptom questionnaire scored as mild or absent at baseline are subsequently scored as absent.

The proportion of participants that achieve symptom improvement at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables, and listed.

In addition, the number of participants that achieve symptom improvement at days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

6.10.3.8. Time to Symptom Improvement

Time to symptom improvement is defined (in days) as:

(Date when symptom improvement status is changed to "Yes" – Infusion Date + 1)

If a patient has not experienced symptom improvement by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to symptom improvement will be evaluated during the study treatment period only and will be summarized by treatment and listed. In addition, a graphical presentation of the symptom improvement will be provided using a KM plot.

6.10.3.9. COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 29)

Proportion (percentage) of participants who experience deterioration by Day 29 will be analyzed and is defined as:

- COVID-19-related hospitalization (defined as ≥24 hours of acute care)
- a COVID-19-related emergency room visit, or
- death

The proportion of participants that experience deterioration by Day 29 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that experience deterioration by Day 29 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

Proportion (percentage) of participants who experience deterioration by Days 60 and 85 will also be analyzed.

6.10.3.10. Change in Symptom Questionnaire Score

Change in symptom questionnaire score (total of ratings from those symptoms scored 0-4) from baseline to Days 7, 11, 15, and 22 will be analyzed using a linear mixed-effect model. The model will contain baseline as a covariate, treatment, day, treatment-by-day interaction as fixed effects, and subject as a random effect. The LS means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. In addition, the geometric mean ratio to baseline and corresponding standard error for each treatment, and ratio of geometric mean ratio to baseline versus placebo, and corresponding 95% CIs will be presented. All available data will be used in the analysis.

6.11. Health Outcomes/Quality-of-Life Analyses

6.11.1. Symptoms and Overall Clinical Status Participant Questionnaire

Participants will rate their overall clinical status and severity of symptoms associated with COVID-19 by a daily questionnaire. This questionnaire is for outparticipants only.

Participants will complete 3 questions about their overall clinical status daily, including

- severity of symptoms
- general physical health, and
- change in overall health

The questionnaire contains these symptoms

- cough
- shortness of breath
- feeling feverish
- fatigue
- body aches and pain
- sore throat
- chills

- headache
- loss of appetite (yes/no), and
- changes in taste and smell (yes/no)

Each symptom will be scored daily by the participant as experienced during the past 24 hours.

Table PYAB.6.7. Symptom and Clinical Status Questionnaire Scores

Rating	Score
None or absent	0
Mild	1
Moderate	2
Severe	3

The Total Symptom Questionnaire score is the sum of the symptoms (excluding the loss of appetite and changes in taste and smell symptoms).

Participants will rate the loss of appetite and changes in taste and smell with yes/no responses. Responses at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

Participants will complete questions about their overall clinical status. Responses at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

Further details regarding the analysis of endpoints based on the symptom questionnaire are described in Section 6.10.3.

Further details regarding the analysis of endpoints based on the derived NIAID, WHO, and National Early Warning Score 2 (NEWS2) ordinal scales are described in Section 6.17.

6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK) analysis will be the responsibility of the Eli Lilly PK/Pharmacodynamics (PD) group prior to database lock.

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

The primary parameters for analysis will be geometric mean of concentration on Day 29. Other noncompartmental parameters, such as half-life (t1/2), AUC from time 0 to infinity (AUC[0-∞]), AUC(0-D29), maximum observed drug concentration (C_{max},) clearance, and volume of distribution may be reported.

Additional population PK model-based analyses may be performed.

Noncompartmental methods, applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the serum concentrations of LY3819253, will be used to determine the following PK parameters (Table PYAB.6.8) when possible.

Table PYAB.6.8. Pharmacokinetic Parameters

Parameter	Units[a]	Definition
AUC(0-D29)	µg.h/mL	Area under the concentration-time curve from time zero to time t, where t is Day 29
AUC(0-t_{last})	µg.h/mL	Area under the concentration-time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	µg.h/mL	Area under the concentration-time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
t_{last}		Time of the last observed drug concentration
C_{max}	µg/mL	Maximum observed drug concentration
C_{D29}	µg/mL	Observed drug concentration on Day 29
t_{max}	h	Time of maximum observed drug concentration
$t_{½}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL	L/h	Total body clearance of drug calculated
V_z	L	Volume of distribution during the terminal phase
V_{ss}	L	Volume of distribution at steady state

[a] Units of source LY3819253 serum concentration data will be ng/mL, to 1 decimal place.

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures, and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: Non-Compartmental Pharmacokinetic Style Guide. The version of the tool effective at the time of PK analysis will be followed.

6.12.1. General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for nonbolus predose sampling times, which will be set to zero.
- Maximum observed drug concentration and time of maximum observed drug concentration (t_{max}) will be reported from observed values. If C_{max} occurs at more than 1 time point, t_{max} will be assigned to the first occurrence of C_{max}.
- Area under the concentration-time curve parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive serum concentrations above the lower limit of quantification, with at least 1 of these concentrations following C_{max}.

- Area under the concentration-time curve from time 0 to infinity values, where the percentage of the total area extrapolated is more than 20%, will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.
- Half-life will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of <2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.
- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.
- The parameters, based on predicted last quantifiable drug concentration, will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters will be reported).

6.12.2. Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (BQL). Serum concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:
    - The compound is nonendogenous.
    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.
    - The time points occur before the first quantifiable concentration.
- All other BQL concentrations that do not meet the above criteria will be set to missing.
- Also, where 2 or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated, and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

6.12.3. Individual Concentration versus Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semilogarithmic plot.

6.12.4. Average Concentration versus Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.
- The predose average concentration for single-dose data from nonendogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ±10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if two-thirds of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ±10%. An average concentration estimated with less than two-thirds, but more than 3 data points, may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

6.12.5. Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

6.12.5.1. Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent postdose samples.
- For PK profiles during single dosing of nonendogenous compounds, the concentration in a predose sample is quantifiable.
- For any questionable data that do not satisfy the above criteria, the profiles will be evaluated and results reported with and without the suspected data.

6.12.5.2. Data Between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.

b. Find the most extreme value from the arithmetic mean of the log-transformed values and exclude that value from the dataset.

c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains other atypical data suspected to be an outlier and n≥6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only 1 suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

6.12.5.3. Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will imply approval of the exclusion.

6.12.6. Pharmacokinetic Statistical Methodology

All PK parameters will be summarized by treatment using descriptive statistics.

The PK parameter estimates will be evaluated to delineate dose proportionality. Log-transformed C_{max}, and AUC(0-∞) of LY3819253 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% CIs. Results of the dose proportionality analysis will be plotted.

The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality.

Example SAS code for the analysis:

```
proc mixed data=pk;
      model log_pk = log_dose / alpha=0.1 cl solution residual
      ddfm=kr2;
      estimate '700 mg'  intercept 1 log_dose 2.87506126 /
      alpha=0.1 cl; /*Log of 700 */
      estimate '2800 mg' intercept 1 log_dose 3.44715803 /
      alpha=0.1 cl; /*Log of 2800 */
      estimate '7000 mg' intercept 1 log_dose 3.84509804 /
      alpha=0.1 cl; /*Log of 7000 */
      estimate '7000 mg - 700 mg'    log_dose 0.97003679 /
      alpha=0.1 cl; /*Difference in log values of 7000 and 700 */
      ods output solutionf=est;
      ods output estimates=estims;
```

```
run;
```

6.13. Safety Analyses

Percentages will be calculated using the safety population as the denominator. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex. In the event of differential dropout rates, additional summary tables comparing exposure-adjusted incidence rates will be generated instead of, or in addition to, percentages.

Generally, the following statistical methods will be used, unless otherwise noted:

- percentage-based analyses:
  - p-values based on Fisher's exact test, and
  - odds ratios with treatment as the numerator and placebo as the denominator
- continuous measurements:
  - p-value based on ANCOVA:
    - model containing terms for treatment and the continuous covariate of baseline measurement, and
    - Type III sums of squares will be used.

6.13.1. Baseline and Postbaseline Definitions for Safety Groups

Table PYAB.6.9 provides conceptual definitions of baseline and postbaseline by analysis type. More specific detail for each submission is provided in an appendix, if necessary.

Table PYAB.6.9. Baseline and Postbaseline Definitions for Safety Groups
Initial Controlled Periods of Individual Studies
Controlled Integrated Analysis Sets

Analysis Type	Baseline	Postbaseline
TEAEs	Start of screening and ends prior to the first dose.	Starts after initiation of the first dose and ends on or prior to the day of study disposition
Treatment-Emergent Abnormal Laboratory Values and Vital Signs	Start of screening and ends prior to the first dose. All scheduled and unscheduled measurements will be included.	Starts after initiation of the first dose and ends on or prior to the day of study disposition. All scheduled and unscheduled measurements will be included.

Baseline and Postbaseline Definitions for Safety Groups
Initial Controlled Periods of Individual Studies
Controlled Integrated Analysis Sets

Analysis Type	Baseline	Postbaseline
Change from Last Baseline to Week *xx* and to Last Postbaseline for Laboratory Values and Vital Signs	Start of screening and ends prior to the first dose. The last scheduled nonmissing assessment recorded prior to the date of the first dose.	Starts after initiation of the first dose and ends on or prior to the day of study disposition. Only scheduled visits will be included. The early termination visits are considered scheduled visits.

Abbreviation: TEAE = treatment-emergent adverse event.

6.13.2. Extent of Exposure

Exposure to therapy will be represented as the total number of complete and incomplete infusions, and will be summarized using descriptive statistics.

6.13.3. Adverse Events

Summaries of AEs will include the number of participants with at least 1 AE for each treatment group. When reporting by System Organ Class (SOC) and PT, the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT will be counted only once in the frequency tables for that PT.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by SOC, PT, severity, and relationship to IP as assessed by the investigator. For each event classification term, the number of subjects experiencing a treatment-emergent AE (TEAE) with that classification term will be tabulated.

In an overview table, the number and percentage of participants who experienced a TEAE, serious adverse event (SAE), AE related to study drug, died due to an AE, discontinued from the study treatment, or discontinued from the study due to an AE will be summarized by treatment. Treatment-emergent AEs may be reported separately for the treatment period and follow-up periods.

Treatment-Emergent Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the baseline period, it will be treated as “mild” in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as

"severe" and treatment emergence will be determined by comparing with baseline severity. Missing severity will be reported as missing, without imputation.

Additional types of AEs to be summarized are described in Table PYAB.6.10.

Table PYAB.6.10. Additional Types of Adverse Events to be Summarized

Event Type	Summary Method
SAEs	SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.
TEAEs Resulting in Death	If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of preferred term.
TEAEs Leading to Study Drug Discontinuation	TEAEs for which the action taken with medication is 'Drug Withdrawal' will be identified as TEAEs that lead to study drug discontinuation. The TEAEs that lead to study drug discontinuation will be summarized for each treatment group by SOC and PT for the safety population. A by-patient listing of the TEAEs that lead to study drug discontinuation will also be provided.
Treatment-Related TEAEs	Every AE will be assessed by the investigator for its relationship to the randomly assigned study treatment.
TEAEs by Maximal Severity	Every AE will be graded by the investigator as mild, moderate, or severe, so for each patient the greatest severity observed can be obtained by comparing the severity of all of a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.
TEAEs (Not Including Serious)	The most common nonserious TEAEs will be summarized. All PT that occur in at least 5% of the safety population participants in any treatment group, when not counting the serious TEAEs, will be tabulated by SOC and PT for each treatment group. These reports will also present the total number of TEAEs for each SOC and PT.

Abbreviations: AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

SOC mapping

Medical Dictionary for Regulatory Activities PTs are assigned to a SOC through primary mappings (defined by MedDRA). Thus MedDRA PTs will appear in only 1 SOC.

Events not summarized

Events considered related by the investigator will not be summarized. Medical representatives may use the relatedness assessment when reviewing individual cases.

6.13.4. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

The following are "notable" events, from start of study drug through end of study participation:

- Deaths

- SAEs, and
- Discontinuations of study treatment due to AEs.

Narratives (patient-level data and summary paragraph) will be provided for participants in the safety population with at least 1 notable event.

Safety topics of interest are not considered notable events, unless 1 of the above criteria is met. Displays with individual patient-level data will be created for safety topics of interest using various formats such as a customized listing and/or a customized graphical patient profile as specified in the section associated with the safety topic of interest. Medical case summaries/vignettes will be provided if deemed relevant for the discussion of the safety topic of interest.

6.13.5. Hospitalization, Clinical Events, Clinical Status, and Environmental Risk Factors

The following events (observed at any time point during the study treatment period) will be summarized using descriptive statistics:

- Proportion of participants hospitalized
- Duration of hospitalization (DOH; in days),
- proportion (percentage) of participants admitted to Intensive Care Unit (ICU),
- proportion (percentage) of participants requiring mechanical ventilation (oxygen source = “Intubation/Mechanical Ventilation”)

All hospitalization events, procedures of special interest, and environmental risk factors will be listed.

In the event that a participant has an ongoing hospitalization event at the time of study disposition, the hospitalization end date will be imputed to the study disposition date.

6.13.6. Clinical Laboratory Evaluation

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol (See Protocol Appendix 2). However, unscheduled measurements of planned analytes will be included/excluded as specified in the relevant sections. Examples of unplanned measurements include those that the clinical investigator orders as a repeat test or “retest” of a laboratory test in case of an abnormal value, and those the investigator orders for a “follow-up visit” due to clinical concerns. Some planned analytes are intended for individual case reviews and will not be included in group-level summaries.

6.13.7. Vital Signs and Other Physical Findings

The planned summaries are provided in Table PYAB.6.11. The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, weight, and temperature.

The criteria for identifying subjects with treatment-emergent abnormalities are based on Table PYAB.6.12.

Some of the analyses of vital signs may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in Table PYAB.6.11 and not provided would be available upon request. For example, box plots for observed values, scatter plots, and shift tables could be provided as interactive displays for medical review.

Table PYAB.6.11. Tables and Figures Produced to Support Vital Signs and Physical Characteristics

Analysis Type	Analysis Details
Box plots for observed values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • No inferential statistics.
Box plots for change from baseline values by visit	• Includes participants who have both a baseline and a postbaseline planned measurement. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot along with a p-value using the ANCOVA model.
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	• Each study individually and studies combined will be displayed. • Includes participants who have both a baseline and postbaseline observation. • Unplanned measurements will be included. • Lines indicating the reference limits will be included. • **Max vs Max:** Maximum baseline versus maximum postbaseline. • **Min vs Min:** Minimum baseline versus minimum postbaseline.

Summary tables for shifts to high/low	• Limits provided by the central lab service will be used to define low and high.
	• **Normal/high to low:** Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low.
	  ○ Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 postbaseline result.
	• **Normal/low to high:** Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high.
	  ○ Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period.
	• Statistical comparisons will be included.

Abbreviations: ANCOVA = anaylsis of covariance; Max = maximum; Min = minimum.

Table PYAB.6.12. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes in Adults

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Temperature	<96°F (<35.6°C) and decrease ≥2°F (≥1.1°C) from baseline	≥101°F (≥38.3°C) and increase ≥2°F (≥1.1°C) from baseline

Abbreviations: BP = blood pressure; bpm = beats per minute.

6.13.8. Electrocardiograms

Results of electrocardiograms (ECGs) performed during the study will not be reported.

6.13.9. Immunogenicity

If data from validated immunogenicity assays are available, treatment-emergent antidrug antibodies (TE-ADAs) may be assessed.

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer compared with the minimum required dilution if no antidrug antibodies (ADAs) were detected at baseline (treatment-induced ADA) or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADAs and who are TE-ADA positive (TE-ADA+) to LY3819253 may be tabulated.

The distribution of titers and frequency of neutralizing antibodies (if assessed) for the TE-ADA+ participants may also be tabulated.

The relationship between the presence of antibodies and PK parameters, efficacy response, or safety to LY3819253 may also be assessed.

6.14. Subgroup Analyses

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

Subgroup analyses will be conducted for the primary endpoint. Subgroups may include

- time from symptom onset to study randomization
- baseline severity of COVID-19

- age group (<65, ≥65 years old) and (<65, ≥65 to <75, ≥75 to <85, ≥85 years old)
- gender (male, female)
- race
- ethnicity
- baseline weight (<60 kg, ≥60 to <100 kg, ≥100 kg)
- baseline BMI (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2 to <40 kg/m^2, and ≥40 kg/m^2)
- concomitant medication of interest use (yes/no)
- High-risk status for severe COVID-19 illness

Treatment group differences will be evaluated within each category of the subgroup regardless of whether the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided, that is, no inferential testing.

The analysis of additional subgroups and/or subgroup analyses on additional endpoints will not require an amendment to the SAP.

Within each subgroup category the relevant summary measure by treatment, treatment differences (compared to placebo) and 95% CIs will be displayed. Also, p-values using appropriate statistical tests for treatment comparison will be provided. Forest plots may be generated to display the treatment difference and 95% CIs for selected efficacy subgroup analyses.

Baseline severity of COVID-19 will be defined using the following definition.

- Severity will be defined to be **Moderate** if
    - "Shortness of breath" symptom score > 0 (i.e., not "None or Absent") on the symptom questionnaire OR
    - Respiration rate ≥20 breaths per minute AND Pulse ≥95 beats per minute.
- Else, severity will be defined to be **Mild**.

Concomitant therapies of interest include remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine, anticoagulants, or other investigational interventions. Details of the medications included in this subgroup are provided below in Table PYAB.6.13.

Table PYAB.6.13. Concomitant Medications of Interest Subgroup

Drug name	ATC Code	ATC Preferred Term
Remdesivir	---	REMDESIVIR
Kaletra	J05AR	KALETRA
Lopinavir	J05AR	LOPINAVIR
Hydroxychloroquine	P01BA	HYDROCHLOROQUINE
Chloroquine	P01BA	CHLOROQUINE
Baricitinib	L04AA	BARICITINIB
Heparin	B01AB	HEPARIN
Fondaparinux	B01AX	FONDIIPARINUX
Argatroban	B01AE	ARGATROBAN

Abbreviation: ATC = anatomical therapeutic chemical.

6.15. Protocol Violations

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) are defined as those deviations from the protocol that would potentially compromise participants' safety, data integrity, or study outcome.

A separate document known as the "PYAB Trial Issues Management Plan" describes the categories and subcategories of IPDs and how the IPDs would be identified.

The number and percentage of participants having IPDs will be summarized within category and subcategory of deviations by dosing regimen.

A by-patient listing of IPDs will be provided.

6.16. Interim Analyses and Data Monitoring

6.16.1. Interim Analyses

The ongoing study may be modified based on planned interim analyses. Based on the observed data at the time of the interim analyses, the study may

- suspend enrollment to an LY3819253 treatment arm (or arms) demonstrating lack of efficacy, and/or
- initiate/expand enrollment to an additional/existing LY3819253 treatment arm (or arms).

The modifications proposed are done so to ensure participants are being exposed to treatment with an acceptable risk-benefit profile during the ongoing trial. Additionally, the potential modifications will provide information to more fully characterize the dose response profile.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by Assessment Committee (AC) members. The AC will review rolling safety data after approximately 20, 40, and 60 participants are enrolled to monitor participant safety. These initial individual reviews of unblinded safety data will occur no less often than every 30 days, in case of slower than anticipated enrollment. This is intended as an individual AC member review and does not require a formal meeting. However, any AC member can ask for a full AC meeting based on the rolling review at any time.

The AC will initially review summary unblinded data after approximately 25% (100) participants have had an opportunity to reach Day 11. It is anticipated that subsequent interim analyses will occur after approximately 50%, 75%, and all participants have had an opportunity to reach Day 11. Safety will be evaluated at each of these interim analyses and benefit/risk of LY3819253 will be assessed if needed. An additional interim analysis is planned when approximately 40% participants in the 7000 mg arm have had an opportunity to reach Day 11. However, this analysis may be combined with the approximately 50% interim analysis if possible.

The PYAB study may be stopped early based on an unacceptable safety signal(s).

Additionally, the pre-planned interim analysis at 40% of participants in the 7000 mg arm completing 11 days will inform potential modification to the PYAB study. These modifications include:

- Dropping the 700 mg dose arm if either of these 2 conditions hold:

$$\mathbf{P(\Delta_{LY700mg} - \Delta_{placebo} > -0.3) > 0.8}$$

or

$$\mathbf{P(\Delta_{LY7,000mg} - \Delta_{LY700mg} < -0.3) > 0.85}$$

- Enrolling up to 100 additional participants to a new or existing dose arm to better characterize the dose-response relationship if:

$$\mathbf{P(\Delta_{LY700mg} - \Delta_{placebo} < -0.3) > 0.85}$$

Note: Δ represents viral load change from baseline in log base 10 scale at Day 11. Details of the Bayesian methodology associated with the SARS-CoV-2 viral load can be found in Section 6.10.2.

Only the AC is authorized to evaluate unblinded interim analyses and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Further details regarding the interim analyses can be found in the AC Charter.

Periodic adjustments to the allocation ratio may be made to achieve an equal allocation across treatment arms at the conclusion of enrollment.

6.16.2. Data Monitoring Committee/Assessment Committee

The sponsor will form an AC to analyze the interim study data. To minimize any bias introduced into the analysis of the study results, analysis plans will be finalized and approved prior to the interim analyses.

The primary goal of the AC is to review the interim results regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Overall committee structure information is in Protocol Section 10.1.5. Details of the AC will be provided in the AC charter. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

6.17. Planned Exploratory Analyses

6.17.1. Protocol-Defined Exploratory Endpoints

Protocol defined exploratory endpoints are described in Section 4.3 and analysis details are provided in the following sections.

6.17.1.1. Viral Resistance

If appropriate, the evaluation of viral resistance will be conducted as described in a separate bioanalytical analysis plan.

6.17.1.2. SpO2 AUC Assessed through Day 29

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the daily SpO2 values. If multiple values are collected on a given day, the average will be used. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC(0-D29) will be summarized and plotted by treatment, and listed.

Additionally, SpO2 AUC(0-D29) data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, SpO2 baseline measurement as a covariate. The LS means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.17.1.3. Symptom Questionnaire AUC assessed through Day 29

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the mean daily Symptom Questionnaire total score. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The Symptom Questionnaire AUC(0-D29) will be summarized and plotted by treatment, and listed.

Additionally, Symptom Questionnaire AUC(0-D29) data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, Symptom Questionnaire baseline measurement as a covariate. The LS means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.17.1.4. Worst NIAID Score

The lowest daily value from Day 1 through Day 28 for a patient on the NIAID ordinal scale will be analyzed using the van Elteren test adjusting for the randomization stratification factors. Mean values will be calculated and differences in treatment effect estimates at Days 7, 11, 15, and 22 will be analyzed. Mean value by treatment group will be plotted over time.

6.17.2. Additional Exploratory Analyses not Defined in the Protocol

In addition to the protocol defined endpoints, additional sensitivity analyses may be performed if deemed appropriate. Additional analyses include:

6.17.2.1. Clinical Worsening based on the NIAID Scale

Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Days 7, 11, 15, and 22.

6.17.2.2. National Early Warning Score

The highest daily value from Day 1 through Day 28 for a patient on the National Early Warning Score (NEWS2) ordinal scale will be analyzed using the van Elteren test adjusting for the randomization stratification factors. Mean values will be calculated and differences in treatment effect estimates at Days 7, 11, 15, and 22 will be analyzed. Mean value by treatment group will be plotted over time.

6.17.2.3. NEWS2 Consciousness Level

Consciousness level assessed by NEWS2 will be summarized using a logistic regression analysis as described in Section 6.1.4.

6.17.2.4. NIAID/NEWS2 Overall Improvement

Treatment comparisons for overall improvement on the ordinal scales (NIAID, NEWS2) between LY3819253 and placebo will be made using proportional odds model with baseline stratification factor and treatment group in the model. Overall improvement will be evaluated at Days 7, 11, 15, and 22.

6.17.2.5. Time to Hospitalization

Time to Hospitalization is defined (in days) as:

(First study day when hospitalized status is changed to "Yes" – Infusion Date +1)

If a patient has been admitted to the hospital or ICU by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to hospitalization will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard methodology will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to hospitalization may be presented graphically.

6.17.2.6. Duration of Hospitalization

Treatment comparisons of the mean DOH (in days) will be compared between LY3819253 and placebo will be made using nonparametric rank-sum test (such as Mann-Whitney or van Elteren test).

6.17.2.7. Time to Admission to ICU

Time to ICU is defined (in days) as:

(First study day when ICU status is changed to "Yes" – Infusion Date +1)

If a patient has been admitted to the hospital or ICU by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to ICU will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard methodology will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to ICU may be presented graphically.

6.17.2.8. Proportions of Participants Hospitalized, Admitted to the ICU, Requiring Mechanical Ventilation

The proportion of participants hospitalized, admitted to the ICU, requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation") will be evaluated separately using a logistic regression analysis with treatment and baseline stratification in the model. These endpoints will be evaluated at Days 7, 11, 15, and 22.

6.17.2.9. Days since Symptom Onset Cutpoint Analysis

An exploratory cutpoint analysis may be performed to determine the number of days since symptom onset maximizes the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load between treatment with LY3819253 and placebo.

6.18. Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.19. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participants/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (e.g., the CSR, manuscripts, and so forth).

7. References

Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics.* 2005;61(3):738-748. https://doi.org/10.1111/j.1541-0420.2005.00344.x

Firth D. Bias reduction of maximum likelihood estimates. *Biometrika.* 1993;80(1):27-38. https://doi.org/10.2307/2336755

Gould, AL. BMA-Mod: a Bayesian model averaging strategy for determining dose-response relationships in the presence of model uncertainty. *Biom J*. 2019;61(5):1141-1159. https://doi.org/10.1002/bimj.201700211

[OCP] Office of Clinical Pharmacology Division of Pharmacometrics. Request for qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. Available at: https://www.fda.gov/media/99313/download. Published 2015.

8. Appendices

Appendix 1. NEWS2 Scoring Scale

The National Early Warning Score 2 (NEWS2) is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when participants present to, or are being monitored in hospital. Six simple physiological parameters form the basis of the scoring system:

1. respiration rate
2. oxygen saturation
3. systolic blood pressure (BP)
4. pulse rate
5. level of consciousness or new confusion
6. temperature.

Figure APP.1.1. NEWS2 Scoring

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Abbreviations: CVPU =Confusion, Voice, Pain, Unresponsive; NEWS2 = National Early Warning Score 2; SpO2 = oxygen saturation.

Figure APP.1.2. NEWS2 Scoring Clinical Risk Thresholds

NEW score	Clinical risk
Aggregate score 0–4	Low
Red score Score of 3 in any individual parameter	Low–medium
Aggregate score 5–6	Medium
Aggregate score 7 or more	High

Abbreviation: NEWS2 = national Early Warning Score 2.

Appendix 2. NIAID Scoring Scale

The National Institute of Allergy and Infectious Diseases (NIAID) scoring scale will be assessed daily and defined as the lowest score achieved for that day.

The scoring is based on the clinical status of the patient as described below.

Table APP.1.2. NIAID Clinical Status Scoring

NIAID Score	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3	Hospitalized, on noninvasive ventilation or high flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

Abbreviation: NIAID = National Institute of Allergy and Infectious Diseases.

Leo Document ID = deed6114-7185-40b1-ab19-95aca275b9cc

Approver:PPD

Approval Date & Time: 19-Jun-2020 12:13:56 GMT

Signature meaning: Approved

1. Statistical Analysis Plan: J2W-MC-PYAB: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of LY3819253 in Participants with Mild to Moderate COVID-19 Illness

LY3819253 - Mild to Moderate COVID-19 Illness

This is a Phase 2, randomized, double-blind, placebo-controlled, single-dose study in participants with mild to moderate COVID-19 illness to evaluate the efficacy and safety of LY3819253.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol J2W-MC-PYAB
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 31-Jul-2020 GMT

2. Table of Contents

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to unblinding.

DOCUMENT HISTORY	
Document	**Date**
Version 2	30-Jul-2020
Original SAP	19-Jun-2020

Overall Rationale for the revision on Version 1:
A new treatment arm is added to this study with the combination of LY3819253 and LY3832479.

Section # and Name	Description of Change	Brief Rationale
4 Study Objectives	Added text for the combination with LY3832479 in objectives	For the addition of LY3832479
4 Study Objectives	Updated PK objective and endpoints	For the addition of LY3832479
5.1.3 Double-Blind Treatment and Assessment Period	Updated text, moved text around and updated the treatment table	Moved text for better flow of information. Updated text and table for the addition of the new combination treatment
5.2 Determination of Sample Size	Added text	Addition of new treatment arms
5.3.1 Randomization	Added text	Addition of new treatment arms
6.1 General Considerations	Added text	Addition of generalized linear model as an optional method for a longitudinal binary endpoint
6.1.1 Analysis Populations	Added text	Addition of new treatment arms
6.1.4 Analysis Methods	Replaced health outcome with pharmacodynamic	For consistency with protocol of health outcome.
6.3.2 Last Observation Carried Forward (LOCF)	Added text	To add an alternative missing data imputation strategy
6.3.5 Modified Last Observation Carried Forward	Added section	To describe an alternative missing data imputation strategy
6.7 Participant Characteristics	Updated text	To add categories on age grouping, symptom onset, SpO_2, and prior therapy of interest
6.10.1 Primary Outcome and Methodology	Removed text: symptom onset strata from the model, imputation of 1 if viral load value of 0.	To avoid collinearity between symptom onset strata and baseline viral load. Viral load data is not going to impute which will be calculated from cycle threshold.
6.10.2.1 Dose Response Modeling	Added text	To add more details for candidate models for dose response.
6.10.3.2 SARS-CoV-2 Viral Load AUC	Added text	AUC0-11(day)

Section # and Name	Description of Change	Brief Rationale
6.10.3.4 Time to SARS-CoV-2 Clearance	Modified definition of time to clearance to reference infusion date as opposed to randomization date.	Time to SARS-CoV-2 clearance definition clarified
6.10.3.4 Time to SARS-CoV-2 Clearance	'methodology' changed to 'model'	Clarification of text
6.10.3.6 Time to Symptom Resolution	'methodology' changed to 'model'	Clarification of text
6.10.3.10 Change in Symptom Questionnaire Score	Changed scoring from 0-4 to 0-3	Clarification of text
6.11 Health Outcomes and Quality of Life Analyses	Removed	It is not in protocol
6.12 Safety Analyses	Added text	Added stratification factor in the model
6.12.5 Hospitalization, Clinical Events, Clinical Status, and Environmental Risk Factors	Updated text	Referred to Section 6.16.2.6 and Section 6.16.2.8 for analysis method.
6.12.7 Vital Signs and Other Physical Findings	Added text	Added SpO_2, respiratory rate, FiO2
6.12.9 Immunogenicity	Added text	For the addition of LY3832479
6.13 Subgroup Analyses	Added text	Added age grouping and the definition of COVID-19 disease severity.
6.15.1 Interim Analyses	Updated text	For consistency with protocol Section 9.5
6.16.1.2	Added new endpoint	For addition of SpO_2 AUC(0-D11)
6.16.1.3	Added new endpoint	For addition of symptoms AUC(0-D11)
6.16.2.5 Time to Hospitalization	'methodology' changed to 'model'	Clarification of text
6.16.2.7 Time to Admission to ICU	'methodology' changed to 'model'	Clarification of text
6.16.2.10	Added new endpoint	For the addition of new SpO2 endpoint using different cutoffs

4. Study Objectives

4.1. Primary Objective

The primary objective of this trial is to characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on upper respiratory tract SARS-CoV-2 (COVID-19) viral load and viral clearance among participants with mild to moderate COVID-19 illness. The primary endpoint is the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load based on nasopharyngeal swab sampling for reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. Statistical hypothesis testing for the primary endpoint will be conducted using a mixed-effects model repeated measures (MMRM) analysis method at the 2-sided 0.05 level.

4.2. Secondary Objectives

Table PYAB.4.1. Secondary Objectives of Study J2W-MC-PYAB

Objectives	Endpoints
Secondary	
Characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on: • safety	• Safety assessments such as AEs and SAEs
• SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
• symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15, and 22 • Change in symptom score (total of ratings) from baseline to Days 7, 11, 15, and 22
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15, and 22
• SARS-CoV-2 viral load and viral clearance	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, and 22) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29

Secondary Objectives of Study J2W-MC-PYAB

Objectives	Endpoints
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 o COVID-19-related hospitalization (defined as ≥24 hours of acute care) o a COVID-19-related emergency room visit, or o death
Additional Secondary	
Characterize the pharmacokinetics of LY3819253 and LY3819253 in combination with LY3832479	• Mean concentration of LY3819253 alone and in the presence of LY3832479 on Day 29 • Mean concentration of LY3832479 in presence of LY3819253 on Day 29

Abbreviations: AE = adverse event; SAE = serious adverse event.

4.3. Exploratory Objectives

Table PYAB.4.2. Exploratory Objectives of Study J2W-MC-PYAB

Objectives	Endpoints
Exploratory	
Characterize emergence of viral resistance to LY3819253 and LY3819253 in combination with LY3832479	• Comparison from baseline to the last evaluable timepoint up to Day 29
Characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on:	
• SpO_2 over time	• SpO_2 AUC assessed through Day 29
• symptom severity	• Symptom severity as assessed by mean AUC through Day 29 of symptom questionnaire
• overall improvement on the NIAID Ordinal Scale	• Comparison of the mean worst daily NIAID ordinal scale values at Days 7, 11, 15, and 22

Abbreviations: AUC = area under the response-time curve; NIAID = National Institute of Allergy and Infectious Diseases.

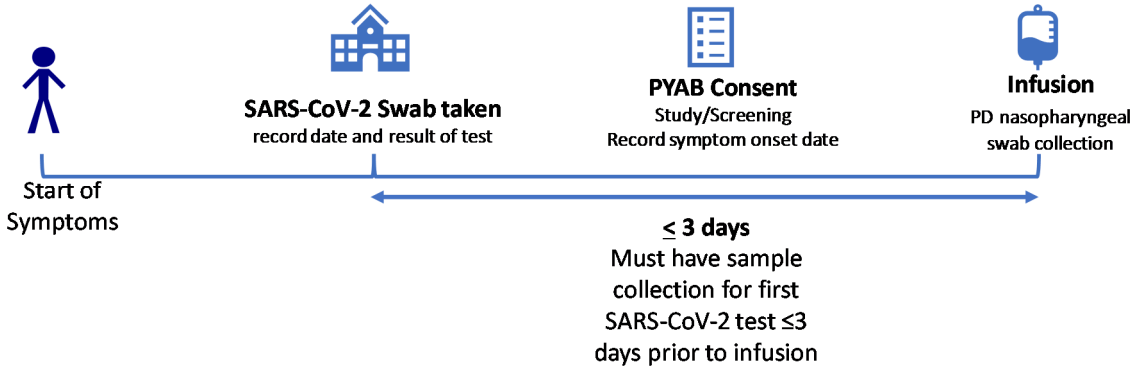
Additional exploratory objectives not previously defined in the protocol are described in Section 6.16.2.

5. Study Design

5.1. Summary of Study Design

This is a Phase 2, placebo-controlled, double-blind, randomized single-dose study in participants with mild to moderate COVID-19 illness.

5.1.1. Design Outline



Abbreviations: IV = intravenous; PD = pharmacodynamic; PYAB = Study J2W-MC-PYAB.

Figure PYAB.5.1. Overview of participant flow from time of SARS-CoV-2 symptoms to IV infusion.

5.1.2. Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures. The participant may enter the study with a previous positive SARS-CoV-2 viral test result from an external testing facility. This test result must be the first time the patient has tested positive for SARS-CoV-2.

The investigator will review symptoms, risk factors, and other noninvasive inclusion and exclusion criteria prior to any invasive procedures. If the participant is eligible after this review, then the site will perform the invasive procedures to confirm eligibility.

5.1.3. Double-Blind Treatment and Assessment Period

This is the general sequence of events during the treatment and assessment period:

- Complete baseline procedures and sample collection
- Participants are randomized to an intervention group
- Participants receive study intervention, and
- Complete all safety monitoring and post-infusion sample collection.

Table PYAB.5.1 describes the planned treatment arms.

Table PYAB.5.1. Treatment Arms of Study J2W-MC-PYAB

Treatment arms	Dose	Intervention
1	---	placebo
2	700 mg	LY3819253
3	2800 mg	LY3819253
4	7000 mg	LY3819253
5	To Be Determined	LY3819253
6	2800 mg + 2800 mg	LY3819253+LY3832479
7	To Be Determined	LY3819253+LY3832479

An optional LY3819253 Treatment Arm 5 may be added based on interim analysis results. An optional combination Treatment Arm 7 may be initiated at the discretion of the sponsor team.

5.1.4. Posttreatment Follow-up

Posttreatment follow-up assessments will be conducted at Day 60 and Day 85 to assess clinical status and for adverse events (AEs). Strategies to manage infection risks and reduce the burden of return visits, such as home visits, may be used by sites.

5.2. Determination of Sample Size

The initial planned sample size is approximately 500 participants equally allocated across 5 treatment arms (Treatment Arms 1 through 4 and 6). Additional placebo participants may be enrolled to ensure up to 50 concurrent controls for each Treatment Arm 5 through 7. Up to 100 additional participants may be introduced for each optional treatment arm. See Protocol Section 9.5 for interim analysis details.

Participants will be stratified by duration since symptom onset category (≤8 days vs >8 days).

A viral dynamic model was used to simulate viral loads over time for participants treated with LY3819253 and placebo. This simulated population and Monte Carlo methods were used to estimate statistical power associated with the comparison of change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load between LY3819253 and placebo. The mean log change from baseline to Day 11 for LY3819253 and placebo in the simulated population were approximately 4.38 and -3.48 (standard deviation [SD] 1.9), respectively, representing an average of 87% viral load reduction.

Given these assumptions, an assumed sample size of 100 participants per arm provides approximately 91% power to test superiority of intervention group versus placebo in effect on viral load, as measured by change from baseline to Day 11 (±4 days), at the 2-sided 0.05 alpha level.

Periodic adjustments to the allocation ratio of participants will be informed by planned interim analyses. See Protocol Section 9.5 for details.

5.3. Method of Assignment to Treatment

5.3.1. Randomization

All participants will be centrally randomized to study intervention using an interactive web-response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Participants will be stratified by duration since symptom onset to randomization (≤8 days vs >8 days).

All eligible participants will be randomized initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made to achieve an equal allocation across the treatment arms at the end of enrollment. If up to 50 additional placebo participants are enrolled, then the allocation ratio may change accordingly. See Protocol Section 9.5 for details.

5.3.2. Blinding

This is a double-blinded study. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base lock at the conclusion of the study.

Table PYAB.5.2 describes general procedures for unblinding.

Table PYAB.5.2. Unblinding Procedures for Study J2W-MC-PYAB

Unblinding (IWRS)	• Emergency unblinding for adverse events may be performed through the IWRS. All actions resulting in an unblinding event are recorded and reported by the IWRS • In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted • Participant safety must always be the first consideration in making such a determination. However, the investigator should make all attempts to contact the Medical Monitor in advance of unblinding • If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance • The date and reason that the blind was broken must be recorded in the source documentation and case report form

Abbreviation: IWRS = interactive web-response system.

If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion stopped. If any amount of study intervention was administered, follow procedures according to the Schedule of Activities (SoA).

6. A Priori Statistical Methods

6.1. General Considerations

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

All tables, figures, and listings will be created using the clinical trial database (unless otherwise noted), including data during study participation. While not reflected in a table, figure, or listing, any data collected after study participation (e.g., in the Lilly Safety System or collected through queries to the investigator) may be discussed in a clinical study report (CSR) or integrated summary document when deemed relevant.

Unless otherwise noted, displays will include columns for each treatment group, and in case of multiple doses of investigational product (IP), another column for IP doses combined will be displayed. A column that combines IP groups with placebo and/or active controls (i.e., a total column) will not be created.

Not all displays described in this statistical analysis plan (SAP) will necessarily be included in the CSR. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of, or in addition to, a static display. Any display described in this SAP and not provided would be available upon request.

For a binary endpoint collected in a longitudinal fashion, a generalized linear mixed-effect model may be applied assuming missing at random (MAR) if deemed appropriate.

All statistical analyses will be performed using SAS software Version 9.4 (or a higher version), FACTS 6.0 (or a higher version), and/or R 3.6 (or a higher version).

6.1.1. Analysis Populations

Patient populations are defined in Table PYAB.6.1 along with the analysis to be used to conduct. The treatment groups and inferential comparisons described in Table PYAB.6.1 will be used unless otherwise specified. Also, unless otherwise specified, for all populations/analysis, participants will be analyzed according to the treatment to which they were assigned.

Table PYAB.6.1. Analysis Populations

Population	Description
Entered	**Definition:** All participants who signed informed consent. **Purpose:** Used for disposition analysis. **Treatment Groups:** None **Inferential Comparisons:** None
Efficacy	**Definition:** All randomized participants who received study intervention and provided baseline and at least 1 postbaseline measure viral load measurement. Participants will be analyzed according to the intervention to which they were randomized (Intention to treat). **Purpose:** Used for efficacy and pharmacodynamic variables analyses. **Treatment Groups (Short Label):** 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), LY total, and placebo (Pbo). Additional optional combination arm may be added if decided. **Inferential Comparisons:** Each LY dose versus placebo
Safety	**Definition:** All participants randomly assigned and who received any amount of study intervention. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses. **Treatment Groups (Short Label):** 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), LY total, and placebo (Pbo). Additional optional combination arm may be added if decided. **Inferential Comparisons:** LY total versus placebo
Pharmacokinetic and PK/PD (exposure-response relationships)	**Definition:** All randomized participants who received study intervention and have at least 1 postdose PK sample. Participants will be analyzed according to the intervention they received. **Purpose:** Used for PK analyses. **Treatment Groups (Short Label):** 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) and placebo (Pbo). Additional optional combination arm may be added if decided. **Inferential Comparisons:** Each LY dose versus placebo

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic.

6.1.2. Definition of Study Baseline

Unless otherwise specified, for efficacy and health outcome, baseline is defined as the last nonmissing assessment recorded on, or prior to, the date of the first study drug administration at study Day 1.

Baseline for safety analysis is described in the safety section.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline values or the value at the visit is missing for a particular variable, then the change from baseline is defined as missing.

6.1.3. Study Time Intervals

To calculate the length of any time interval or time period in this study, the following formula will be used:

$$Length\ of\ interval\ (days) = End\ Date - Interval\ Start\ Date + 1$$

To convert any time length from days to weeks, the following formula will be used:

$$Length\ of\ interval\ (weeks) = Length\ of\ interval\ (days)/7$$

Only for the purpose of calculating the length of study period time intervals, the words "prior to" in Table PYAB.6.2 should be understood to mean "the day before" while the words "after" should be understood to mean "the day after." For the purpose of determining whether a date/time lies within an interval, these words are intended to convey whether the start or end of the period is inclusive of the specified date.

Table PYAB.6.2. Definition of Study Period Time Intervals

Study Period	Interval Start Definition	Interval End Definition
Screening: All participants who sign informed consent are considered as entering the Screening Period.	Informed consent date	Prior to the start of Treatment and Assessment Period.
Treatment and Assessment Period: All participants who are randomized to the study are considered as entering the Treatment Period.	At the start of study drug administration date/time following randomization. For participants who are randomized but not dosed, the Treatment and Assessment Period starts on the date of randomization.	The minimum of treatment period discontinued date, study discontinuation date, or first Post Treatment Follow-Up visit date.
Post-Treatment Follow-Up: All participants who had a follow up visit are considered as entering follow-up period.	After the Treatment and Assessment Period ends.	The maximum of the last study visit date or study disposition date.

6.1.4. Analysis Methods

Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. SARS-CoV-2 viral load data will be evaluated in log base 10 scale. The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, Mann-Whitney, or van Elteren tests, is deemed to be more appropriate.

All hypothesis tests will be 2-sided at an alpha level of 0.05. No adjustment for multiplicity will be performed in this study.

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. Additional exploratory analyses of the data may be conducted as deemed appropriate, including PK/PD model-based exposure-response analyses.

Table PYAB.6.3. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Method	Analysis
Descriptive Statistics	Number of participants, mean, standard deviation, median, minimum, and maximum for continuous measures, and frequency counts and percentages for categorical measures
Kaplan-Meier curves and summary statistics, Cox proportional hazards	Treatment comparisons of time-to-event based endpoints
Logistic regression analysis	Treatment comparisons of binary variables with treatment and randomization stratification variables in the model
Nonparametric (e.g., Mann-Whitney or van Elteren tests)	Treatment comparison of ordinal, nominal, and non-normally distributed continuous variables
Mixed-effects model repeated measures (MMRM) analysis	Treatment comparisons of continuous efficacy and health outcome variables

Treatment comparisons of continuous efficacy, and pharmacodynamic variables with multiple postbaseline measurements will be made using MMRM analysis. When MMRM is used, it includes: (a) treatment group, (b) stratification factor of duration since symptom onset to randomization (≤8 days vs >8 days), (c) baseline value in the model, (d) visit, and (e) the interactions of treatment-by-visit as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The first structure to yield convergence will be used for inference. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% confidence interval (CI) will also be reported. Unless otherwise specified, for MMRM, reported data from only planned visits will be used as the primary analysis.

Treatment comparisons of continuous efficacy, safety, and health outcome variables with a single postbaseline timepoint will be made using analysis of covariance (ANCOVA) with:- (a) treatment group, (b) stratification factor of duration since symptom onset to randomization (≤8 days vs >8 days), and (c) baseline value in the model. Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value-, and 95% CI, unless otherwise specified, will also be reported. Missing data imputation method for the ANCOVA model is specified in Section 6.3.

Treatment comparisons for binary endpoints will be made using logistic regression with a Firth penalized likelihood (Firth 1993). The model will include the treatment groups and duration since symptom onset to randomization category (≤8 days vs >8 days). The Firth correction can be implemented in PROC Logistic by including *'firth'* as an option in the model statement. The

odds ratio and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be reported.

The Kaplan-Meier (KM) product limit method will be used for time-to-event analyses. The hazard ratio and log-rank test, stratified by duration since symptom onset to randomization (≤8 days vs >8 days), will be reported. Time for all analyses will be described in units of days.

6.2. Adjustments for Covariates

Unless otherwise specified, efficacy analyses will adjust for the baseline value of the endpoint and by the randomization stratification factor, duration since symptom onset to randomization (≤8 days vs >8 days), when modeling estimates and calculating p-values.

6.3. Handling of Dropouts or Missing Data

The SoA, outlined in the protocol, specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis but may be reported as a protocol deviation (see Section 6.14).

6.3.1. Non-Responder Imputation (NRI)

For analysis of categorical efficacy and pharmacodynamic variables, missing data will be imputed using an NRI method. Participants will be considered nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest.

In addition, participants who were not adequately assessed to determine if they meet the clinical requirements for response at the time point of interest are also considered to have failed treatment.

6.3.2. Last Observation Carried Forward (LOCF)

A last observation analysis is performed by carrying forward the last postbaseline assessment for the continuous measures or ordinal scale measures. For participants discontinuing the study, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation.

After LOCF imputation, data from participants with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. These LOCF analyses help ensure that the maximum number of randomized participants who were assessed postbaseline will be included in the analyses.

Similarly, for analysis of viral clearance (yes/no), missing data will be imputed using the LOCF method. Specifically:

- For patients that demonstrate a last nonmissing postbaseline viral clearance status of ‘Yes’ (see Section 6.10), subsequent missing viral clearance status assessments will be considered to be ‘Yes.’

- For patients that demonstrate a last nonmissing postbaseline viral clearance status of 'No' (see Section 6.10), subsequent missing viral clearance status assessments will be considered to be 'No.'

After imputation, data from participants with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. The application of LOCF imputation to viral clearance helps ensure that the maximum number of randomized participants who were assessed postbaseline will be included in the analyses and favorable terminal events (clearance) are represented.

6.3.3. Mixed-Effects Model Repeated Measures (MMRM)

For continuous variables, the primary analysis will be MMRM with the MAR assumption for handling missing data. This analysis considers both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis.

6.3.4. Highest Disease States Imputation (HDSI)

For the analyses related to National Institute of Allergy and Infectious Diseases (NIAID)/World Health Organization (WHO) ordinal scales, the following imputation will be considered if applicable.

For participants whose data is missing during the hospitalization period (not yet recovered), a score of 7, which is the highest value for a hospitalization status, will be used for imputation.

For participants whose data is missing after recovery or discharged, a score of 3, the highest value for a recovery or nonhospitalized status, will be used for imputation.

6.3.5. Modified Last Observation Carried Forward

Analyses of symptom data will utilize a modified last observation analysis (mLOCF). The mLOCF method is performed by carrying forward the last nonmissing postbaseline assessment to the subsequent missing assessments for analysis. For patients who die, all missing collection time points subsequent to the date of death will be imputed to Severe.

After mLOCF imputation, data from participants with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. The mLOCF imputation helps ensure that the maximum number of randomized participants who were assessed postbaseline will be included in the analyses and unfavorable terminal events are represented.

6.4. Multicenter Studies

Differences between study centers will not be a feature of the statistical analyses for this study. Baseline variables and demographics may be described by site.

Individual center results may be presented, where appropriate, when the centers have sufficient numbers of participants to make such analysis potentially valuable. The possibility of qualitative or quantitative treatment-by-center interaction may be explored.

6.5. Multiple Comparisons/Multiplicity

As this is a Phase 2 (nonconfirmatory) dose-finding study; no adjustments for multiple comparisons will be made.

6.6. Participant Disposition

The treatment period disposition and study disposition will be summarized for the safety population. Disposition summaries will be by treatment group. Summaries will also include reason for discontinuation from the study tabulated by treatment group.

All participants who are randomized and discontinued from study treatment or from the study will be listed, and the timing of discontinuing (from randomization) the study will be reported. If known, a reason for their discontinuation will be given.

In addition, a graphical summary (i.e., KM plot) of time from randomization to early permanent discontinuation of study or study treatment due to AEs may be generated if there are a substantial number of such events. This graphical summary would be by treatment group and include the log-rank test results.

Table PYAB.6.4. Tables and Figures Related to Disposition

Analysis	Details
Patient Disposition	Number and percentage of participants by reason for • study discontinuation and • study treatment period discontinuation A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) No inferential statistics
Listing of study and study treatment disposition	--
Listing of participants discontinuing due to a decision-related reason (loss to follow-up, patient decision, or investigator decision)	Variables included the reason for study discontinuation, the text collected in the specify field associated with the reasons for discontinuation, and the dates of discontinuation The text in the specified field should provide information to support that the reason is unrelated to efficacy or safety
Time to early discontinuation of study treatment due to adverse events (AEs)	Presented as a figure (if necessary)

6.7. Participant Characteristics

Patient demographic variables and baseline characteristics will be summarized by treatment and overall for the safety population. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline covariates across treatment groups will be performed. By-patient listings of basic demographic characteristics (i.e., age, sex, race, racial subgroup, ethnicity, and body weight) for the efficacy population will be provided.

Table PYAB.6.5. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Analysis	Details
Baseline Demographic Characteristics	**Variables to be included:** • Age • Age groups (<65, ≥65 years old), (<35, ≥35 to <45, ≥45 to <55, ≥55 to <65, ≥65 years old), and (<65, ≥65 to <75, ≥75 to <85, ≥85 years old) • Sex • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported) • Height • Weight • Body mass index, and • Days since COVID-19 symptom onset. • Days since COVID-19 symptom onset (≤8 days, >8 days) • SpO_2 • SpO_2 category (≤96%, >96%) • COVID-19 disease severity category • High-risk status for severe COVID-19 illness **Statistics to be included:** Continuous: Mean, standard deviation, min, max, median, and first quartile and third quartile Categorical: n and percent (denominator for percentages will be the number of participants with nonmissing values) A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) No inferential statistics
Medical History and Preexisting conditions	Number and percentage of participants with medical history events and preexisting conditions using MedDRA PT nested within SOC • Ordered by decreasing frequency within SOC on the LY total arm Preexisting conditions are defined as those conditions with a start date prior to the first dose of the study drug and stop dates that are at or after the informed consent date or have no stop date (i.e., are ongoing).
Prior Therapy of Interest	Number and percentage of participants with prior medication of interest will be displayed as "Prior medications"
Listing demographics	--

Abbreviations: max = maximum; MedDRA = Medical Dictionary for Regulatory Activities; min = minimum; PT = preferred term; SOC = System Organ Class.

6.8. Treatment Compliance

As all study drug doses will be administered at the study site, treatment compliance will not be reported.

6.9. Prior Medication and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the WHO drug dictionary. Medication start and stop dates will be compared to the date of the first dose of treatment to allow medications to be classified as concomitant.

Prior medications are those medications that start and stop prior to the date of the first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment and continue into the treatment period.

For all summary tables of concomitant medications, Preferred Terms of concomitant medication will be sorted by descending frequency in the LY total arm.

Table PYAB.6.6. Summary Tables Related to Concomitant Medications

Analysis	Details
Prior medications	Number and percentage of participants using Preferred Terms of prior medication • Ordered by decreasing frequency No inferential statistics
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication • Ordered by decreasing frequency No inferential statistics

6.10. Efficacy Analyses

The analysis of the of viral load lab results will utilize the following conventions:

For qualitative endpoints in the trial (viral clearance yes/no, time to viral clearance) the lab determination of "positive"/"negative" will be used. SARS-CoV-2 clearance (yes/no) is defined as 2 consecutive negative tests for the SARS-CoV-2 virus. The date of viral clearance is defined as the earliest date of the 2 consecutive negative tests.

For quantitative endpoints in the trial (change from baseline, area under the response viral load curve [AUC]), the viral load will be derived based on cycle threshold (Ct) values with the following considerations:

- Two Ct values will be provided on 2 different genes: N1 and N2. N1 will be used as the primary measure; N2 will only be used when the Ct value for N1 is not available.
- Ct values range between 0 and 45.
- Negative CoV-2 tests will be associated with a Ct value of 45.
- The (log base 10) viral load will be calculated from the Ct value $(45\text{-Ct})/\log_2 10$, or (45-Ct)/3.321928.

6.10.1. Primary Outcome and Methodology

Primary endpoint is the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load. Statistical hypothesis testing for the primary endpoint will be conducted using an MMRM analysis method at the 2-sided 0.05 level.

SARS-CoV-2 viral load, including changes from baseline, will be summarized and plotted by treatment and listed. Baseline is defined as the Day 1 predose assessment.

Changes from baseline to Day 11 in SARS-CoV-2 viral load data in the log base 10 scale will be statistically analyzed using a linear mixed-effect model. The model will contain log base 10 transformed baseline as a covariate, treatment, day, treatment-by-day interaction) as fixed effects. The symptom onset stratification factor is not included in order to avoid the collinearity with the baseline viral load. The LS means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. In addition, the geometric mean ratio to baseline and corresponding standard error for each treatment, and ratio of geometric mean ratio to baseline vs placebo, and corresponding 95% CIs will be presented. All available data will be used in the analysis.

If Day 11 SARS-CoV-2 viral load is missing, the earliest measurement closest to the Day 11 visit, but within 4 days (Day 7-Day 15), will be used for the Day 11 value. If no measurements are available, the Day 11 viral load will treated as MAR in the analysis.

6.10.2. Additional Analyses of the Primary Outcome

6.10.2.1. Dose Response Modeling

A Bayesian model averaging approach may be explored to estimate the dose-response relationship with change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load being the response variable of interest. This Bayesian model averaging approach is the Bayesian analog of the Multiple Comparisons - Modeling (MCP-Mod) methodology (Bretz et al. 2005), and the Qualification of the MCP-Mod procedure (OCP 2015) is supportive in the use of MCP-Mod or Bayesian model averaging to assist in dose selection decisions.

Bayesian model averaging is a general mixture distribution, where each mixture component is a different parametric model. Prior weights are placed on each model and the posterior model weights are updated based on how well each model fits the data. Let $\mu(d)$ represent the mean of the dose response curve at dose d, $y = \{y_1, \ldots, y_n\}$ be the observed data, and $m \in \{1, \ldots, M\}$ be an index on the M parametric models. Then the posterior of the dose response curve, $\mu(d)$, of the Bayesian model averaging model is

$$p(\mu(d) \mid y) = \sum_{m=1}^{M} p(\mu(d) \mid y, m)\, p(m \mid y)$$

$$p(m \mid y) = \frac{p(y \mid m)p(m)}{\sum_{m^*} p(y \mid m^*)p(m^*)}$$

where $p(\mu(d) \mid y, m)$ is the posterior mean dose response curve from model m, $p(m \mid y)$ is the posterior weight of model m, $p(y \mid m)$ is the marginal likelihood of the data under model m, and $p(m)$ is the prior weight assigned to model m. In cases where $p(y \mid m)$ is difficult to compute, Gould (2019) proposes using the observed data's fit to the posterior predictive distribution as a surrogate in calculating the posterior weights; this is the approach used in this analysis.

Similar dose response methodology may be applied to additional efficacy endpoints as appropriate.

6.10.2.2. Bayesian Modeling

A Bayesian linear mixed-effect model will be fitted to evaluate the success criteria by the Lilly statistics group with the model listed below:

$$y_{ijk} = \mu + \alpha \times base + \alpha_i + \beta_k + (\alpha\beta)_{ik} + \varepsilon_{ij} + \varepsilon_{ijk}$$

Where y_{ijk}: the change from baseline in log 10 scale for treatment i, subject j at day k

μ: a constant common to all observations

α: a fixed coefficient on the covariate log base 10 baseline viral load

α_i: a parameter corresponding to treatment i

β_k: a parameter corresponding to day k

$(\alpha\beta)_{ik}$: an interaction parameter corresponding to treatment i and day k

ε_{ij}, ε_{ijk}: random error for between- and within-subject variability

prior μ, α, α_i, β_k, $(\alpha\beta)_{ik} \sim N(0, 100)$

$\varepsilon_{ij} \sim N(0, \sigma_1)$, $\varepsilon_{ijk} \sim N(0, \sigma_2)$

$\sigma_1, \sigma_2 \sim uniform(0, 100)$ or $igamma(0.01,0.01)$

6.10.3. Secondary Efficacy Analyses

6.10.3.1. SARS-CoV-2 Viral Load Among Participants Enrolled with ≤8 Days of Symptoms Prior to Randomization

Similar methodology, as described in Section 6.10.1, will be utilized on the subset of participants enrolled with ≤8 days of symptoms prior to randomization.

6.10.3.2. SARS-CoV-2 Viral Load AUC

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) will be also calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification. No imputations of missing data will be conducted. No AUC(0-D11) values will be calculated when Day 1 predose and/or Day 11 values are missing, or if more than 1 value is missing in the profile.

The AUC will be summarized and plotted by treatment and listed.

Additionally, AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, log base 10 transformed baseline viral load as a covariate. The least square (LS) means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

If deemed appropriate, the data may be log-transformed prior to analysis, and the LS means and treatment differences will be back-transformed.

A similar Bayesian model listed in Section 6.10.2, by removing the day, interaction, and within subject error term, will be applied for log base 10 transformed AUC measure analysis.

6.10.3.3. SARS-CoV-2 Clearance at Days 7, 11, 15, and 22

See Section 6.10 for more details on the definition of viral clearance.

The proportion of participants that achieve SARS-CoV-2 clearance at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that achieve SARS-Cov-2 clearance at Days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

6.10.3.4. Time to SARS-CoV-2 Clearance

See Section 6.10 for more details on the definition of viral clearance and date of viral clearance.

Time to SARS-CoV-2 clearance is defined (in days) as:

(Date when SARS-CoV-2 clearance status is first changed to "Yes" – Infusion Date + 1)

If a patient has not experienced SARS-CoV-2 clearance by completion or early discontinuation of study/study treatment period, the patient will be censored at the date of their last visit during the treatment period.

Time to SARS-CoV-2 clearance will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to SARS-CoV-2 clearance will be presented graphically.

6.10.3.5. Symptom Resolution

Symptom resolution is defined as all symptoms (those scored 0-3) on the symptom questionnaire scored as absent.

The proportion of participants that achieve symptom resolution at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables, and listed.

In addition, the number of participants that achieve symptom resolution at Days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

6.10.3.6. Time to Symptom Resolution

Time to symptom resolution is defined (in days) as:

(First study day when symptom resolution status is changed to "Yes" – Infusion Date + 1)

If a patient has not experienced symptom resolution by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to symptom resolution will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to symptom resolution will be presented graphically.

6.10.3.7. Symptom Improvement

Symptom improvement is defined as a patient experiencing both:

- Symptoms on the symptom questionnaire scored as moderate or severe at baseline are subsequently scored as mild or absent, AND
- Symptoms on the symptom questionnaire scored as mild or absent at baseline are subsequently scored as absent.

The proportion of participants that achieve symptom improvement at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables, and listed.

In addition, the number of participants that achieve symptom improvement at days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

6.10.3.8. Time to Symptom Improvement

Time to symptom improvement is defined (in days) as:

(Date when symptom improvement status is changed to "Yes" – Infusion Date + 1)

If a patient has not experienced symptom improvement by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to symptom improvement will be evaluated during the study treatment period only and will be summarized by treatment and listed. In addition, a graphical presentation of the symptom improvement will be provided using a KM plot.

6.10.3.9. COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 29, 60, and 85)

Proportion (percentage) of participants who experience deterioration by Day 29 will be analyzed and is defined as:

- COVID-19-related hospitalization (defined as ≥24 hours of acute care)
- a COVID-19-related emergency room visit, or
- death

The proportion of participants that experience deterioration by Day 29 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that experience deterioration by Day 29 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

Proportion (percentage) of participants who experience deterioration by Days 60 and 85 will also be analyzed.

6.10.3.10. Change in Symptom Questionnaire Score

Change in symptom questionnaire score (total of ratings from those symptoms scored 0-3) from baseline to Days 7, 11, 15, and 22 will be analyzed using an MMRM. The model will contain baseline as a covariate, symptom onset strata, treatment, day, and treatment-by-day interaction as fixed effects. The LS means and treatment differences (each dose or dose combination group minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.10.4. Symptoms and Overall Clinical Status Participant Questionnaire

Participants will rate their overall clinical status and severity of symptoms associated with COVID-19 by a daily questionnaire. This questionnaire is for outparticipants only.

Participants will complete 3 questions about their overall clinical status daily, including

- severity of symptoms
- general physical health, and
- change in overall health

The questionnaire contains these symptoms

- cough

- shortness of breath
- feeling feverish
- fatigue
- body aches and pain
- sore throat
- chills
- headache
- loss of appetite (yes/no), and
- changes in taste and smell (yes/no)

Each symptom will be scored daily by the participant as experienced during the past 24 hours.

Table PYAB.6.7. Symptom and Clinical Status Questionnaire Scores

Rating	Score
None or absent	0
Mild	1
Moderate	2
Severe	3

The Total Symptom Questionnaire score is the sum of the symptoms (excluding the loss of appetite and changes in taste and smell symptoms).

Participants will rate the loss of appetite and changes in taste and smell with yes/no responses. Responses at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

Participants will complete questions about their overall clinical status. Responses at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

Further details regarding the analysis of endpoints based on the symptom questionnaire are described in Section 6.10.3.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK) analysis will be the responsibility of the Eli Lilly PK/Pharmacodynamics (PD) group prior to database lock.

Pharmacokinetic parameter estimates for LY3819253 and LY3832479 will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be geometric mean of concentration on Day 29. Other noncompartmental parameters, such as half-life (t1/2), AUC from time 0 to infinity (AUC[0-∞]), AUC(0-D29), maximum observed drug concentration (C_{max},) clearance, and volume of distribution may be reported.

Additional population PK model-based analyses may be performed and are responsibilities of Eli Lilly and Company PK/PD group. Exploratory exposure-response relationship to safety and efficacy may be performed. Alternative approaches to efficacy analysis (including viral load definition in Section 6.10) may be performed.

Noncompartmental methods, applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the serum concentrations of LY3819253, will be used to determine the following PK parameters (Table PYAB.6.8) when possible.

Table PYAB.6.8. Pharmacokinetic Parameters

Parameter	Units[a]	Definition
AUC(0-D29)	µg.h/mL	Area under the concentration-time curve from time zero to time t, where t is Day 29
AUC(0-t_{last})	µg.h/mL	Area under the concentration-time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	µg.h/mL	Area under the concentration-time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
t_{last}		Time of the last observed drug concentration
C_{max}	µg/mL	Maximum observed drug concentration
C_{D29}	µg/mL	Observed drug concentration on Day 29
t_{max}	h	Time of maximum observed drug concentration
$t_{½}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL	L/h	Total body clearance of drug calculated
V_z	L	Volume of distribution during the terminal phase
V_{ss}	L	Volume of distribution at steady state

[a] Units of source LY3819253 serum concentration data will be ng/mL, to 1 decimal place.

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures, and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: Non-Compartmental Pharmacokinetic Style Guide. The version of the tool effective at the time of PK analysis will be followed.

6.11.1. General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for nonbolus predose sampling times, which will be set to zero.

- Maximum observed drug concentration and time of maximum observed drug concentration (t_{max}) will be reported from observed values. If C_{max} occurs at more than 1 time point, t_{max} will be assigned to the first occurrence of C_{max}.
- Area under the concentration-time curve parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive serum concentrations above the lower limit of quantification, with at least 1 of these concentrations following C_{max}.
- Area under the concentration-time curve from time 0 to infinity values, where the percentage of the total area extrapolated is more than 20%, will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.
- Half-life will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of <2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.
- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.
- The parameters, based on predicted last quantifiable drug concentration, will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters will be reported).

6.11.2. Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (BQL). Serum concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:
    - The compound is nonendogenous.
    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.
    - The time points occur before the first quantifiable concentration.
- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where 2 or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated, and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

6.11.3. Individual Concentration versus Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semilogarithmic plot.

6.11.4. Average Concentration versus Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The predose average concentration for single-dose data from nonendogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ±10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if two-thirds of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ±10%. An average concentration estimated with less than two-thirds, but more than 3 data points, may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

6.11.5. Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

6.11.5.1. Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent postdose samples.

- For PK profiles during single dosing of nonendogenous compounds, the concentration in a predose sample is quantifiable.
- For any questionable data that do not satisfy the above criteria, the profiles will be evaluated and results reported with and without the suspected data.

6.11.5.2. Data Between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log-transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains other atypical data suspected to be an outlier and n≥6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only 1 suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

6.11.5.3. Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will imply approval of the exclusion.

6.11.6. Pharmacokinetic Statistical Methodology

All PK parameters will be summarized by treatment using descriptive statistics.

The PK parameter estimates will be evaluated to delineate dose proportionality. Log-transformed C_{max}, and AUC(0-∞) of LY3819253 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% CIs. Results of the dose proportionality analysis will be plotted.

The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality.

Example SAS code for the analysis:

```
proc mixed data=pk;
      model log_pk = log_dose / alpha=0.1 cl solution residual
      ddfm=kr2;
      estimate '700 mg'  intercept 1 log_dose 2.87506126 /
      alpha=0.1 cl; /*Log of 700 */
      estimate '2800 mg' intercept 1 log_dose 3.44715803 /
      alpha=0.1 cl; /*Log of 2800 */
      estimate '7000 mg' intercept 1 log_dose 3.84509804 /
      alpha=0.1 cl; /*Log of 7000 */
      estimate '7000 mg - 700 mg'    log_dose 1 / alpha=0.1 cl;
      /*Difference in log values of 7000 and 700 */
      ods output solutionf=est;
      ods output estimates=estims;
run;
```

6.12. Safety Analyses

Percentages will be calculated using the safety population as the denominator. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex.

Generally, the following statistical methods will be used, unless otherwise noted:

- percentage-based analyses:
  - p-values based on Fisher's exact test, and
  - odds ratios with treatment as the numerator and placebo as the denominator
- continuous measurements:
  - p-value based on ANCOVA:
    - model containing terms for treatment, stratification factor of symptom onset (<=8 and >8 days) and the continuous covariate of baseline measurement, and
    - Type III sums of squares will be used.

6.12.1. Baseline and Postbaseline Definitions for Safety Groups

Table PYAB.6.9 provides conceptual definitions of baseline and postbaseline by analysis type. More specific detail for each submission is provided in an appendix, if necessary.

Table PYAB.6.9. Baseline and Postbaseline Definitions for Safety Groups Initial Controlled Periods of Individual Studies Controlled Integrated Analysis Sets

Analysis Type	Baseline	Postbaseline
TEAEs	Start of screening and ends prior to the first dose.	Starts after initiation of the first dose and ends on or prior to the day of study disposition
Treatment-Emergent Abnormal Laboratory Values and Vital Signs	Start of screening and ends prior to the first dose. All scheduled and unscheduled measurements will be included.	Starts after initiation of the first dose and ends on or prior to the day of study disposition. All scheduled and unscheduled measurements will be included.
Change from Baseline to Study Day *xx* and to Last Postbaseline for Laboratory Values and Vital Signs	Start of screening and ends prior to the first dose. The last scheduled nonmissing assessment recorded prior to the date of the first dose.	Starts after initiation of the first dose and ends on or prior to the day of study disposition. Only scheduled visits will be included. The early termination visits are considered scheduled visits.

Abbreviation: TEAE = treatment-emergent adverse event.

6.12.2. Extent of Exposure

Exposure to therapy will be represented as the total number of complete and incomplete infusions, and will be summarized using descriptive statistics.

6.12.3. Adverse Events

Summaries of AEs will include the number of participants with at least 1 AE for each treatment group. When reporting by System Organ Class (SOC) and PT, the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT will be counted only once in the frequency tables for that PT.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by SOC, PT, severity, and relationship to IP as assessed by the investigator. For each event classification term, the number of subjects experiencing a treatment-emergent AE (TEAE) with that classification term will be tabulated.

In an overview table, the number and percentage of participants who experienced a TEAE, serious adverse event (SAE), AE related to study drug, died due to an AE, discontinued from the study treatment, or discontinued from the study due to an AE will be summarized by treatment. Treatment-emergent AEs may be reported separately for the treatment period and follow-up periods.

Treatment-Emergent Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the baseline period, it will be treated as "mild" in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment emergence will be determined by comparing with baseline severity. Missing severity will be reported as missing, without imputation, for data listing.

Additional types of AEs to be summarized are described in Table PYAB.6.10.

Table PYAB.6.10. Additional Types of Adverse Events to be Summarized

Event Type	Summary Method
SAEs	SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.
TEAEs Resulting in Death	If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of preferred term.
TEAEs Leading to Study Drug Discontinuation	TEAEs for which the action taken with medication is 'Drug Withdrawal' will be identified as TEAEs that lead to study drug discontinuation. The TEAEs that lead to study drug discontinuation will be summarized for each treatment group by SOC and PT for the safety population. A by-patient listing of the TEAEs that lead to study drug discontinuation will also be provided.
Treatment-Related TEAEs	Every AE will be assessed by the investigator for its relationship to the randomly assigned study treatment.
TEAEs by Maximal Severity	Every AE will be graded by the investigator as mild, moderate, or severe, so for each patient the greatest severity observed can be obtained by comparing the severity of all of a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.
TEAEs (Not Including Serious)	The most common nonserious TEAEs will be summarized. All PT that occur in at least 5% of the safety population participants in any treatment group, when not counting the serious TEAEs, will be tabulated by SOC and PT for each treatment group. These reports will also present the total number of TEAEs for each SOC and PT.

Abbreviations: AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

SOC mapping

Medical Dictionary for Regulatory Activities PTs are assigned to a SOC through primary mappings (defined by MedDRA). Thus, MedDRA PTs will appear in only 1 SOC.

Events not summarized

Events considered related by the investigator will not be summarized for CSR. Medical representatives may use the relatedness assessment when reviewing individual cases.

6.12.4. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

The following are "notable" events, from start of study drug through end of study participation:

- Deaths
- SAEs, and
- Discontinuations of study treatment due to AEs.

Narratives (patient-level data and summary paragraph) will be provided for participants in the safety population with at least 1 notable event.

Safety topics of interest are not considered notable events, unless 1 of the above criteria is met. Displays with individual patient-level data will be created for safety topics of interest using various formats such as a customized listing and/or a customized graphical patient profile as specified in the section associated with the safety topic of interest. Medical case summaries/vignettes will be provided if deemed relevant for the discussion of the safety topic of interest.

6.12.5. Hospitalization, Clinical Events, Clinical Status, and Environmental Risk Factors

The following events (observed at any time point during the study treatment period) will be analyzed with the method described in Section 6.16.2.6 and Section 6.16.2.8:

- Proportion of participants hospitalized
- Duration of hospitalization (DOH; in days),
- proportion (percentage) of participants admitted to Intensive Care Unit (ICU),
- proportion (percentage) of participants requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation")

All hospitalization events, procedures of special interest, and environmental risk factors will be listed.

In the event that a participant has an ongoing hospitalization event at the time of study disposition, the hospitalization end date will be imputed to the study disposition date.

6.12.6. Clinical Laboratory Evaluation

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol (See Protocol Appendix 2). However, unscheduled measurements of planned analytes will be included/excluded as specified in the relevant sections. Examples of unplanned

measurements include those that the clinical investigator orders as a repeat test or "retest" of a laboratory test in case of an abnormal value, and those the investigator orders for a "follow-up visit" due to clinical concerns. Some planned analytes are intended for individual case reviews and will not be included in group-level summaries.

6.12.7. Vital Signs and Other Physical Findings

The planned summaries are provided in Table PYAB.6.11. The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, weight, peripheral oxygen saturation (SpO_2), respiratory rate, fraction of inspired oxygen (FiO_2), and temperature if data warrant.

The criteria for identifying subjects with treatment-emergent abnormalities are based on Table PYAB.6.12.

Some of the analyses of vital signs may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in Table PYAB.6.11 and not provided would be available upon request. For example, box plots for observed values, scatter plots, and shift tables could be provided as interactive displays for medical review.

Table PYAB.6.11. Tables and Figures Produced to Support Vital Signs and Physical Characteristics

Analysis Type	Analysis Details
Box plots for observed values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • No inferential statistics.
Box plots for change from baseline values by visit	• Includes participants who have both a baseline and a postbaseline planned measurement. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot along with a p-value using the ANCOVA model.
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	• Each study individually and studies combined will be displayed. • Includes participants who have both a baseline and postbaseline observation. • Unplanned measurements will be included. • Lines indicating the reference limits will be included. • **Max vs Max:** Maximum baseline versus maximum postbaseline. • **Min vs Min:** Minimum baseline versus minimum postbaseline.

Summary tables for shifts to high/low	• Limits provided by the central lab service will be used to define low and high.
	• **Normal/high to low:** Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low.
	  o Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 postbaseline result.
	• **Normal/low to high:** Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high.
	  o Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period.
	• Statistical comparisons will be included.

Abbreviations: ANCOVA = analysis of covariance; Max = maximum; Min = minimum.

Table PYAB.6.12. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes in Adults

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Temperature	<96°F (<35.6°C) and decrease ≥2°F (≥1.1°C) from baseline	≥101°F (≥38.3°C) and increase ≥2°F (≥1.1°C) from baseline

Abbreviations: BP = blood pressure; bpm = beats per minute.

6.12.8. Electrocardiograms

Results of electrocardiograms (ECGs) performed during the study will not be reported.

6.12.9. Immunogenicity

If data from validated immunogenicity assays are available, treatment-emergent antidrug antibodies (TE-ADAs) may be assessed.

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer compared with the minimum required dilution if no antidrug antibodies (ADAs) were detected at baseline (treatment-induced ADA) or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of participants with preexisting ADAs and who are TE-ADA positive (TE-ADA+) to LY3819253 and/or LY3832479 may be tabulated.

The distribution of titers and frequency of neutralizing antibodies (if assessed) for the TE-ADA+ participants may also be tabulated.

The relationship between the presence of antibodies and PK parameters, efficacy response, or safety to LY3819253 and/or LY3832479 may also be assessed.

6.13. Subgroup Analyses

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

Subgroup analyses will be conducted for the primary endpoint. Subgroups may include

- time from symptom onset to study randomization
- baseline severity of COVID-19

- age group (<65, ≥65 years old), (<35, ≥35 to <45, ≥45 to <55, ≥55 to <65, ≥65 years old), and (<65, ≥65 to <75, ≥75 to <85, ≥85 years old)
- gender (male, female)
- race
- ethnicity
- baseline weight (<60 kg, ≥60 to <100 kg, ≥100 kg)
- baseline BMI (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2 to <40 kg/m^2, and ≥40 kg/m^2)
- concomitant medication of interest use (yes/no)
- High-risk status for severe COVID-19 illness

Treatment group differences will be evaluated within each category of the subgroup regardless of whether the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided, that is, no inferential testing.

The analysis of additional subgroups and/or subgroup analyses on additional endpoints will not require an amendment to the SAP.

Within each subgroup category the relevant summary measure by treatment, treatment differences (compared to placebo) and 95% CIs will be displayed. Also, p-values using appropriate statistical tests for treatment comparison will be provided. Forest plots may be generated to display the treatment difference and 95% CIs for selected efficacy subgroup analyses.

Baseline severity of COVID-19 will be defined using the following definition.

- Severity will be defined to be **Moderate** if the participant demonstrates the following at baseline:
    - Symptoms:
        - Shortness of breath (with symptom questionnaire severity score ≥1)

          OR

        - Symptoms of moderate illness with COVID-19, (any symptom questionnaire score >1, excluding loss of appetite)

      AND
    - Clinical signs suggestive of moderate illness with COVID-19, such as:
        - Respiration rate ≥20 breaths per minute

          OR

        - Pulse ≥ 90 beats per minute.

- Else, severity will be defined to be **Mild**.

Concomitant therapies of interest include remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine, anticoagulants, dexamethasone, or other investigational interventions. Details of the medications included in this subgroup are provided below in Table PYAB.6.13.

Table PYAB.6.13. Concomitant Medications of Interest Subgroup

Drug name	ATC Code	WhoDrug Preferred Term
Remdesivir	---	REMDESIVIR
Kaletra	J05AR	KALETRA
Lopinavir	J05AR	LOPINAVIR
Hydroxychloroquine	P01BA	HYDROCHLOROQUINE
Chloroquine	P01BA	CHLOROQUINE
Baricitinib	L04AA	BARICITINIB
Heparin	B01AB	HEPARIN
Fondaparinux	B01AX	FONDAPARINUX
Argatroban	B01AE	ARGATROBAN
Dexamethasone	H02AB	DEXAMETHASONE

Abbreviation: ATC = anatomical therapeutic chemical.

6.14. Protocol Violations

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) are defined as those deviations from the protocol that would potentially compromise participants' safety, data integrity, or study outcome.

A separate document known as the "PYAB Trial Issues Management Plan" describes the categories and subcategories of IPDs and how the IPDs would be identified.

The number and percentage of participants having IPDs will be summarized within category and subcategory of deviations by dosing regimen.

A by-patient listing of IPDs will be provided.

6.15. Interim Analyses and Data Monitoring

6.15.1. Interim Analyses

Monotherapy LY3819253

The ongoing study may be modified based on planned interim analyses. Based on the observed data at the time of the interim analyses, the study may

- suspend enrollment to an LY3819253 treatment arm (or arms) demonstrating lack of efficacy, and/or
- initiate/expand enrollment to an additional/existing treatment arm (or arms).

The modifications proposed are done so to ensure participants are being exposed to treatment with an acceptable risk-benefit profile during the ongoing trial. Additionally, the potential modifications will provide information to more fully characterize the dose response profile.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by Assessment Committee (AC) members. The AC will review rolling safety data after approximately 20, 40, and 60 participants are enrolled and have had an opportunity to reach Day 4 to monitor participant safety. These initial individual reviews of unblinded safety data will occur no less often than every 30 days, in case of slower than anticipated enrollment. This is intended as an individual AC member review and does not require a formal meeting. However, any AC member can ask for a full AC meeting based on the rolling review at any time.

The AC will initially review summary unblinded data after approximately 25% (100) participants have had an opportunity to reach Day 11. It is anticipated that subsequent interim analyses will occur after approximately 50%, 75%, and all participants have had an opportunity to reach Day 11. Safety will be evaluated at each of these interim analyses and benefit/risk of LY3819253 will be assessed if needed. An additional interim analysis is planned when approximately 40% participants in the 7000 mg arm have had an opportunity to reach Day 11. However, this analysis may be combined with the approximately 50% interim analysis if possible.

The PYAB study may be stopped early based on an unacceptable safety signal(s).

Additionally, the pre-planned interim analysis at 40% of participants in the 7000 mg arm completing 11 days will inform potential modification to the PYAB study. These modifications include:

- Dropping the 700 mg dose arm if either of these 2 conditions hold:

$$\mathbf{P(\Delta_{LY700mg} - \Delta_{placebo} > -0.3) > 0.8}$$

or

$$\mathbf{P(\Delta_{LY7,000mg} - \Delta_{LY700mg} < -0.3) > 0.85}$$

- Enrolling up to 100 additional participants to a new or existing dose arm to better characterize the dose-response relationship if:

$$\mathbf{P(\Delta_{LY700mg} - \Delta_{placebo} < -0.3) > 0.85}$$

Note: Δ represents viral load change from baseline in log base 10 scale at Day 11. Details of the Bayesian methodology associated with the SARS-CoV-2 viral load can be found in Section 6.10.2.

Combination Therapy with LY3819253 and LY3832479 (Treatment Arm 6 and/or 7)

The AC will review rolling safety data after approximately 25 participants are enrolled and have had an opportunity to reach Day 2 to monitor participant safety. The individual AC member reviews of unblinded safety data doesn't require a formal meeting.

The interim analyses to evaluate the benefit/risk of the combination therapy may occur after approximately 75, 150, and all participants have had an opportunity to reach Day 11. The last interim analysis with approximately all participants will be conducted ONLY IF the optional Treatment Arm 7 is added per the sponsor decision.

Only the AC is authorized to evaluate unblinded interim analyses and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Further details regarding the interim analyses can be found in the AC Charter.

Periodic adjustments to the allocation ratio may be made to achieve an equal allocation across treatment arms at the conclusion of enrollment. If up to 50 additional placebo participants are enrolled, then the allocation ratio may change accordingly.

6.15.2. Data Monitoring Committee/Assessment Committee

The sponsor will form an AC to analyze the interim study data. To minimize any bias introduced into the analysis of the study results, analysis plans will be finalized and approved prior to the interim analyses.

The primary goal of the AC is to review the interim results regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Overall committee structure information is in Protocol Section 10.1.5. Details of the AC will be provided in the AC charter. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

6.16. Planned Exploratory Analyses

6.16.1. Protocol-Defined Exploratory Endpoints

Protocol defined exploratory endpoints are described in Section 4.3 and analysis details are provided in the following sections.

6.16.1.1. Viral Resistance

If appropriate, the evaluation of viral resistance will be conducted as described in a separate bioanalytical analysis plan.

6.16.1.2. SpO_2 AUC Assessed through Day 29

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the daily SpO_2 values. If multiple values are collected on a given day, the average will be used. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) will also be calculated according to the linear trapezoidal rule using the mean daily SpO_2 values. No imputations of missing data will be conducted. No AUC(0-D11) values will be calculated when Day 1 predose and/or Day 11 values are missing, or if there are more than 1 value missing in the profile.

The AUC will be summarized and plotted by treatment, and listed.

Additionally, SpO_2 AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, SpO2 baseline measurement as a covariate, and oxygen source. The LS means and treatment differences (each intervention arm minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.16.1.3. Symptom Severity Assessed by Mean AUC through Day 29 of Symptom Questionnaire

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the mean daily Symptom Questionnaire total score. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) will also be calculated according to the linear trapezoidal rule using the mean daily Symptom Questionnaire total score. No imputations of missing data will be conducted. No AUC(0-D11) values will be calculated when Day 1 predose and/or Day 11 values are missing, or if there are more than 1 value missing in the profile.

The Symptom Questionnaire AUC will be summarized and plotted by treatment, and listed.

Additionally, Symptom severity AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, baseline symptom severity as a covariate. The LS means and treatment differences (each non-placebo group minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.16.1.4. Worst NIAID Score

The lowest daily value from Day 1 through Day 29 for a patient on the NIAID ordinal scale will be analyzed using the van Elteren test adjusting for the randomization stratification factors. Mean values will be calculated and differences in treatment effect estimates at Days 7, 11, 15, and 22 will be analyzed. Mean value by treatment group will be plotted over time.

6.16.2. Additional Exploratory Analyses not Defined in the Protocol

In addition to the protocol defined endpoints, additional sensitivity analyses may be performed if deemed appropriate. Additional analyses include:

6.16.2.1. Clinical Worsening Based on the NIAID Scale

Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Days 7, 11, 15, and 22.

6.16.2.2. National Early Warning Score

The highest daily value from Day 1 through Day 29 for a patient on the National Early Warning Score (NEWS2) ordinal scale will be analyzed using the van Elteren test adjusting for the randomization stratification factors. Mean values will be calculated and differences in treatment effect estimates at Days 7, 11, 15, and 22 will be analyzed. Mean value by treatment group will be plotted over time.

6.16.2.3. NEWS2 Consciousness Level

Consciousness level assessed by NEWS2 will be summarized using a logistic regression analysis as described in Section 6.1.4.

6.16.2.4. NIAID/NEWS2 Overall Improvement

Treatment comparisons for overall improvement on the ordinal scales (NIAID, NEWS2) between LY3819253 and placebo will be made using proportional odds model with baseline stratification factor and treatment group in the model. Overall improvement will be evaluated at Days 7, 11, 15, and 22.

6.16.2.5. Time to Hospitalization

Time to Hospitalization is defined (in days) as:

(First study day when hospitalized status is changed to "Yes" – Infusion Date +1)

If a patient has been admitted to the hospital or ICU by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to hospitalization will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to hospitalization may be presented graphically.

6.16.2.6. Duration of Hospitalization

Treatment comparisons of the mean DOH (in days) will be compared between LY3819253 and placebo will be made using nonparametric rank-sum test (such as Mann-Whitney or van Elteren test).

6.16.2.7. Time to Admission to ICU

Time to ICU is defined (in days) as:

(First study day when ICU status is changed to "Yes" – Infusion Date +1)

If a patient has been admitted to the hospital or ICU by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to ICU will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days vs >8 days).

Time to ICU may be presented graphically.

6.16.2.8. Proportions of Participants Hospitalized, Admitted to the ICU, Requiring Mechanical Ventilation

The proportion of participants hospitalized, admitted to the ICU, requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation") will be evaluated separately using a logistic regression analysis with treatment and baseline stratification in the model. These endpoints will be evaluated at Days 7, 11, 15, and 22.

6.16.2.9. Days since Symptom Onset Cutpoint Analysis

An exploratory cutpoint analysis may be performed to determine the number of days since symptom onset maximizes the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load between treatment with LY3819253, LY3819253/LY3832479, and placebo.

6.16.2.10. SpO2 Measurements of Interest

The proportion of participants experiencing an SpO_2 measurement of interest (<96%, ≥ 96%), (<92%, ≥92%) through Day 11 and through Day 29 will be evaluated separately using a logistic regression analysis with treatment and baseline stratification as fixed effects and baseline SpO_2 as a covariate in the model. Missing values will be considered to be missing completely at random (MCAR).

6.17. Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.18. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participants/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (e.g., the CSR, manuscripts, and so forth).

7. References

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8. Appendices

Appendix 1. NEWS2 Scoring Scale

The National Early Warning Score 2 (NEWS2) is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when participants present to, or are being monitored in hospital. Six simple physiological parameters form the basis of the scoring system:

1. respiration rate
2. oxygen saturation
3. systolic blood pressure (BP)
4. pulse rate
5. level of consciousness or new confusion
6. temperature.

Figure APP.1.1. NEWS2 Scoring

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Abbreviations: CVPU =Confusion, Voice, Pain, Unresponsive; NEWS2 = National Early Warning Score 2; SpO2 = oxygen saturation.

Figure APP.1.2. NEWS2 Scoring Clinical Risk Thresholds

NEW score	Clinical risk
Aggregate score 0–4	Low
Red score Score of 3 in any individual parameter	Low–medium
Aggregate score 5–6	Medium
Aggregate score 7 or more	High

Abbreviation: NEWS2 = national Early Warning Score 2.

Appendix 2. NIAID Scoring Scale

The National Institute of Allergy and Infectious Diseases (NIAID) scoring scale will be assessed daily and defined as the lowest score achieved for that day.

The scoring is based on the clinical status of the patient as described below.

Table APP.1.2. NIAID Clinical Status Scoring

NIAID Score	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3	Hospitalized, on noninvasive ventilation or high flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

Abbreviation: NIAID = National Institute of Allergy and Infectious Diseases.

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