

# Protocol

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

Protocol for: Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2102685

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

## Title Page

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**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)**

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

Approval Date: 30-May-2020 GMT

**Medical Monitor Name and Contact Information will be provided separately**

## Table of Contents

<b>1.</b>	<b>Protocol Summary .....</b>	<b>6</b>
1.1.	Synopsis .....	6
1.2.	Schema.....	10
1.3.	Schedule of Activities (SoA) .....	11
<b>2.</b>	<b>Introduction .....</b>	<b>18</b>
2.1.	Study Rationale .....	18
2.2.	Background .....	18
2.3.	Benefit/Risk Assessment .....	18
<b>3.</b>	<b>Objectives and Endpoints.....</b>	<b>20</b>
<b>4.</b>	<b>Study Design .....</b>	<b>22</b>
4.1.	Overall Design.....	22
4.1.1.	Design Outline.....	22
4.2.	Scientific Rationale for Study Design .....	23
4.3.	Justification for Dose.....	24
4.4.	End of Study Definition.....	24
<b>5.</b>	<b>Study Population .....</b>	<b>25</b>
5.1.	Inclusion Criteria .....	25
5.2.	Exclusion Criteria.....	26
5.3.	Lifestyle Considerations .....	26
5.4.	Screen Failures .....	26
<b>6.</b>	<b>Study Intervention.....</b>	<b>28</b>
6.1.	Study Intervention(s) Administered .....	28
6.1.1.	Special Treatment Considerations .....	28
6.1.2.	Temporary Stopping Criteria .....	30
6.2.	Preparation/Handling/Storage/Accountability .....	31
6.3.	Measures to Minimize Bias: Randomization and Blinding.....	31
6.4.	Study Intervention Compliance.....	32
6.5.	Concomitant Therapy .....	32
6.6.	Dose Modification .....	33
6.7.	Intervention after the End of the Study.....	33
<b>7.</b>	<b>Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal.....</b>	<b>34</b>
7.1.	Discontinuation of Study Intervention .....	34
7.2.	Participant Discontinuation/Withdrawal from the Study .....	34
7.2.1.	Discontinuation of Inadvertently Enrolled Participants .....	34
7.3.	Lost to Follow up .....	35
<b>8.</b>	<b>Study Assessments and Procedures .....</b>	<b>36</b>
8.1.	Efficacy Assessments .....	36
8.1.1.	Symptoms and Overall Clinical Status Participant Questionnaire.....	36
8.2.	Safety Assessments .....	37
8.2.1.	Physical Examinations.....	37
8.2.2.	Vital Signs.....	37

8.2.3.	Clinical Laboratory Assessments .....	37
8.2.4.	Hospitalization events.....	38
8.2.5.	Procedures of Special Interest.....	38
8.2.6.	Respiratory Support.....	39
8.3.	Adverse Events and Serious Adverse Events .....	39
8.3.1.	Time Period and Frequency for Collecting AE and SAE Information.....	39
8.3.2.	Method of Detecting AEs and SAEs .....	39
8.3.3.	Follow-up of AEs and SAEs .....	40
8.3.4.	Regulatory Reporting Requirements for SAEs.....	40
8.3.5.	Pregnancy.....	40
8.3.6.	Hypersensitivity Reactions .....	40
8.3.7.	Infusion-related Reactions .....	41
8.3.8.	Product Complaints .....	41
8.4.	Treatment of Overdose .....	42
8.5.	Pharmacokinetics.....	42
8.5.1.	Bioanalytical .....	42
8.6.	Pharmacodynamics.....	43
8.7.	Genetics .....	43
8.8.	Biomarkers.....	43
8.9.	Immunogenicity Assessments.....	43
8.10.	Health Economics.....	44
<b>9.</b>	<b>Statistical Considerations.....</b>	<b>45</b>
9.1.	Statistical Hypotheses.....	45
9.2.	Sample Size Determination.....	45
9.3.	Populations for Analyses .....	45
9.4.	Statistical Analyses.....	46
9.4.1.	General Considerations.....	46
9.4.2.	Primary Endpoints .....	46
9.4.3.	Secondary Endpoints .....	47
9.4.4.	Exploratory Analyses.....	48
9.4.5.	Immunogenicity Analyses.....	48
9.4.6.	Subgroup Analyses .....	48
9.5.	Interim Analyses.....	49
9.6.	Data Monitoring Committee (DMC).....	50
<b>10.</b>	<b>Supporting Documentation and Operational Considerations .....</b>	<b>51</b>
10.1.	Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.....	51
10.1.1.	Regulatory and Ethical Considerations.....	51
10.1.2.	Financial Disclosure .....	51
10.1.3.	Informed Consent Process .....	52
10.1.4.	Data Protection.....	52
10.1.5.	Committees Structure .....	53
10.1.6.	Dissemination of Clinical Study Data .....	53
10.1.7.	Data Quality Assurance .....	53
10.1.8.	Source Documents.....	54

10.1.9.	Study and Site Start and Closure .....	55
10.1.10.	Publication Policy.....	55
10.1.11.	Investigator Information .....	55
10.1.12.	Long-Term Sample Retention.....	56
10.2.	Appendix 2: Clinical Laboratory Tests.....	57
10.3.	Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.....	60
10.3.1.	Definition of AE .....	60
10.3.2.	Definition of SAE.....	61
10.3.3.	Recording and Follow-Up of AE and/or SAE .....	62
10.3.4.	Reporting of SAEs.....	64
10.4.	Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information .....	65
10.5.	Appendix 5: Genetics .....	68
10.6.	Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events. ....	69
10.7.	Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments .....	71
10.8.	Appendix 8: Abbreviations .....	75
<b>11.</b>	<b>References .....</b>	<b>77</b>

## 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
<b>Primary</b>	
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm</math> 4 days) in SARS-CoV-2 viral load</li> </ul>
<b>Secondary</b>	
Characterize the effect of LY3819253 compared to placebo on safety	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load among participants with $\leq$ 8 days since symptom onset	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm</math> 4 days) in SARS-CoV-2 viral load among participants enrolled with <math>\leq</math> 8 days of symptoms prior to randomization</li> </ul>
Characterize the effect of LY3819253 compared to placebo on symptom resolution	<ul style="list-style-type: none"> <li>Time to symptom resolution</li> <li>Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22</li> <li>Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22</li> </ul>



Characterize the effect of LY3819253 compared to placebo on symptom improvement	<ul style="list-style-type: none"> <li>• Time to symptom improvement</li> <li>• Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	<ul style="list-style-type: none"> <li>• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 15 and 22)</li> <li>• Time to SARS-CoV-2 clearance</li> <li>• SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed at Day 29</li> </ul>
Characterize the pharmacokinetics of LY3819253	<ul style="list-style-type: none"> <li>• LY3819253 mean concentration on Day 29</li> </ul>
Characterize the effect of LY3819253 compared to placebo on overall participant clinical status	<ul style="list-style-type: none"> <li>• Proportion (percentage) of participants who experience these events by Day 29 <ul style="list-style-type: none"> <li>○ COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care)</li> <li>○ a COVID-19 related emergency room visit, or</li> <li>○ death</li> </ul> </li> </ul>

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.

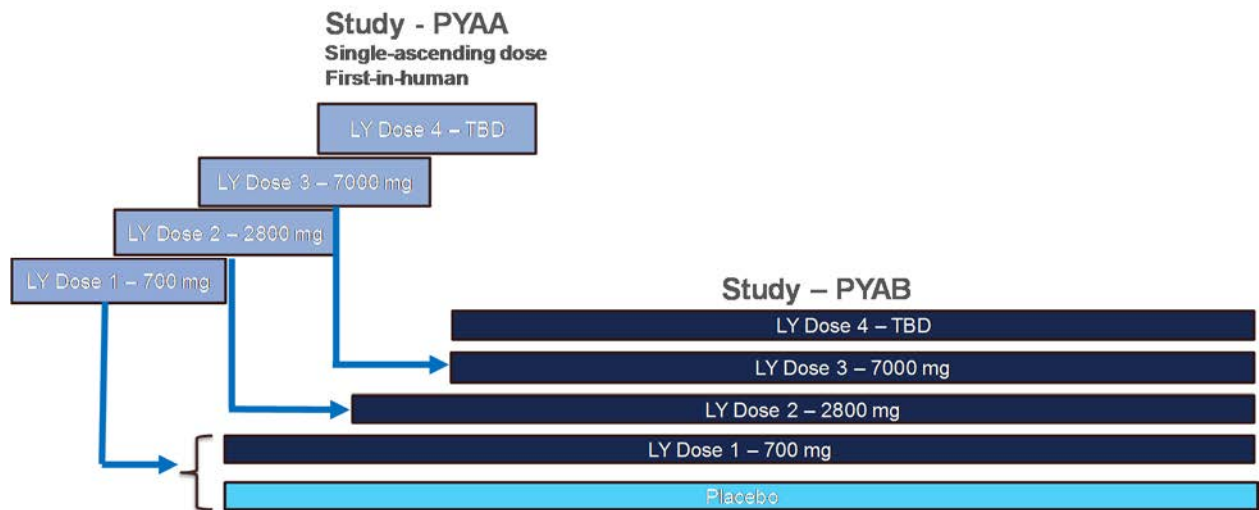
**Intervention Groups and Duration:**

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
		1	2*	3	4-6*	7	11	15	18	22	25	29	60			85		
<b>Study Day</b>		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)	
<b>Visit window (± number of days)</b>		--	--	1	--	2	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.	
<b>Procedures</b>																		
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
		1	2*	3	4-6*	7	11	15	18	22	25	29	60			85		
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.	
<b>Physical Evaluation or Clinical Assessments</b>																		
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. <b>Screening visit only:</b> SpO2 while breathing room air. <b>Day 1 timing:</b>	

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
		1	2*	3	4-6*	7	11	15	18	22	25	29	60			85		
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.	
																	<ul style="list-style-type: none"> <li>immediately before the infusion,</li> <li>every 30 minutes during the infusion, as possible</li> <li>30 minutes after infusion.</li> </ul> During infusion, only record pulse rate, BP and SpO2. Automation may be used. <b>All other study days:</b> once daily.	
Hospitalization events			Daily										X	X	X	X	Record if the following events occur: <ul style="list-style-type: none"> <li>Emergency room visits</li> <li>hospitalized</li> <li>ICU admittance,</li> <li>Extended care facility admittance, and</li> <li>discharge</li> </ul>	
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 <ul style="list-style-type: none"> <li>Ongoing hospital medical care</li> <li>Supplemental oxygen</li> </ul>	

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
		1	2*	3	4-6*	7	11	15	18	22	25	29			60	85	
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.
																	<ul style="list-style-type: none"> <li>• Non-invasive ventilation or high flow oxygen device</li> <li>• Mechanical ventilation</li> <li>• ECMO, or</li> <li>• Additional organ support (e.g. pressors, renal replacement).</li> </ul>
<b>Laboratory Tests and Sample Collection</b>																	
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
		1	2*	3	4-6*	7	11	15	18	22	25	29	60			85		
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.	
<ul style="list-style-type: none"> <li>• C-reactive protein (CRP); high - sensitivity</li> <li>• Ferritin</li> <li>• D-dimer</li> <li>• Procalcitonin</li> <li>• Troponin</li> </ul>		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
		1	2*	3	4-6*	7	11	15	18	22	25	29	60			85		
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			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	
<b>Randomization and Dosing</b>																		
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
		1	2*	3	4-6*	7	11	15	18	22	25	29	60			85		
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.	
<b>Participant Questionnaire</b>																		
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
<b>Primary</b>	
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm</math> 4 days) in SARS-CoV-2 viral load</li> </ul>
<b>Secondary</b>	
Characterize the effect of LY3819253 compared to placebo on safety	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load among participants with $\leq$ 8 days since symptom onset	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm</math> 4 days) in SARS-CoV-2 viral load among participants enrolled with <math>\leq</math> 8 days of symptoms prior to randomization</li> </ul>
Characterize the effect of LY3819253 compared to placebo on symptom resolution	<ul style="list-style-type: none"> <li>Time to symptom resolution</li> <li>Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22</li> <li>Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22</li> </ul>
Characterize the effect of LY3819253 compared to placebo on symptom improvement	<ul style="list-style-type: none"> <li>Time to symptom improvement</li> <li>Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	<ul style="list-style-type: none"> <li>Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 15 and 22)</li> <li>Time to SARS-CoV-2 clearance</li> <li>SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed at Day 29</li> </ul>
Characterize the pharmacokinetics of LY3819253	<ul style="list-style-type: none"> <li>LY3819253 mean concentration on Day 29</li> </ul>
Characterize the effect of LY3819253 compared to placebo on overall participant clinical status	<ul style="list-style-type: none"> <li>Proportion (percentage) of participants who experience these events by Day 29 <ul style="list-style-type: none"> <li>COVID-19 related hospitalization (defined as <math>\geq</math>24 hours of acute care)</li> <li>a COVID-19 related emergency room visit, or</li> <li>death</li> </ul> </li> </ul>

Objectives	Endpoints
<b>Exploratory</b>	
Characterize emergence of viral resistance to LY3819253	<ul style="list-style-type: none"> <li>• Comparison from baseline to Day 29</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SpO2 over time	<ul style="list-style-type: none"> <li>• SpO2 AUC assessed at Day 29</li> </ul>
Characterize the effect of LY3819253 compared to placebo on symptom severity	<ul style="list-style-type: none"> <li>• Symptom severity as assessed by mean AUC at Day 29 of symptom questionnaire</li> </ul>

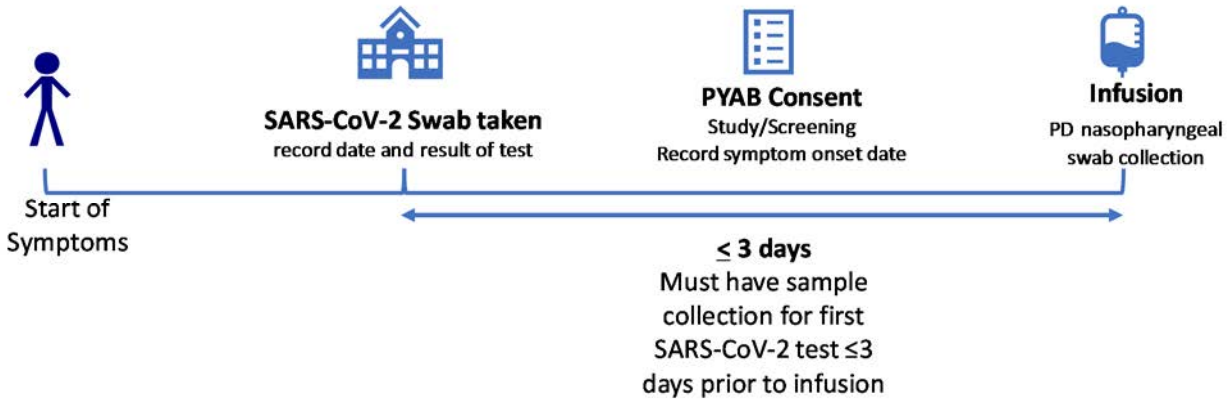
Abbreviations: AE = adverse event; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = saturation of peripheral oxygen.

## 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  $\geq 18$  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  $\leq 3$  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  $SpO_2 \leq 93\%$  on room air at sea level or  $PaO_2/FiO_2 < 300$ , respiratory rate  $\geq 30$  per minute, heart rate  $\geq 125$  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 4<sup>th</sup> 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 <sup>a</sup>	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 $\leq 24$ hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

<sup>a</sup> = 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.

<b>Topic</b>	<b>Location</b>
DAIDS table describing severity of reactions	Section <a href="#">6.1.1.2</a>
Definition of AEs	Section <a href="#">10.3.1</a>
Assessment of Intensity/Severity	Section <a href="#">10.3.3</a>

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 ( $\leq 8$  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)	<ul style="list-style-type: none"> <li>• 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</li> <li>• In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted</li> <li>• 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</li> <li>• If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance</li> <li>• The date and reason that the blind was broken must be recorded in the source documentation and case report form.</li> </ul>
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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, FiO<sub>2</sub> 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  $\geq 24$  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 <a href="#">6.1.1</a>
Premedication for infusions	Section <a href="#">6.1.1.1</a>
Management of infusion reactions	Section <a href="#">6.1.1.2</a>
DAIDS table describing severity	Section <a href="#">6.1.1.2</a>
Treatment guidelines for infusion-related reactions	Section <a href="#">6.1.1.2</a>

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 ( $\leq 8$  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 ( $\pm 4$  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 ( $\pm 4$  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 ( $\pm 4$  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 ( $\pm$  4 days) in SARS-CoV-2 viral load among participants enrolled with  $\leq$ 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  $\geq$  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.

<b>Sample Type</b>	<b>Custodian</b>	<b>Retention Period After Last Participant Visit</b>
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.

<b>Clinical Laboratory Tests</b>	<b>Comments</b>
<b>Hematology</b>	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)	
<b>Clinical Chemistry</b>	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)	
<b>Calculations</b>	
eGFR	Calculated by CKD-EPI equation. Results will not be provided to the investigative sites.

<b>Clinical Laboratory Tests</b>	<b>Comments</b>
<b>SARS-CoV-2 viral infection determination</b>	Local laboratory and/or Point-of-Care testing
<b>SARS-CoV-2 Test Panel</b>	Assayed by Lilly-designated laboratory.
C-reactive protein (CRP); high-sensitivity	
Ferritin	
D-dimer	
Procalcitonin	
Troponin	
<b>Hormones (female)</b>	
Urine Pregnancy	Local laboratory
Serum Pregnancy	Local laboratory
<b>Pharmacokinetic Samples</b>	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
<b>Pharmacodynamic sample</b>	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
SARS-CoV-2 nasopharyngeal swab	
<b>Pharmacogenetics sample</b>	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
<b>Exploratory Biomarker Samples</b>	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
RNA (PAXGene)	
Whole Blood (EDTA)	
Whole Blood (EDTA) Epigenetics	
<b>Immunogenicity Samples</b>	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
<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> </ul>

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none"> <li>• 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).</li> <li>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</li> <li>• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.</li> <li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li> <li>• 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.</li> <li>• “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.</li> </ul>

Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> <li>• 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: <ul style="list-style-type: none"> <li>○ Hypoxemia due to COVID-19 requiring supplemental oxygen;</li> <li>○ Hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices;</li> </ul> </li> </ul>

- 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).

<b>An SAE is defined as any untoward medical occurrence that, at any dose:</b>
<b>a. Results in death</b>
<b>b. Is life-threatening</b> 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.
<b>c. Requires inpatient hospitalization or prolongation of existing hospitalization</b> <ul style="list-style-type: none"> <li>● 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.</li> <li>● Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.</li> </ul>
<b>d. Results in persistent disability/incapacity</b> <ul style="list-style-type: none"> <li>● The term disability means a substantial disruption of a person’s ability to conduct normal life functions.</li> </ul>

<ul style="list-style-type: none"> <li>• 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.</li> </ul>
<p><b>e. Is a congenital anomaly/birth defect</b></p>
<p><b>f. Other situations:</b></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> </ul>

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

<p><b>AE and SAE Recording</b></p>
<ul style="list-style-type: none"> <li>• 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.</li> <li>• The investigator will then record all relevant AE/SAE information in the CRF.</li> <li>• It is <b>not</b> 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.</li> <li>• 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.</li> <li>• 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.</li> </ul>
<p><b>Assessment of Intensity</b></p>
<p>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).</p>



**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  $\geq$ 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**

<b>Hypersensitivity Tests</b>	<b>Notes</b>
LY3819253 anti-drug antibodies (immunogenicity/ADA)	Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions. 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. <b>Note:</b> 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. <b>NOTE:</b> 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 $\geq 3x$ ULN with hepatic signs/symptoms*, <u>or</u> ALT or AST $\geq 5x$ ULN
ALP <1.5x ULN	ALP $\geq 3x$ ULN
TBL <1.5x ULN	TBL $\geq 2x$ ULN (except for participants with Gilbert's syndrome)
ALT or AST $\geq 1.5x$ ULN	ALT or AST $\geq 2x$ baseline with hepatic signs/symptoms*, <u>or</u> ALT or AST $\geq 3x$ baseline
ALP $\geq 1.5x$ ULN	ALP $\geq 2x$ baseline
TBL $\geq 1.5x$ ULN	TBL $\geq 1.5x$ 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:

<b>If a participant with baseline...</b>	<b>has the following elevations...</b>
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.

<b>Hematology</b>	<b>Clinical Chemistry</b>
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	<b>Other Chemistry</b>
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
<b>Coagulation</b>	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin

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

<sup>a</sup> Not required if anti-actin antibody is tested.

<sup>b</sup> Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

<sup>c</sup> Not required if anti-smooth muscle antibody (ASMA) is tested.

<sup>d</sup> Assayed ONLY by investigator-designated local laboratory; no central testing available.

**10.8. Appendix 8: Abbreviations**

<b>Term</b>	<b>Definition</b>
<b>AC</b>	assessment committee
<b>ADA</b>	anti-drug antibody
<b>ADE</b>	antibody-dependent enhancement
<b>blinding/masking</b>	<p>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.</p> <p>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.</p>
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>complaint</b>	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.
<b>compliance</b>	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
<b>CRP</b>	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.
<b>DMC</b>	data monitoring committee
<b>ECG</b>	electrocardiogram
<b>FiO2</b>	fraction of inspired oxygen in the aire
<b>enroll</b>	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.
<b>enter</b>	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>GCP</b>	good clinical practice
<b>IB</b>	Investigator's Brochure
<b>ICF</b>	informed consent form
<b>ICH</b>	International Council for Harmonisation
<b>IMP</b>	Investigational Medicinal Product

<b>Informed consent</b>	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.
<b>interim analysis</b>	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.
<b>intervention</b>	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.
<b>IWRS</b>	interactive web-response system
<b>NP</b>	nasopharyngeal
<b>participant</b>	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
<b>PK/PD</b>	pharmacokinetics/pharmacodynamics
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>screen</b>	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.
<b>SpO2</b>	saturation of peripheral oxygen

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## Title Page

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**Protocol Title:**

A Randomized, Double-blind, Placebo-Controlled, Phase 2/3 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: k****Compound(s):** LY3819253, LY3832479**Study Phase: 2/3****Short Title:** A randomized, double-blind, placebo-controlled, Phase 2/3 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 (k) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 20-Jan-2021 GMT

**Medical Monitor Name and Contact Information will be provided separately**

## Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment (j)	07-January-2021
Amendment (i)	30-November-2020
Amendment (h)	Not applicable. Not approved or submitted to regulatory agencies or independent review boards.
Amendment (g)	17-November-2020
Amendment (f)	20-October-2020
Amendment (e)	13-October-2020
Amendment (d)	18-September-2020
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment k

#### Overall Rationale for the Amendment:

This amendment allows participants in the study who have received the SARS-CoV-2 vaccine. SARS-CoV-2 vaccines are now available to the public and those who received a vaccine or have participated in a SARS-CoV-2 vaccine study are allowed in the study.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.2 Schedule of Activities for Treatment Arms 7-9,13-14	Updated Prior treatments of special interest to allow the SARS-CoV-2 vaccine	The SARS-CoV-2 vaccine is now allowed
2.3 Benefit/Risk Assessment	Updated risk information for LY3819253	Emerging data
4.2 Scientific Rationale for Study Design	Added a sub-section for participants who have received the SARS-CoV-2 vaccine	Vaccines are now available to the public and those who received a vaccine are allowed in the study
5.2 Exclusion Criteria	Criterion #21 is removed	SARS-CoV-2 vaccines are now available to the public and those who received a vaccine or have participated in a SARS-CoV-2 vaccine study are allowed in the study
6.5 Concomitant Therapy	Added vaccines to prior treatment list that should be recorded. Added "non-SARS-CoV-2" to clarify what vaccines are recorded for adolescents.	Need a record of those who received a SARS-Cov-2 vaccine.  Need a record of non-SARS-CoV-2 vaccines that adolescents received 90 days prior to signing informed consent.
9.2 Sample Size	Added clarification that there is no set sample size for participants with prior vaccine use.	Those who received a SARS-CoV-2 vaccine are allowed in the study.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
	Added stratification factor for whether a participant received a vaccine or not prior to screening	
9.3 Populations for Analyses	Added the Modified Efficacy population to table	To distinguish a population for analysis that will not include those that received a SARS-CoV-2 vaccine.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

## Table of Contents

<b>1.</b>	<b>Protocol Summary .....</b>	<b>8</b>
1.1.	Synopsis .....	8
1.2.	Schema.....	14
1.3.	Schedule of Activities (SoA) .....	15
1.3.1.	Treatment Arms 1-4 and 6 .....	16
1.3.2.	Treatment Arms 7-9, 13-14.....	24
<b>2.</b>	<b>Introduction .....</b>	<b>32</b>
2.1.	Study Rationale .....	32
2.2.	Background .....	32
2.3.	Benefit/Risk Assessment .....	33
<b>3.</b>	<b>Objectives and Endpoints.....</b>	<b>36</b>
3.1.	Treatment arms 1-4 and 6 .....	36
3.2.	Treatment arms 7-9, 13-14.....	38
<b>4.</b>	<b>Study Design .....</b>	<b>40</b>
4.1.	Overall Design.....	40
4.1.1.	Design Outline.....	40
4.2.	Scientific Rationale for Study Design .....	42
4.3.	Justification for Dose.....	43
4.4.	End of Study Definition.....	44
<b>5.</b>	<b>Study Population .....</b>	<b>45</b>
5.1.	Inclusion Criteria .....	45
5.2.	Exclusion Criteria.....	46
5.3.	Lifestyle Considerations .....	47
5.4.	Screen Failures .....	47
<b>6.</b>	<b>Study Intervention.....</b>	<b>48</b>
6.1.	Study Intervention(s) Administered .....	48
6.1.1.	Special Treatment Considerations .....	49
6.1.2.	Temporary Stopping Criteria .....	50
6.2.	Preparation/Handling/Storage/Accountability .....	51
6.3.	Measures to Minimize Bias: Randomization and Blinding.....	51
6.4.	Study Intervention Compliance.....	52
6.5.	Concomitant Therapy .....	52
6.6.	Dose Modification .....	53
6.7.	Intervention after the End of the Study.....	53
<b>7.</b>	<b>Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal.....</b>	<b>54</b>
7.1.	Discontinuation of Study Intervention .....	54
7.2.	Participant Discontinuation/Withdrawal from the Study .....	54
7.2.1.	Discontinuation of Inadvertently Enrolled Participants .....	54
7.3.	Lost to Follow up .....	55
<b>8.</b>	<b>Study Assessments and Procedures .....</b>	<b>56</b>
8.1.	Efficacy Assessments .....	56

8.1.1.	Symptoms and Overall Clinical Status Participant Questionnaire .....	56
8.2.	Safety Assessments .....	57
8.2.1.	Physical Examinations .....	57
8.2.2.	Vital Signs .....	57
8.2.3.	Clinical Laboratory Assessments .....	58
8.2.4.	Hospitalization events .....	59
8.2.5.	Procedures of Special Interest .....	59
8.2.6.	Respiratory Support .....	60
8.3.	Adverse Events and Serious Adverse Events .....	60
8.3.1.	Time Period and Frequency for Collecting AE and SAE Information .....	60
8.3.2.	Method of Detecting AEs and SAEs .....	60
8.3.3.	Follow-up of AEs and SAEs .....	61
8.3.4.	Regulatory Reporting Requirements for SAEs .....	61
8.3.5.	Pregnancy .....	61
8.3.6.	Hypersensitivity Reactions .....	61
8.3.7.	Infusion-related Reactions .....	62
8.3.8.	Product Complaints .....	62
8.4.	Treatment of Overdose .....	63
8.5.	Pharmacokinetics .....	63
8.5.1.	Bioanalytical .....	63
8.6.	Pharmacodynamics .....	64
8.7.	Genetics .....	64
8.8.	Biomarkers .....	64
8.9.	Immunogenicity Assessments .....	64
8.10.	Health Economics .....	65
<b>9.</b>	<b>Statistical Considerations .....</b>	<b>66</b>
9.1.	Statistical Hypotheses .....	66
9.2.	Sample Size Determination .....	66
9.3.	Populations for Analyses .....	68
9.4.	Statistical Analyses .....	68
9.4.1.	General Considerations .....	69
9.4.2.	Primary Endpoints .....	69
9.4.3.	Secondary Endpoints .....	70
9.4.4.	Exploratory Analyses .....	71
9.4.5.	Immunogenicity Analyses .....	72
9.4.6.	Subgroup Analyses .....	72
9.5.	Interim Analyses .....	73
9.6.	Data Monitoring Committee (DMC) .....	74
<b>10.</b>	<b>Supporting Documentation and Operational Considerations .....</b>	<b>75</b>
10.1.	Appendix 1: Regulatory, Ethical, and Study Oversight Considerations .....	75
10.1.1.	Regulatory and Ethical Considerations .....	75
10.1.2.	Financial Disclosure .....	75
10.1.3.	Informed Consent Process .....	76
10.1.4.	Data Protection .....	76

10.1.5.	Committees Structure .....	77
10.1.6.	Dissemination of Clinical Study Data .....	77
10.1.7.	Data Quality Assurance .....	77
10.1.8.	Source Documents.....	79
10.1.9.	Study and Site Start and Closure.....	79
10.1.10.	Publication Policy.....	80
10.1.11.	Investigator Information .....	80
10.1.12.	Long-Term Sample Retention.....	80
10.2.	Appendix 2: Clinical Laboratory Tests.....	81
10.3.	Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.....	84
10.3.1.	Definition of AE .....	84
10.3.2.	Definition of SAE.....	85
10.3.3.	Recording and Follow-Up of AE and/or SAE .....	86
10.3.4.	Reporting of SAEs.....	88
10.4.	Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information .....	89
10.5.	Appendix 5: Genetics .....	92
10.6.	Appendix 6: Recommended Laboratory Testing for Hypersensitivity Events. ....	93
10.7.	Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments .....	95
10.8.	Appendix 8: Abbreviations .....	99
10.9.	Appendix 9: Protocol Amendment History .....	101
<b>11.</b>	<b>References.....</b>	<b>121</b>

## 1. Protocol Summary

### 1.1. Synopsis

**Protocol Title:** A Randomized, Double-blind, Placebo-Controlled, Phase 2/3 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:

##### Treatment arms 1-4 and 6

Objectives	Endpoints
<b>Primary</b>	
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 ( $\pm$ 4 days) in SARS-CoV-2 viral load
<b>Secondary</b> The secondary objectives are to characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on...	
<ul style="list-style-type: none"> <li>safety</li> </ul>	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral load among participants with <math>\leq</math>8 days since symptom onset</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm</math> 4 days) in SARS-CoV-2 viral load among participants enrolled with <math>\leq</math> 8 days of symptoms prior to randomization</li> </ul>
<ul style="list-style-type: none"> <li>symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>Time to symptom resolution</li> </ul>



	<ul style="list-style-type: none"> <li>• Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22</li> <li>• Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22</li> </ul>
<ul style="list-style-type: none"> <li>• symptom improvement</li> </ul>	<ul style="list-style-type: none"> <li>• Time to symptom improvement</li> <li>• Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22</li> </ul>
<ul style="list-style-type: none"> <li>• SARS-CoV-2 viral load and viral clearance</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15 and 22)</li> <li>• Time to SARS-CoV-2 clearance</li> <li>• SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29</li> </ul>
<ul style="list-style-type: none"> <li>• overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion (percentage) of participants who experience these events by Days 29, 60 and 85 <ul style="list-style-type: none"> <li>○ COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care)</li> <li>○ a COVID-19 related emergency room visit, or</li> <li>○ death</li> </ul> </li> </ul>
<b>Additional Secondary</b>	
Characterize the pharmacokinetics of LY3819253 and LY3819253 in combination with LY3832479	<ul style="list-style-type: none"> <li>• Mean concentration of LY3819253 and LY3819253 in the presence of LY3832479 on Day 29</li> <li>• Mean concentration of LY3832479 in the presence of LY3819253 on Day 29</li> </ul>

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

**Treatment arms 7-9, 13-14**

Objectives	Endpoints
<b>Primary</b>	
Characterize the effect of LY3819253 in combination with LY3832479 compared to placebo on overall participant clinical status	Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as $\geq 24$ hours of acute care) or death from any cause by Day 29.
<b>Key Secondary</b> The key secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on...	
<ul style="list-style-type: none"> <li>• the reduction of SARS-CoV-2 viral load</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline to Day 7 (<math>\pm 2</math> days)</li> </ul>
<ul style="list-style-type: none"> <li>• Persistently high SARS-CoV-2 viral load</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)</li> </ul>
<ul style="list-style-type: none"> <li>• overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion (percentage) of participants who experience these events by Day 29               <ul style="list-style-type: none"> <li>○ COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care), or</li> <li>○ a COVID-19 related emergency room visit, or</li> <li>○ death from any cause</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• sustained symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>• time to sustained symptom resolution</li> </ul>
<b>Additional Secondary</b>	
<ul style="list-style-type: none"> <li>• SARS-CoV-2 viral load reduction</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline to               <ul style="list-style-type: none"> <li>○ Day 3 (+1 day)</li> <li>○ Day 5 (<math>\pm 2</math> days)</li> </ul> </li> <li>• SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7</li> </ul>
<ul style="list-style-type: none"> <li>• SARS-CoV-2 viral clearance</li> </ul>	<ul style="list-style-type: none"> <li>• Time to SARS-CoV-2 clearance</li> </ul>
<ul style="list-style-type: none"> <li>• symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>• Time to symptom resolution</li> <li>• Time to complete symptom resolution</li> <li>• Time to sustained complete symptom resolution</li> <li>• Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11</li> </ul>
<ul style="list-style-type: none"> <li>• symptom improvement</li> </ul>	<ul style="list-style-type: none"> <li>• Time to symptom improvement</li> <li>• Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11</li> </ul>
<ul style="list-style-type: none"> <li>• safety</li> </ul>	<ul style="list-style-type: none"> <li>• Safety assessments such as AEs and SAEs</li> </ul>

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

**Overall Design:**

This is a Phase 2/3, randomized, double-blind, placebo-controlled, single-dose study in participants with mild to moderate COVID-19 illness.

**Design Outline*****Screening***

Interested participants or their legally authorized representative will sign the appropriate informed consent and child/adolescent assent document(s), as appropriate, 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.

***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 treatment arms 1-4 and 6.

Study Day	Visit Type
1	Site
2, 4, 5 and 6	Telephone visits
3, 7, 11, 15, 18, 22, 25 and 29	May be conducted as outpatient clinic or home visits
Early discontinuation and follow-up	May be conducted as outpatient clinic or home visits

This table describes the visit types for treatment arms 7-9, 13-14.

Study Day	Activity	Visit Type
1	Follow SoA	Site
2, 4, 6 and 22	Follow SoA	Telephone visits
3, 5, 7, 11, and 29	Follow SoA	May be conducted as outpatient clinic or home visits
8, 9, and 10	Collect participant questionnaire symptom and overall clinical status assessments	Telephone visits
Early discontinuation and follow-up	Follow SoA	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)***

<b>If hospital discharge...</b>	<b>Then...</b>
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. All treatment arms are participant and investigator blinded.

**Number of Participants:**

Approximately 500 participants 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 treatment arm 6.

Up to 100 additional participants may be introduced for optional treatment arm 5. See Section 9.5 for interim analysis details.

Participants in treatment arms 7-9, 13-14 are adults and adolescents with at least 1 risk factor for developing severe COVID-19 illness. There is no set sample size for the adolescent participants.

The planned sample size for the primary comparison of treatment arms 7 and 8 is approximately 1000 participants equally randomized to placebo or the combination of LY3819253 and LY3832479.

The planned sample size for treatment arm 9 is approximately 500 participants. Since treatment arm 9 begins enrollment after treatment arm 7, additional participants will be enrolled in treatment arm 8 to ensure at least a 33% increase in placebo participants and adequate placebo control for the primary comparison of treatment arms 8 and 9.

The planned sample size for the primary comparison of treatment arms 13 and 14 is approximately 1000 participants randomized 2:3, placebo:combination of LY3819253 and LY3832479.

**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
7	2800 mg + 2800 mg	LY3819253+LY3832479
8	---	placebo
9	700 mg + 1400 mg	LY3819253+LY3832479
13	---	placebo
14	350 mg + 700 mg	LY3819253+LY3832479

The optional LY3819253 treatment arm 5 may be added based on interim analysis results.

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

Treatment arm 1 is the corresponding placebo control for treatment arms 2-4 and 6.

Treatment arm 8 is the corresponding placebo control for treatment arms 7 and 9.

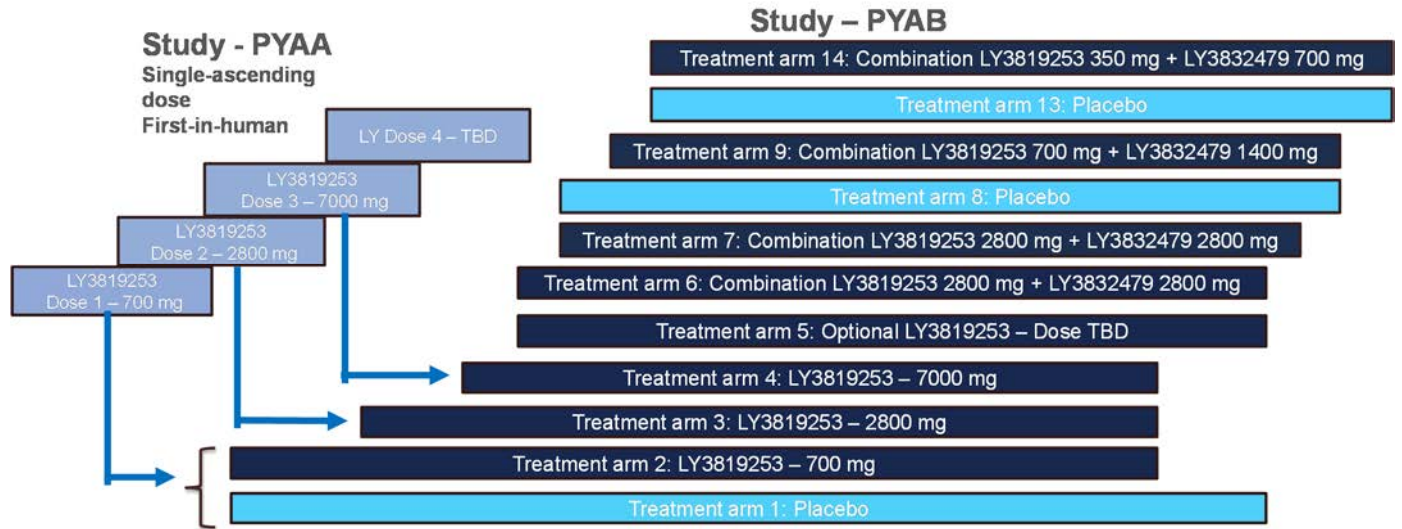
Treatment arm 13 is the concurrent placebo control for treatment arm 14.

**Data Monitoring Committee:** Yes.

An assessment committee will analyze the interim study data for treatment arms 1-4 and 6.

An external data monitoring committee (DMC) will analyze unblinded safety data for treatment arms 7-9 and 13-14.

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. Refer to the study day and visit type table in Section [4.1.1](#) for additional clarification.

**1.3.1. Treatment Arms 1-4 and 6**

This SoA is for participants in treatment arms 1-4 and 6.

Schedule of Activities for Treatment Arms 1-4 and 6																			
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2 *	3	4 *	5 *	6 *	7	11	15	18	22	25	29	E D	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				+1	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. 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																	



Schedule of Activities for Treatment Arms 1-4 and 6																			
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2 *	3	4 *	5 *	6 *	7	11	15	18	22	25	29	E D	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				+1	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
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	X	X	
Adverse events (AEs)	X	X	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.

Schedule of Activities for Treatment Arms 1-4 and 6																			
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2 *	3	4 *	5 *	6 *	7	11	15	18	22	25	29	E D	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				+1	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
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. <b>Screening visit only:</b> SpO2 while breathing room air. Data not collected on CRF. <b>Day 1 timing:</b> <ul style="list-style-type: none"> <li>immediately before the infusion</li> <li>every 15 minutes during the infusion, as possible, and</li> <li>every 30 minutes for 2 hours after the infusion.</li> </ul> During infusion, only record pulse rate, BP and SpO2. Automation may be used. See Section 8.2.2 for data collected on CRF. <b>All other study days:</b> once daily.

Schedule of Activities for Treatment Arms 1-4 and 6																					
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments		
Study Day		1	2 *	3	4 *	5 *	6 *	7	11	15	18	22	25	29	E D	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				+1	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.		
Hospitalization events																Daily	X	X	X	X	Record if the following events occur: <ul style="list-style-type: none"> <li>• Emergency room visits</li> <li>• hospitalized</li> <li>• ICU admittance,</li> <li>• Extended care facility admittance, and</li> <li>• discharge</li> </ul>
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 <ul style="list-style-type: none"> <li>• Ongoing hospital medical care</li> <li>• Supplemental oxygen</li> <li>• Non-invasive ventilation or high flow oxygen device</li> <li>• Mechanical ventilation</li> <li>• ECMO, or</li> <li>• Additional organ support (e.g. pressors, renal replacement).</li> </ul>

Schedule of Activities for Treatment Arms 1-4 and 6																			
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2	3	4	5	6	7	11	15	18	22	25	29	E D	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				+1	2	2	2	2	2	2	2	2	4	4	Visits may not be combined.
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
<ul style="list-style-type: none"> <li>• C-reactive protein (CRP); high-sensitivity</li> <li>• Ferritin</li> <li>• D-dimer</li> <li>• Procalcitonin</li> <li>• Troponin</li> </ul>		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

Schedule of Activities for Treatment Arms 1-4 and 6																			
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2	3	4	5	6	7	11	15	18	22	25	29	E D	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				+1	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
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

Schedule of Activities for Treatment Arms 1-4 and 6																			
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
		1	2 *	3	4 *	5 *	6 *	7	11	15	18	22	25	29			E D	Every 7 days until discharge or Day 60	
Study Day																			Screening and Day 1 procedures may occur on the same day. * = telephone visit(s)
Visit window (± number of days)		--	--	+1				+1	2	2	2	2	2	2	2	2	2	2	Visits may not be combined.
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
<b>Randomization and Dosing</b>																			
Randomization		X																	

Schedule of Activities for Treatment Arms 1-4 and 6																			
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments													E D	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2 *	3	4 *	5 *	6 *	7	11	15	18	22	25	29	E D	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				+1	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 1-29 for outpatients only													X		X	X	Day 1: 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.

**1.3.2. Treatment Arms 7-9, 13-14**

This SoA is for participants in treatment arms 7 through 9, and 13 and 14.

Schedule of Activities for Treatment Arms 7-9, 13-14																
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments										ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2*	3	4*	5	6*	7	11	22*	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Procedures																
Informed Consent	X															
Informed Assent for adolescent participants	X															Parent or legal guardian signs informed consent form and participant signs assent form, as appropriate per local requirements.
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. Includes: risk factors and comorbidities associated with severe COVID-19 illness, such as living in a nursing home or long-term care facility.
Prespecified medical history for COVID-19	X															Includes COVID-19 diagnosis date and onset of COVID-19 symptoms.
Height		X														
Weight		X														



Schedule of Activities for Treatment Arms 7-9, 13-14																	
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments											ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2*	3	4*	5	6*	7	11	22*	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.	
Procedures																	
Prior treatments of special interest	X															Within the last 30 days: NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or other investigational treatments. At any time: SARS-CoV-2 vaccine.	
Prior non-SARS- CoV-2 vaccine treatments within the last 90 days	X															For adolescents only	
Substance use (Tobacco)	X															Includes use of e-cigarettes, such as vaping	
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	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3. Additional details regarding reporting frequency and method of detecting AEs and SAEs can be found in Section 8.3.	
Physical Evaluation or Clinical Assessments																	
Physical examination	X																

Schedule of Activities for Treatment Arms 7-9, 13-14																
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments										ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2*	3	4*	5	6*	7	11	22*	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Procedures																
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 and Oxygen Support Includes: body temperature, pulse rate, BP, respiratory rate, SpO2, and supplemental oxygen flow rate, FiO2 if known, method of delivery, if applicable, and oxygen support procedures.	X	X		X		X		X	X			X	X	X	X	Documentation of hospital-based exam is acceptable. Record SpO2 while participant is at rest. <b>Screening visit only:</b> SpO2 while breathing room air. Data not collected on CRF. <b>Day 1 timing:</b> <ul style="list-style-type: none"> <li>immediately before administration</li> <li>every 15 minutes during the infusion, as possible and applicable if infusion is &lt;15 minutes, immediately following completion of infusion</li> <li>every 30 minutes for 1 hour after the administration.</li> </ul> During infusion, only record pulse rate, BP and SpO2. Automation may be used. See Section 8.2.2 for data collected on CRF. <b>All other study days:</b> once daily.

Schedule of Activities for Treatment Arms 7-9, 13-14																				
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments										ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments				
Study Day		1	2*	3	4*	5	6*	7	11	22*	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.				
Procedures																				
Hospitalization events													Daily	X	X	X	X	X	X	Record if the following events occur or occurred since prior visit: <ul style="list-style-type: none"> <li>• Emergency room visits</li> <li>• hospitalized</li> <li>• ICU admittance,</li> <li>• Extended care facility admittance, and</li> <li>• Discharge</li> </ul>
Clinical status and concomitant procedures if participant is hospitalized													Daily if hospitalized	X	X	X	X			Documentation from hospital records is acceptable if hospitalized at any time. Includes: <ul style="list-style-type: none"> <li>• NEWS 2 Consciousness (ACVPU)</li> <li>• Limitation on activities due to COVID-19 using the Patient Global Assessment for Daily Activities of Physical Function</li> <li>• Concomitant procedures of interest for organ support (e.g., proning, renal support)</li> <li>• Additional organ support (e.g. pressors, renal replacement).</li> </ul> Oxygen support and vital signs data should be collected while participant is hospitalized.

Schedule of Activities for Treatment Arms 7-9, 13-14																
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments										ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2*	3	4*	5	6*	7	11	22*	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
<b>Procedures</b>																
<b>Laboratory Tests and Sample Collection</b>																
Hematology		X		X						X		X	X			Day 1: before treatment administration 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 treatment administration All other days: sample may occur at any time during the day No samples needed if participant is hospitalized Lilly-designated central laboratory
<ul style="list-style-type: none"> <li>• C-reactive protein (CRP); high - sensitivity</li> <li>• Ferritin</li> <li>• D-dimer</li> <li>• Procalcitonin</li> <li>• Troponin</li> </ul>		X		X						X		X	X			For adults only Day 1: before treatment administration All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory

Schedule of Activities for Treatment Arms 7-9, 13-14																
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments										ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments
Study Day		1	2*	3	4*	5	6*	7	11	22 *	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.
Procedures																
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). Not applicable for females pregnant at screening. Local laboratory
Pharmacokinetic (PK) sample		X							X		X	X		X	X	Day 1: before IV infusion (adults only) 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

Schedule of Activities for Treatment Arms 7-9, 13-14																	
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments										ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments	
Study Day		1	2*	3	4*	5	6*	7	11	22*	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.	
Procedures																	
Immunogenicity (ADA) sample		X								X		X	X		X	X	Day 1: collect before treatment administration. 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				Swab is taken from both nostrils. Day 1: swab before treatment administration. No samples needed if participant is hospitalized Lilly-designated central laboratory
Exploratory biomarker samples		X		X		X			X			X	X		X	X	Day 1: before treatment administration. Day 60 and 85: serum sample only No samples needed if participant is hospitalized Lilly-designated central laboratory
Pharmacogenetics sample		X															For adults only Lilly-designated central laboratory
Randomization and Dosing																	
Randomization		X															

Schedule of Activities for Treatment Arms 7-9, 13-14																	
Study J2W-MC-PYAB	Screen	Double-blind treatment and assessments										ED	Follow-up if hospital inpatient on Day 29	Post- treatment follow-up		Comments	
Study Day		1	2*	3	4*	5	6*	7	11	22*	29	ED	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	--	+1	--	+1	-2/+3	±3	±3	±2	±2	±4	±4	Visits may not be combined.	
Procedures																	
Administer study intervention		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 administration of study intervention, complete dialysis first followed by the study treatment. Participants will be monitored for at least 1 hour after completion of treatment administration.	
Participant Questionnaire																	
Symptoms and overall clinical status		Daily on Days 1-11 for outpatients only									X	X	X		X	X	Day 1: assess prior to dosing

Abbreviations: ACVPU = alert, consciousness, verbal, pain, unresponsive scale; ADA = anti-drug antibody; AEs = adverse events; BP = blood pressure; CRF = case report form; ED = early discontinuation visit; FiO2 = fraction of inspired oxygen in the air; ICU = intensive care unit; NP = nasopharyngeal; NSAIDS = non-steroidal anti-inflammatory drugs; SAEs = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; 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 LY3832479 in combination with LY3819253 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.



### 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.

#### Risk of Neutralizing Antibodies

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 LY3819253.

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.

#### Risk of Infusion-related Reactions

Additional manageable risks associated with most therapeutic monoclonal antibodies are 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. and Section 6.1.2.

#### LY3819253

As of 2 October 2020, 727 participants received blinded treatment of LY3819253 700 mg, 2800 mg, or 7000 mg, or placebo. Serious infusion-related reactions, including events consistent with anaphylaxis, were reported in these ongoing studies with LY3819253 (FDA EUA fact sheet 2020).

Clinical worsening of COVID-19 after administration of LY3819253 has been reported and may include symptoms of pyrexia, hypoxia or increased respiratory difficulty, rapid heart rate (e.g. atrial fibrillation, sinus tachycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is unknown if these events were related to LY3819253 use or were due to progression of COVID-19.

### ***Combination of LY3819253 and LY3832479***

As of 04 November 2020, 542 participants in Study PYAB received blinded treatment of either placebo or the combination of 2800 mg LY3819253 and 2800 mg LY3832479. Three participants reported single immediate non-serious events of pruritis (2 events) and dyspnea (1 event).

### **Benefit/Risk in the Adolescent Population**

With respect to adolescents, there are no approved vaccines for the prevention of COVID-19 or approved drugs to treat COVID-19. The SARS-CoV-2 infections in the adolescent population generally are less severe than adults and may even be asymptomatic (Hoang et al. 2020). However, the risks of serious illness requiring hospitalization and sometimes resulting in death, is higher in pediatric patients with a number of risk factors that generally correspond to those in adults, such as obesity, diabetes, chronic lung disease, and immunocompromised status, as well as some conditions that are unique to pediatrics, such as congenital heart disease (Kim et al. 2020; Shekerdemian et al. 2020).

Adolescents with risk factors for severe disease and hospitalization may benefit from early administration of experimental anti-viral therapies such as the combination of LY3819253 and LY3832479, especially given the current safety profile. Based on FDA guidance documents, the data from even a small number of adolescents is useful in making regulatory science decisions (FDA May 2020 and FDA June 2020).

### **Benefit/Risk in the Pregnant Population**

In vitro tissue cross-reactivity assays with LY3819253 and LY3832479 determined that there is no binding to human fetal tissues.

Interim analysis from this study suggest treatment with LY3819253 may decrease the risk of hospitalization in mild to moderate COVID-19 patients (Chen et al. 2020). Pregnant females and pregnant females with additional risk factors for severe disease and hospitalization may benefit from early administration of experimental anti-viral therapies such as the combination of LY3819253 and LY3832479, especially given the current safety profile. Based on the FDA guidance document, the data from this population may be useful in making regulatory science decisions and enrollment is encouraged in clinical trials (FDA May 2020).

**Overall Benefit/Risk Assessment**

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 for 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

#### 3.1. Treatment arms 1-4 and 6

Objectives	Endpoints
<b>Primary</b>	
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 ( $\pm$ 4 days) in SARS-CoV-2 viral load
<b>Secondary</b> The secondary objectives are to characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on...	
<ul style="list-style-type: none"> <li>safety</li> </ul>	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral load among participants with <math>\leq 8</math> days since symptom onset</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm</math> 4 days) in SARS-CoV-2 viral load among participants enrolled with <math>\leq 8</math> days of symptoms prior to randomization</li> </ul>
<ul style="list-style-type: none"> <li>symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>Time to symptom resolution</li> <li>Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22</li> <li>Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22</li> </ul>
<ul style="list-style-type: none"> <li>symptom improvement</li> </ul>	<ul style="list-style-type: none"> <li>Time to symptom improvement</li> <li>Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22</li> </ul>
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral load and viral clearance</li> </ul>	<ul style="list-style-type: none"> <li>Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15 and 22)</li> <li>Time to SARS-CoV-2 clearance</li> <li>SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29</li> </ul>
<ul style="list-style-type: none"> <li>overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>Proportion (percentage) of participants who experience these events by Days 29, 60 and 85 <ul style="list-style-type: none"> <li>COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care)</li> <li>a COVID-19 related emergency room visit, or</li> <li>death</li> </ul> </li> </ul>

Objectives	Endpoints
<b>Additional Secondary</b>	
Characterize the pharmacokinetics of LY3819253 and LY3819253 in combination with LY3832479	<ul style="list-style-type: none"> <li>• Mean concentration of LY3819253 and LY3819253 in the presence of LY3832479 on Day 29</li> <li>• Mean concentration of LY3832479 in presence of LY3819253 on Day 29</li> </ul>
<b>Exploratory</b> The exploratory objectives are to characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on...	
<ul style="list-style-type: none"> <li>• SpO2 over time</li> </ul>	<ul style="list-style-type: none"> <li>• SpO2 AUC assessed through Day 29</li> </ul>
<ul style="list-style-type: none"> <li>• symptom severity</li> </ul>	<ul style="list-style-type: none"> <li>• Symptom severity as assessed by mean AUC through Day 29 of symptom questionnaire</li> </ul>
<ul style="list-style-type: none"> <li>• overall improvement using the NIAID ordinal scale</li> </ul>	<ul style="list-style-type: none"> <li>• Comparison of the mean worst daily NIAID ordinal eight-point scale values at Days 7, 11, 15 and 22</li> </ul>
<b>Additional Exploratory</b>	
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.

### 3.2. Treatment arms 7-9, 13-14

Objectives	Endpoints
<b>Primary</b>	
Characterize the effect of LY3819253 in combination with LY3832479 compared to placebo on overall participant clinical status	Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as $\geq 24$ hours of acute care) or death from any cause by Day 29.
<b>Key Secondary</b> The secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on...	
<ul style="list-style-type: none"> <li>the reduction of SARS-CoV-2 viral load</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline to Day 7 (<math>\pm 2</math> days)</li> </ul>
<ul style="list-style-type: none"> <li>persistently high SARS-CoV-2 viral load</li> </ul>	<ul style="list-style-type: none"> <li>Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)</li> </ul>
<ul style="list-style-type: none"> <li>overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>Proportion (percentage) of participants who experience these events by Day 29 <ul style="list-style-type: none"> <li>COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care), or</li> <li>a COVID-19 related emergency room visit, or</li> <li>death from any cause</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>sustained symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>time to sustained symptom resolution</li> </ul>
<b>Additional Secondary</b>	
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral load reduction</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline to <ul style="list-style-type: none"> <li>Day 3 (+1 day)</li> <li>Day 5 (<math>\pm 2</math> days)</li> </ul> </li> <li>SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7</li> </ul>
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral clearance</li> </ul>	<ul style="list-style-type: none"> <li>Time to SARS-CoV-2 clearance</li> </ul>
<ul style="list-style-type: none"> <li>symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>Time to symptom resolution</li> <li>Time to complete symptom resolution</li> <li>Time to sustained complete symptom resolution</li> <li>Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11</li> </ul>
<ul style="list-style-type: none"> <li>symptom improvement</li> </ul>	<ul style="list-style-type: none"> <li>Time to symptom improvement</li> <li>Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11</li> </ul>
<ul style="list-style-type: none"> <li>safety</li> </ul>	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>

Objectives	Endpoints
<b>Exploratory</b>	
<ul style="list-style-type: none"> <li>• overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion (percentage) of participants who experience these events by Days 22, 60 and 85                             <ul style="list-style-type: none"> <li>○ COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care), or</li> <li>○ death from any cause</li> </ul> </li> </ul>
Characterize the pharmacokinetics of LY3819253 in combination with LY3832479	Mean concentration of LY3832479 in presence of LY3819253 on Day 29

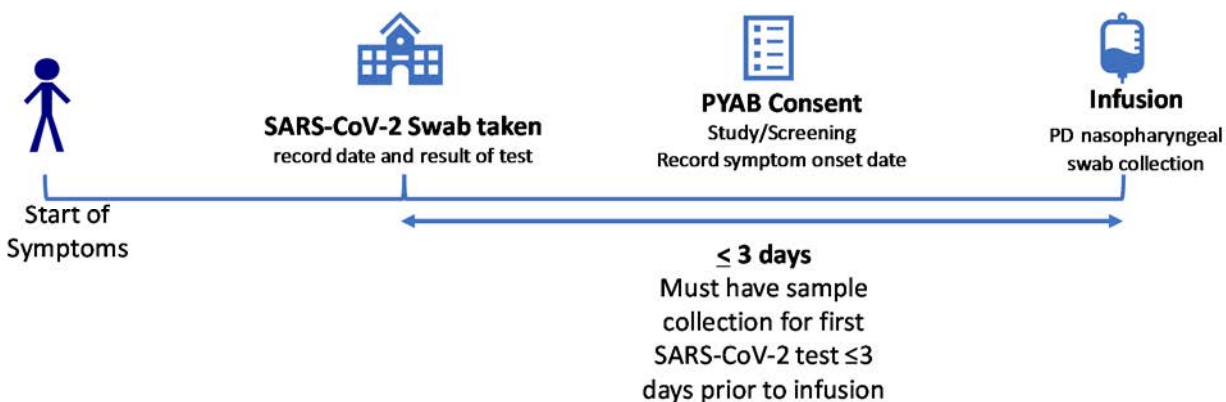
Abbreviations: AE = adverse event; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 4. Study Design

### 4.1. Overall Design

This is a Phase 2/3, 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 or their legally authorized representative will sign the appropriate informed consent and child/adolescent assent document(s), as appropriate, 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.

#### 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.



**Treatment Arms**

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
7	2800 mg + 2800 mg	LY3819253+LY3832479
8	---	Placebo
9	700 mg + 1400 mg	LY3819253+LY3832479
13	---	Placebo
14	350 mg + 700 mg	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.

Treatment arm 1 is the corresponding placebo control for treatment arms 2-4 and 6.

Treatment arm 8 is the corresponding placebo control for treatment arms 7 and 9.

Treatment arm 13 is the concurrent placebo control for treatment arm 14.

**Visit Types during the Treatment and Assessment Period**

This table describes the visit types for treatment arms 1-4 and 6.

Study Day	Visit Type
1	Site
2, 4, 5 and 6	Telephone visits
3, 7, 11, 15, 18, 22, 25 and 29	May be conducted as outpatient clinic or home visits.
Early discontinuation and follow-up	May be conducted as outpatient clinic or home visits

This table describes the visit types for treatment arms 7-9, 13-14.

Study Day	Activity	Visit Type
1	Follow SoA	Site
2, 4, 6 and 22	Follow SoA	Telephone visits
3, 5, 7, 11, and 29	Follow SoA	May be conducted as outpatient clinic or home visits
8, 9, and 10	Collect participant questionnaire symptom and overall clinical status assessments	Telephone visits
Early discontinuation and follow-up	Follow SoA	May be conducted as outpatient clinic or home visits

***Guidelines if a Participant is Hospitalized***

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.

<b>If hospital discharge...</b>	<b>Then...</b>
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.

The population of participants in treatment arms 7-9 are required to have at least 1 risk factor for developing severe COVID-19 illness. The risk factors were based on the Centers for Disease

Control guidance (CDC resource page, available at: [https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-increased-risk.html?CDC\\_AA\\_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fpeople-at-higher-risk.html](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-increased-risk.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fpeople-at-higher-risk.html)). Participants with these risk factors are at higher risk for more severe disease and hospitalization. This population was chosen to evaluate if effective antiviral antibody therapy may prevent hospitalization or death.

### ***Adolescent Participants***

There are no approved treatments for adolescents infected with SARS-CoV-2 or to prevent infection in adolescents with comorbidities that place them at increased risk should they become exposed to SARS-CoV-2. Per FDA request, adolescents at higher risk for severe disease and hospitalization are included in this study.

To minimize invasive procedures and blood volume collection concerns in adolescents, certain laboratory tests and sample collections are excluded for this population.

### ***Pregnant Participants***

Interim analysis from this study suggest treatment with LY3819253 may decrease the risk of hospitalization in mild to moderate COVID-19 patients (Chen et al. 2020). Pregnant females and pregnant females with additional risk factors for severe disease and hospitalization may benefit from early administration of experimental anti-viral therapies such as the combination of LY3819253 and LY3832479, especially given the current safety profile. Per FDA guidance, pregnant individuals may be included in this study (FDA, May 2020).

### ***Participants who have received a SARS-CoV-2 vaccination***

SARS-CoV-2 vaccines are now available to the public. Those who received a SARS-CoV-2 vaccine are now allowed in the study to assess the safety of LY3819253 and LY3832479 after a person received the vaccine.

### **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* IC<sub>90</sub> 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* IC<sub>90</sub> of viral cell-entry neutralization (95<sup>th</sup> percentile of the estimates) in the lung tissue for at least 28 days in greater than 90% of the participant population. The PK included additional variability to cover translational uncertainty. The 95<sup>th</sup> percentile was chosen as a conservative measure.

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.

In treatment arms 7 and 8, adult participants are currently randomized 1:1 to receive placebo or a combination of 2800mg LY3819253 and 2800mg LY3832479. Based on PK extrapolation (exposure-matching), adolescents  $\geq$  40 kg dosed with 2800 mg are expected to reach the same exposure ( $C_{max}$  and AUC) as adults for both LY3819253 and LY3832479. Exclusion criterion #29 was added to ensure all participants have a body weight  $\geq$  40 kg. Thus, adolescent participants will receive the same dose level as the adult participants.

In treatment arm 9, participants will receive a combination of 700 mg LY3819253 and 1400 mg LY3832479. To provide coverage of the different but overlapping epitopes on SARS-CoV-2 receptor binding domain sites for the combination of LY3819253 and LY3832479, the dose selection rationale for each single mAb in the combination is the same as for the dose rationale for a single mAb. The dose of 700 mg LY3819253 was confirmed as the maximum therapeutic dose in the PYAB interim analysis based on viral load, symptoms and clinical outcomes. The dose of 1400 mg LY3832479 is selected as the maximum therapeutic dose based on an approximate 2-fold higher IC<sub>50</sub> to LY3819253. At these dose levels, the combination is expected to reduce viral load based on viral dynamic PK/PD modeling (updated with reduced translational uncertainty) and have a sustained concentration above the respective IC<sub>90</sub> of viral neutralization for at least 28 days in 90% of the participant population.

In treatment arm 14, participants will receive a combination of 350 mg LY3819253 and 700 mg LY3832479. The doses were selected based on PK/PD modeling, in addition to interim PK, viral load, symptoms, clinical outcome and safety data from Study J2X-MC-PYAH (BLAZE-4).

**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  $\geq 12$  years of age at the time of screening

#### Disease Characteristics

2. Are currently not hospitalized
3. Have one or more mild or moderate COVID-19 symptoms (FDA May 2020, 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  $\leq 3$  days prior to start of the infusion

#### Sex

5. Are males or females, including pregnant females  
Reproductive and Contraceptive agreements and guidance is provided in Section 10.4, Appendix 4. Contraceptive use by males or females 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 and/or assent 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.

## Treatment arms 7-9, 13-14

27. Are  $\geq 18$  years of age and satisfy at least one of the following at the time of screening
- Are  $\geq 65$  years of age
  - Have a BMI  $\geq 35$
  - Have chronic kidney disease
  - Have type 1 or type 2 diabetes
  - Have immunosuppressive disease
  - Are currently receiving immunosuppressive treatment, or
  - Are  $\geq 55$  years of age AND have
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease or other chronic respiratory disease

Note: BMI is rounded to the nearest whole number, for example, 34.5 is rounded to 35.

28. Are 12-17 years of age (inclusive) AND satisfy at least one of the following at the time of screening
- Have a BMI  $\geq 85^{\text{th}}$  percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm)
  - Have sickle cell disease
  - Have congenital or acquired heart disease
  - Have neurodevelopmental disorders, for example, cerebral palsy
  - Have a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
  - Have asthma or reactive airway or other chronic respiratory disease that requires daily medication for control
  - Have type 1 or type 2 diabetes
  - Have chronic kidney disease
  - Have immunosuppressive disease, or
  - Are currently receiving immunosuppressive treatment.

## 5.2. Exclusion Criteria

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

### Medical Conditions

9. Have  $\text{SpO}_2 \leq 93\%$  on room air at sea level or  $\text{PaO}_2/\text{FiO}_2 < 300$ , respiratory rate  $\geq 30$  per minute, heart rate  $\geq 125$  per minute (FDA May 2020)
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 received convalescent COVID-19 plasma treatment
21. Exclusion criterion [21] removed in amendment (k)
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 breast feeding
25. Are investigator site personnel directly affiliated with this study, and
29. Have body weight <40 kg.

### **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.

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

<b>Intervention Name</b>	Placebo	LY3819253				LY3832479		
<b>Dose Formulation</b>	0.9% sodium chloride solution	Solution						
<b>Dosage Level(s) (mg)</b>	Not applicable	350	700	2800	7000	700	1400	2800
<b>Use</b>	placebo	experimental						
<b>IMP and NIMP</b>	IMP	IMP						
<b>Sourcing</b>	Commercially available 0.9% sodium chloride solution	From Lilly						
<b>Packaging and Labeling</b>	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 preparation instructions.

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 1 hour after completion of the infusion.

The site must have age-appropriate resuscitation equipment, emergency drugs and appropriately training staff available during the infusion and for at least 1 hour 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.

<b>Parameter</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Severe and Potentially Life-threatening</b>
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 <sup>a</sup>	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 $\leq 24$ hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

<sup>a</sup> = 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).

### 6.1.2. Temporary Stopping Criteria

The Assessment Committee (AC) members individually will review unblinded safety data for treatment arms 1-4 and 6, 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).

The Data Monitoring Committee (DMC) may stop enrollment or change other study parameters based on their review for treatment arms 7-9, 13-14.

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

<b>Topic</b>	<b>Location</b>
DAIDS table describing severity of reactions	Section <a href="#">6.1.1.2</a>
Definition of AEs	Section <a href="#">10.3.1</a>
Assessment of Intensity/Severity	Section <a href="#">10.3.3</a>

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 storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

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

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

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

The investigator or designee 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 ( $\leq 8$  days versus  $> 8$  days) and age at the time of screening ( $< 18$  years of age versus  $\geq 18$  years of age).

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)	<ul style="list-style-type: none"> <li>• 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</li> <li>• In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted</li> <li>• 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</li> <li>• If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance</li> <li>• The date and reason that the blind was broken must be recorded in the source documentation.</li> </ul>
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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**

Any prior therapy, such as antivirals, antibiotics, vaccines, 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.

For adolescent participants, record any non-SARS-CoV-2 vaccines received 90 days prior to signing informed consent.

##### **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 the remainder of the assessment visits through Day 29 and also for the post-treatment follow-up visits on Days 60 and 85 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, 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 discontinuation, if possible, an early discontinuation visit should be conducted as described in the SoA. The participant should also return for the post-treatment follow-up visits.

If the participant discontinues on the same day as a normally scheduled visit, only one set of laboratory tests, sample collection and assessments are collected.

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.

#### **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.

<b>Rating</b>	<b>Score</b>
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, FiO<sub>2</sub> if known, and method of delivery, if applicable.

### Treatments 1-4 and 6

This table outlines Day 1 vital signs data collection on the CRF in relation to the infusion for treatment arms 1-4 and 6. 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

### Treatment arms 7-9, 13-14

This table outlines Day 1 vital signs data collection on the CRF in relation to the infusion for treatment arms 7-9, 13-14. Infusion times may vary depending on the participant.

Timepoint (minutes)	Collect data on CRF
Immediately before infusion	Yes
If infusion is <15 minutes, immediately following completion of infusion	Yes
During Infusions > 15 minutes, as possible	--
15	No
30	Yes
45	No
60	Yes
After Infusion – every 30 minutes for 1 hour after the end of the infusion	--
end of infusion +30 minutes	Yes
end of infusion +60 minutes	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.

#### **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  $\geq 24$  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 the alert, consciousness, verbal, pain, unresponsive scale (ACVPU), limitation on activities due to COVID-19 using the patient global assessment for daily activities of physical function, 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**

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**

If a hypersensitivity 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 <a href="#">6.1.1</a>
Premedication for infusions	Section <a href="#">6.1.1.1</a>
Management of infusion reactions	Section <a href="#">6.1.1.2</a>
DAIDS table describing severity	Section <a href="#">6.1.1.2</a>
Treatment guidelines for infusion-related reactions	Section <a href="#">6.1.1.2</a>

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 used for exploratory analyses 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 in adult participants 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.



Samples used for immunogenicity may be used for exploratory analyses as deemed appropriate.

**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

For treatment arm 7, the hypothesis is whether there is a difference in the proportion of participants who experience a COVID-related hospitalization or death from any cause compared to concurrently enrolled placebo data from treatment arm 8.

For treatment arm 9, the hypothesis is whether there is a difference in the proportion of participants who experience a COVID-related hospitalization or death from any cause compared to all placebo data from treatment arm 8. The same hypothesis will be tested for treatment arm 14 compared to all placebo data from treatment arm 13.

### 9.2. Sample Size Determination

#### Sample Size

##### *Treatment arms 1-4 and 6*

The initial planned sample size is approximately 500 participants 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 treatment arm 6.

Up to 100 additional participants may be introduced for optional treatment arm 5. See Section 9.5 for interim analysis details.

##### *Treatment arms 7-9*

Participants in treatment arms 7-9 are adults and adolescents with at least 1 risk factor for developing severe COVID-19 illness. There is no set sample size for the adolescent participants.

The planned sample size for the primary comparison of treatment arms 7 and 8 is approximately 1000 participants equally randomized to placebo or the combination of LY3819253 and LY3832479.

The planned sample size for treatment arm 9 is approximately 500 participants. Since treatment arm 9 begins enrollment after treatment arm 7, additional participants will be enrolled in treatment arm 8 to ensure at least a 33% increase in placebo participants and adequate placebo control for the primary comparison of treatment arms 8 and 9.

##### *Treatment arms 13 and 14*

Participants in treatment arms 13 and 14 are adults and adolescents with at least 1 risk factor for developing severe COVID-19 illness. There is no set sample size for the adolescent participants or those with prior SARS-CoV-2 vaccine use.

The planned sample size for the primary comparison of treatment arms 13 and 14 is approximately 1000 participants randomized 2:3, placebo:combination of LY3819253 and LY3832479.

**Stratification**

Participants will be stratified by

- duration since symptom onset category ( $\leq 8$  days versus  $> 8$  days)
- age at the time of screening ( $< 18$  years of age versus  $\geq 18$  years of age), and
- and whether a participant received a SARS-CoV-2 vaccine or not prior to screening.

**Treatment arms 1-4 and 6*****Simulations***

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 of interest in SARS-CoV-2 viral load between LY3819253 and placebo.

The mean log change from baseline to Day 11 ( $\pm 4$  days) 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 treatment 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 ( $\pm 4$  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.

**Treatment arms 7-9**

Sample size justification is based on the endpoint of proportion of participants experiencing COVID-related hospitalization or death from any cause. A sample size of approximately 500 adult participants per treatment arm provides greater than 90% power to demonstrate that LY3819253 in combination with LY3832479 is statistically significantly better than placebo, defined as odds ratio  $< 1$  in the proportion of participants experiencing a COVID-related hospitalization or death from any cause. This sample size calculation assumes a placebo event rate of 8.7% and a relative reduction of 60% for LY3819253 in combination with LY3832479, which were informed from available data on hospitalization or death events.

**Treatment arms 13-14**

Sample size justification is based on the endpoint of proportion of participants experiencing COVID-related hospitalization or death from any cause. A sample size of approximately 1000 adult participants randomized 2:3 provides greater than 90% power to demonstrate that LY3819253 in combination with LY3832479 is statistically significantly better than placebo, defined as odds ratio  $< 1$  in the proportion of participants experiencing a COVID-related hospitalization or death from any cause. This sample size calculation assumes a placebo event rate of 8.7% and a relative reduction of 60% for LY3819253 in combination with LY3832479, which were informed from available data on hospitalization or death events.

### 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.
Modified Efficacy	Includes the efficacy population and excludes participants who received a SARS-CoV-2 vaccine. This population will be used for treatment arms 13-14 efficacy analysis.

### 9.4. Statistical Analyses

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

Unless otherwise specified, treatment effects using frequentist approaches will be conducted using 2-sided tests at an alpha level of 0.05. When Bayesian methods are used for analyses, and posterior mean, posterior standard deviation, credible intervals, and posterior probability of the effect of interest will be summarized. For the Bayesian analyses, the prior distributions and success definitions will be fully described in the statistical analysis plan (SAP). 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 SAP.

Analyses will be performed separately for treatment arms

- 1-4 and 6
- 7 and concurrently enrolled 8
- 8 and 9, and
- 13 and 14.

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

#### Treatment Arms 1-4 and 6

Primary endpoint for treatment arms 1-4 and 6 is the change from baseline to Day 11 ( $\pm 4$  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.

#### Treatment Arms 7-9, 13-14

The primary endpoint is the overall participant clinical status, measured by the proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as  $\geq 24$  hours of acute care) or death from any cause by Day 29.

The primary analysis method will be a logistic regression with a primary success criterion of one-sided alpha level 0.025.

Full details will be provided in the SAP.

### **9.4.3. Secondary Endpoints**

#### **9.4.3.1. Key Secondary Endpoints**

Key secondary endpoints for treatment arms 7-9, 13-14 include

- Reduction of SARS-CoV-2 viral load measured by change from baseline to Day 7 ( $\pm 2$  days)
- The proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
- Proportion (percentage) of participants who experience these events by Day 29
  - COVID-19 related hospitalization (defined as  $\geq 24$  hours of acute care), or
  - a COVID-19 related emergency room visit, or
  - death from any cause, and
- Time to sustained symptom resolution
  - symptoms are scored as absent.

#### **9.4.3.2. 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.

#### **9.4.3.3. Additional Secondary Endpoints**

##### **Treatment Arms 1-4 and 6**

Additional secondary endpoints for treatment arms 1-4 and 6 include

- Change from baseline to Day 11 ( $\pm 4$  days) in SARS-CoV-2 viral load among participants enrolled with  $\leq 8$  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  $\geq 24$  hours of acute care)
  - a COVID-19 related emergency room visit, or
  - death.

### **Treatment Arms 7–9, 13-14**

Additional secondary endpoints for treatment arms 7-9, 13-14 include

- SARS-CoV-2 viral load reduction change from baseline to
  - Day 3 (+ 1 day)
  - Day 5 ( $\pm 2$  days)
- SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
- Time to SARS-CoV-2 clearance
- Time to symptom resolution
- Time to complete symptom resolution
- Time to sustained complete symptom resolution
- Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11
- 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, and
- Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11.

Full details of the analyses will be in the SAP.

#### **9.4.3.4. Pharmacokinetic Analyses**

Pharmacokinetic analyses will be conducted on data from all participants who receive intervention and have evaluable PK. LY3819253 and LY3832479 concentration data will be summarized descriptively by sample collection time (e.g., Day 29). Additional population analysis approaches using non-linear mixed effects modeling may be used to evaluate exposure-response of safety and efficacy.

Study data may be pooled with the results of other studies for population PK and PK/PD analysis purposes.

#### **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 arms 1-4, 6).

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

### Treatment Arms 1-4 and 6

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 any treatment arm 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.

Prior to the primary endpoint, 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.

### Treatment Arms 7-9, 13-14

Unblinded assessments of efficacy will be done separately for treatment arms 7 and 8, 8 and 9, and 13 and 14.

#### *Treatment Arms 7 and 8*

Assessments will begin when all participants for treatment arm 7 and concurrently enrolled treatment arm 8 complete the Day 29 visit. Equal allocation to treatment arms 7 and 8 is planned.

#### *Treatment Arms 8 and 9*

Assessments will begin when all additional participants from treatment arm 8 and participants from treatment arm 9 complete the Day 29 visit. Additional participants will be enrolled in treatment arm 8 to ensure at least a 33% increase in placebo participants and adequate placebo control for the primary comparison of treatment arms 8 and 9.

#### *Treatment Arms 13 and 14*

Assessments will begin when all participants from treatment arms 13 and 14 complete the Day 29 visit.

### Safety Reviews

Safety reviews will occur as specified in the DMC charter.

**PK/PD**

A limited number of pre-identified individuals may gain access to unblinded data, as specified in the unblinding plan prior to the primary lock, in order to initiate the population PK/PD model development processes. Following the database lock, the sponsor will be unblinded to analyze and report the data.

**Unblinding**

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)****Treatment Arms 1-4 and 6**

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.

**Treatment Arms 7-9, 13-14**

An external DMC will analyze unblinded safety data as specified in a DMC charter.

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 DMC will be provided in the DMC 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 (CTA).

#### **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 and child/adolescent assent, as appropriate, 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 or child/adolescent assent 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 or child/adolescent assent was obtained before the participant was entered in the study and the date the written consent or assent was obtained. The authorized person obtaining the informed consent or child/adolescent assent, and, if applicable, the individual designated to witness a verbal consent, must also sign the ICF. The medical record should also describe how the investigator determined that the person signing the ICF was the participant's legally authorized representative (parent/guardian).

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study, per the re-consenting guidelines as appropriate. Verbal re-consenting and alternative methods of obtaining consent may be utilized if approved by the IRB.

Minor participants must be re-consented if they reach the age of majority during the course of study, in order to continue participating.

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.

The DMC will consist of members external to the sponsor (Lilly). The membership will include, at a minimum, a chair (physician), a statistician and another physician. The DMC 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 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.

<b>Clinical Laboratory Tests</b>	<b>Comments</b>
<b>Hematology</b>	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)	
<b>Clinical Chemistry</b>	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)	
<b>SARS-CoV-2 viral infection determination</b>	Local laboratory and/or Point-of-Care testing
<b>SARS-CoV-2 Test Panel</b>	Assayed by Lilly-designated laboratory.
C-reactive protein (CRP); high-sensitivity	For adults only

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

<b>An SAE is defined as any untoward medical occurrence that, at any dose:</b>
<b>a. Results in death</b>
<b>b. Is life-threatening</b> 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.
<b>c. Requires inpatient hospitalization or prolongation of existing hospitalization</b> <ul style="list-style-type: none"> <li>● 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.</li> <li>● Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.</li> </ul>
<b>d. Results in persistent disability/incapacity</b> <ul style="list-style-type: none"> <li>● The term disability means a substantial disruption of a person’s ability to conduct normal life functions.</li> </ul>

<ul style="list-style-type: none"> <li>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.</li> </ul>
<p><b>e. Is a congenital anomaly/birth defect</b></p>
<p><b>f. Other situations:</b></p> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>

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

<p><b>AE and SAE Recording</b></p> <ul style="list-style-type: none"> <li>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.</li> <li>The investigator will then record all relevant AE/SAE information in the CRF.</li> <li>It is <b>not</b> 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.</li> <li>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.</li> <li>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.</li> </ul>
<p><b>Assessment of Intensity</b></p> <p>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).</p>

**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:
  - d. 12 months of amenorrhea for women >55, with no need for FSH
  - e. 12 months of amenorrhea for women >40 years old with FSH  $\geq$ 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 and not of child-bearing potential may participate in this study.

Women of child-bearing potential who are not pregnant at the time of study entry, and 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 who are not pregnant at the time of study entry, 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 and assent (if applicable) 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, this information will include a follow-up of at least 5 half-lives after last exposure or birth. 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 or are pregnant at the time of study entry**

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study or is pregnant at the time of study entry. 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, this information will include a follow-up of at least 5 half-lives after last exposure or birth. 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.

## 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**

<b>Hypersensitivity Tests</b>	<b>Notes</b>
LY3819253 and LY3832479 anti-drug antibodies (immunogenicity/ADA)	Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions. 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. <b>Note:</b> 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. <b>NOTE:</b> 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 $\geq 3x$ ULN with hepatic signs/symptoms*, <u>or</u> ALT or AST $\geq 5x$ ULN
ALP <1.5x ULN	ALP $\geq 3x$ ULN
TBL <1.5x ULN	TBL $\geq 2x$ ULN (except for participants with Gilbert's syndrome)
ALT or AST $\geq 1.5x$ ULN	ALT or AST $\geq 2x$ baseline with hepatic signs/symptoms*, <u>or</u> ALT or AST $\geq 3x$ baseline
ALP $\geq 1.5x$ ULN	ALP $\geq 2x$ baseline
TBL $\geq 1.5x$ ULN	TBL $\geq 1.5x$ 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:

<b>If a participant with baseline...</b>	<b>has the following elevations...</b>
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.

<b>Hematology</b>	<b>Clinical Chemistry</b>
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	<b>Other Chemistry</b>
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
<b>Coagulation</b>	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin

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

<sup>a</sup> Not required if anti-actin antibody is tested.

<sup>b</sup> Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

<sup>c</sup> Not required if anti-smooth muscle antibody (ASMA) is tested.

<sup>d</sup> Assayed ONLY by investigator-designated local laboratory; no central testing available.

**10.8. Appendix 8: Abbreviations**

<b>Term</b>	<b>Definition</b>
<b>AC</b>	assessment committee
<b>ADA</b>	anti-drug antibody
<b>ADE</b>	antibody-dependent enhancement
<b>adolescent</b>	Participant 12 to 17 years of age
<b>assent</b>	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study.
<b>blinding/masking</b>	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.
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>Complaint</b>	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.
<b>Compliance</b>	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
<b>CRP</b>	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.
<b>CTA</b>	Clinical trial agreement
<b>DMC</b>	data monitoring committee
<b>ECG</b>	electrocardiogram
<b>FiO2</b>	fraction of inspired oxygen in the air
<b>Enroll</b>	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.
<b>Enter</b>	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>GCP</b>	good clinical practice
<b>IB</b>	Investigator's Brochure

<b>ICF</b>	informed consent form
<b>ICH</b>	International Council for Harmonisation
<b>IMP</b>	Investigational Medicinal Product
<b>Informed consent</b>	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.
<b>interim analysis</b>	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.
<b>Intervention</b>	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.
<b>IWRS</b>	interactive web-response system
<b>Legal representative</b>	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective participant, to their participation in the clinical study.
<b>NP</b>	Nasopharyngeal
<b>Participant</b>	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
<b>PK/PD</b>	pharmacokinetics/pharmacodynamics
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>Screen</b>	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.
<b>SpO2</b>	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 j: 07 January 2021

#### Overall Rationale for the Amendment:

This amendment addresses changes in response to emerging data, discussions with the FDA and the addition of treatment arms 13 and 14. Treatment arms 10-12 were skipped due to internal programming capabilities.

Section # and Name	Description of Change	Brief Rationale
Throughout protocol	Added treatment arms 13-14 identifiers where applicable	Addition of treatment arms 13 and 14
1.1 Synopsis	Updated treatment arms 7-9 Objectives and Endpoint table. This table is now also applicable for treatment arms 13-14.	Alignment with FDA feedback and emerging data. Identified key secondary objectives, updated other secondary endpoints.
1.1 Synopsis	Updated Disclosure Statement to accommodate all treatment arms	Statement applies to all treatment arms
1.1 Synopsis	Updated Number of Participants for treatment arms 7-9 and 13-14	Correction of sample size for 7-9 and addition of treatment arms 13 and 14
1.1 Synopsis	Updated Intervention Groups and Duration table with new treatment arms. Added information about placebo control for treatment arms 13 and 14.	Addition of treatment arms 13 and 14.
1.1 Synopsis	Updated Data Monitoring Committee to include treatment arms 13 and 14	Addition of treatment arms 13 and 14.
1.2 Schema	Updated Schema and Figure title	Addition of treatment arms 13 and 14.
1.3.2 Schedule of Activities (SoA) for 7-9	Will use this SoA for treatment arms 7-9, 13-14	Addition of treatment arms 13 and 14.
1.3.2 Schedule of Activities (SoA) for 7-9, 13-14	Clarified collection of prior “non-COVID” vaccine treatments for adolescents	clarification
1.3.2 Schedule of Activities (SoA) for 7-9, 13-14	Updated vital signs and Oxygen Support timing for Day 1 for an infusion that is <15 minutes	Addition of treatment arms 13 and 14.
1.3.2 Schedule of Activities (SoA) for 7-9, 13-14	Added clarification that pregnancy testing is not applicable for females pregnant at screening	Pregnant females are eligible in this study.
2.3 Benefit/Risk Assessment	Updated the risk associated with administration of LY3819253	From emerging clinical data
2.3 Benefit/Risk Assessment	Added benefit/risk information for the pregnant population	Pregnant females are eligible in this study.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
3.2 Objectives and Endpoints for Treatment arms 7-9, 13-14	Added treatment arms 13-14. Identified key secondary objectives, updated other secondary and exploratory endpoints.	Addition of treatment arms 13 and 14. Alignment with FDA feedback and emerging data.
4.1.1 Design Outline	Updated treatment arm table with new treatment arms. Added information about placebo control for treatment arms 13 and 14.	Addition of treatment arms 13 and 14.
4.2 Scientific Rationale for Study Design	Added information for pregnant participants	Pregnant females are eligible in this study
4.3 Justification for Dose	Added information for new treatment arms	Addition of treatment arms 13 and 14.
5.1 Inclusion Criteria	Updated Criterion #5 to include pregnant females	Pregnant females are eligible in this study
5.1 Inclusion Criteria	Added “requires daily medication for control” to Criterion #28	Per the Emergency Use Authorization (EUA) for adolescents
5.2 Exclusion Criteria	Added “or have received a SARS-CoV-2 vaccine” to Criterion #21	Clarification of criterion because of the availability of the vaccine.
5.2 Exclusion Criteria	Removed “pregnant or” from Criterion #24	Pregnant females are eligible in this study
6.1 Study Intervention(s) Administered	Added new dose levels to Study Intervention table	Addition of treatment arm 14.
6.1 Study Intervention(s) Administered	Replaced “pharmacy preparation instructions” for “pharmacy manual”	Correction. Infusion information may be found in the pharmacy preparation instructions.
6.1.1.2. Management of Infusion Reactions	Removed duplicate text about premedication for infusions	This information is located in Section 6.1.1.1. and was inadvertently repeated in Section 6.1.1.2.
7.2 Participant Discontinuation/Withdrawal from Study	Removed “if the participant becomes pregnant during the study” from the bulleted list	Pregnant females are eligible in this study
8.2.2 Vital Signs	Updated Treatment arms 7-9, 13-14 table for Day 1 data collection for an infusion that is <15 minutes	Addition of treatment arms 13 and 14.
8.2.3 Clinical Laboratory Assessments	Removed text from Pregnancy testing sub-section “Participants who are pregnant will be discontinued from the study	Pregnant females are eligible in this study
8.3.5 Pregnancy	Removed text from section so that it is aligned with Section 10.4, Appendix 4.	Correction

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
8.3.6 Hypersensitivity Reactions	Removed text about the risk of systemic hypersensitivity reactions	The risks are outlined in Section 2.3. Benefit/Risk Assessment
9.1 Statistical Hypotheses	Updated text according to changes to primary endpoint and added text for new treatment arms	Alignment with FDA feedback and emerging data. Addition of treatment arms 13 and 14.
9.2 Sample Size Determination	Added sub-headers for clarity. Updated sample size for treatment arms 7-9. Added sample size and randomization for treatment arms 13-14.	Statistician decision and addition of treatment arms 13 and 14.
9.4 Statistical Analyses	Added treatment arms 13 and 14	Addition of treatment arms 13 and 14.
9.4.2 Primary Endpoints	Updated text according to changes to primary endpoint and for new treatment arms	Alignment with FDA feedback and emerging data. Addition of treatment arms 13 and 14.
9.4.3.1 Key Secondary Endpoints	New Section	Alignment with FDA feedback and emerging data.
9.4.3.2 Safety	This section is renumbered	Section moved down due to new Key Secondary Endpoints section
9.4.3.3 Additional Secondary Endpoints	This section is renumbered. Updated endpoints for treatment arms 7-9 and added arms 13 and 14	Renumbered due to new Key Secondary Endpoints section. Alignment with FDA feedback and emerging data.
9.4.3.4 Pharmacokinetic Analyses	This section is renumbered.	Renumbered due to new Key Secondary Endpoints section.
9.4.6 Subgroup Analyses	Removed incorrect text	Correction
9.5 Interim Analyses	Added sub-headers and updated text for treatment arms 7-9. Added text for new treatment arms	Updates made for clarification and addition of treatment arms 13 and 14.
9.6 Data Monitoring Committee	Added treatment arms 13-14 to Treatment Arms 7-9 sub-header and updated first sentence under this header	Removed text that was not applicable to these treatment arms.
10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Updated text for the inclusion of pregnant females	Pregnant females are eligible in this study
11 References	Added Chen et.al.2020 reference	Source for information in Section 2.3
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

**Amendment i: 30 November 2020****Overall Rationale for the Amendment:**

This amendment addresses changes in response to discussions with the FDA to enable independent confirmation of the safety and efficacy of LY3819253 in combination with LY3832479 for the treatment of COVID-19. The decision was made to remove treatment arms 10 and 11, and change the primary objective, statistical methods and sample size for treatment arms 7-9.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
Title Page	Updated Phase 2 to Phase 2/3	Per FDA feedback to more accurately describe study
1.1 Synopsis	Updated protocol title to Phase 2/3	Per FDA feedback to more accurately describe study
1.1 Synopsis	Updated Objectives and Endpoints table for treatment arms 7-9 to reflect changes in Section 3.	Removed treatment arm 10, updated the primary objective for treatment arms 7-9, moved reduction in viral load from primary to first secondary endpoint, and added Day 29 to symptom resolution and symptom improvement endpoints.
1.1 Synopsis	Removed treatment arm 11 objectives and endpoints table	Treatment arm 11 is removed from this study
1.1 Synopsis	Updated Overall Design to say Phase 2/3	Per FDA feedback to more accurately describe study
1.1 Synopsis	Updated visit type table	Treatment arms 10 and 11 are removed from this study
1.1 Synopsis	Updated Disclosure Statement	Treatment arms 10 and 11 are removed from this study
1.1 Synopsis	Updated Number of Participants	Treatment arms 10 and 11 are removed from this study and the sample size increased for treatment arms 7-9
1.1 Synopsis	Removed treatment arms 10 and 11 and updated placebo control information in Intervention Groups and Duration	Treatment arms 10 and 11 are removed from this study
1.1 Synopsis	Removed treatment arms 10 and 11 from Data Monitoring Committee	Treatment arms 10 and 11 are removed from this study
1.2 Schema	Updated existing figure for treatment arms 1-9 and removed treatment arm 11 figure	Treatment arms 10 and 11 are removed from this study
1.3.2. Schedule of Activities	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
1.3.2. Schedule of Activities	Changed visit window for Study Day 11 to -2/+3 from $\pm 3$	In order to avoid overlapping visits with study day 7 and more flexibility with study day 11 visit
2.3 Benefit/Risk Assessment	Removed text for Risks and Benefits Associated with Faster Rates of Infusion and removed text related to treatment arm 11	Removed treatment arm 11



<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
3.2 Objectives and Endpoints	Updated table for treatment arms 7-9.	Removed treatment arm 10, updated the primary objective for treatment arms 7-9, moved reduction in viral load from primary to first secondary endpoint, and added Day 29 to symptom resolution and symptom improvement endpoints.
3 Objectives and Endpoints	Removed treatment arm 11 objectives and endpoints table	Treatment arm 11 is removed from this study
4.1 Overall Design	Updated Overall Design to say Phase 2/3	Per FDA feedback to more accurately describe study
4.1.1 Design Outline	Removed treatment arms 10 and 11 from Treatment Arm table and text	Treatment arms 10 and 11 are removed from this study
4.1.1 Design Outline	Updated text to describe that treatment arm 8 will be the corresponding placebo control for treatment arms 7 and 9	Will increase the sample size for 8 and enroll with both treatment arms 7 and 9.
4.1.1 Design Outline	Removed information for treatment arms 10 and 11 for visit types	Treatment arms 10 and 11 are removed from this study
4.2 Scientific Rationale for Study Design	Removed rationale for treatment arm 11 and updated text to remove reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
4.3 Justification for Dose	Removed references to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
5.1 Inclusion Criteria	Removed reference to treatment arms 10 and 11 for inclusion criteria #27 and #28	Treatment arms 10 and 11 are removed from this study
5.1 Inclusion Criteria	Added "have chronic kidney disease" to criterion #28	Medical decision
6.1.1.2 Management of Infusion Reactions	Added footnote and source back to table describing the severity of reactions according to Division of Allergy and Infectious Diseases (DAIDS)	This information was inadvertently removed in a previous version of the protocol
6.1.2 Temporary Stopping Criteria	Removed reference to treatment arms 10 and 11 and removed specific stopping criteria for treatment arm 11	Treatment arms 10 and 11 are removed from this study
6.3 Measures to Minimize Bias: Randomization and Blinding	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
8.2.2 Vital Signs	Removed reference to treatment arms 10 and 11 for vital signs data collection table	Treatment arms 10 and 11 are removed from this study

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Hypotheses	Removed reference to treatment arms 10 and 11 and updated hypothesis for treatment arm 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes for the primary objective and endpoint.
9.2 Sample Size Determination	Removed reference to treatment arms 10 and 11 and updated sample size information for treatment arms 7 - 9	Change in strategy per discussions with FDA
9.4 Statistical Analyses	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes in analyses
9.4.2 Primary Endpoints	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes in analyses
9.4.3.2 Additional Secondary Endpoints	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect the move of viral load from primary to secondary endpoint, and the addition of Day 29 to symptom improvement and symptom resolution endpoints
9.4.6 Subgroup Analyses	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
9.5 Interim Analyses	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes in analyses
9.6 Data Monitoring Committee (DMC)	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

### Amendment g: 17 November 2020

#### Overall Rationale for the Amendment:

This amendment addresses the addition of treatment arms 9-11. Treatment arm 9 will explore a lower dose level of the combination of LY3819253 and LY3832479. Treatment arm 10 will provide a bridge to the existing placebo arms. Treatment arm 11 is an open-label sub-study comprised of two cohorts to evaluate a faster IV infusion rate of the combination of LY3819253 and LY3832479.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Added Objectives and Endpoints tables for treatment arms 9-11	Addition of new treatments
1.1 Synopsis	Updated sub-headings under Design Outline to remove "double-blind"	Addition of the open-label treatment arm 11

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.1 Synopsis	Updated Disclosure Statement for treatment arms 7-11	Addition of new treatments
1.1 Synopsis	Added Number of Participants for treatment arms 9-11	Addition of new treatments
1.1 Synopsis	Added information for treatment arms 9-11 to Intervention Groups and Duration	Addition of new treatments
1.1 Synopsis	Updated text under Data Monitoring Committee	Addition of new treatments
1.2 Schema	Updated existing figure and added figure for treatment arm 11	Addition of new treatments
1.3.2. Schedule of Activities	Updated to include the new treatments	New treatments will use the same SoA as treatment arms 7-8
2.3 Benefit/Risk	Added sub-headings for clarification of information. Added the potential benefit/risks associated with an increased rate of infusion	Treatment arm 11 will use a faster infusion rate than the other treatment arms
3 Objectives and Endpoints	Added new sub-headings for the separate tables for the different treatment arms	Easier document navigation
3 Objectives and Endpoints	The table for treatment arms 7-8 is now applicable for treatment arms 7-10. Added clarifying text for secondary objectives in this table to describe differences between treatment arms 7-8 versus 9-10	Treatment arms 9-10 will have basically the same objectives and endpoints, but will need more flexibility for the secondary objectives.
3 Objectives and Endpoints	Added a new table for treatment arm 11	Addition of new treatment
4.1.1 Design Outline	Added sub-headings for clarification	Addition of new treatments
4.1.1 Design Outline	Updated sub-headings to remove "double-blind"	Addition of the open-label treatment arm 11
4.1.1 Design Outline	Added information for treatment arms 9-11 in treatment arm table and text	Addition of new treatments
4.1.1 Design Outline	Added information for treatment arms 9-11 for visit types	Addition of new treatments
4.2 Scientific Rationale for Study Design	Added rationale for the addition of treatment arm 11	This treatment arm is an open-label sub-study to evaluate a faster infusion rate.
4.2 Scientific Rationale for Study Design	Updated participant characteristics to add new treatment arms	Addition of new treatments
4.3 Justification for Dose	Section was updated to include the new treatment information	Addition of new treatments

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
5.1 Inclusion Criteria	Added sub-headings for criteria #27 and #28	Addition of new treatments
6.1 Study Intervention(s) Administered	Added new dose level for LY3832479	Addition of new treatments
6.1.2 Temporary Stopping Criteria	Added sub-headings for treatment arms 1-10 and criteria for treatment arm 11	Addition of new treatments and the 2 cohorts in treatment arm 11
6.3 Measures to Minimize Bias: Randomization and Blinding	Added sub-headings for treatment arms 1-11 and indicate that treatment arm 11 is open label	Addition of new treatment
8.2.2 Vital Signs	Added new treatment arms to table outlining Day 1 vital signs data collection and added the 90 and 120 minute collection to the treatment arms 7-11 table	Addition of new treatments
9.1 Statistical Hypotheses	Added information for treatment arms 9-10	Addition of new treatments
9.2 Sample Size Determination	Added sample size for new treatment arms Added text to clarify stratification is not applicable for treatment arm 11.	Addition of new treatments
9.2 Sample Size Determination	Added information for treatment arm 11 under stratification	Stratification is not applicable to treatment arm 11.
9.4 Statistical Analyses	Added information for treatment arms 9-11	Addition of new treatments
9.4.2 Primary Endpoints	Added information for new treatment arms	Addition of new treatments
9.4.3.2 Additional Secondary Endpoints	Updates made to include treatment arms 9-10 and added text for treatment arm 11	Addition of new treatments
9.4.3.3 Pharmacokinetic Analyses	Removed reference to noncompartmental analysis and replaced with descriptive summary.	Number of study participants with evaluable PK concentration data has increased.
9.4.6 Subgroup Analyses	Updates made to include treatment arms 9-10 and added text for treatment arm 11	Addition of new treatments
9.5 Interim Analyses	Updates made to include treatment arms 9-10, added text to explain that unblinded assessments will be done separately for treatment arms 7 and 8, and 9 and 10, and added text for treatment arm 11	Addition of new treatments

Section # and Name	Description of Change	Brief Rationale
9.6 Data Monitoring Committee (DMC)	Updates made to include treatment arms 9-10 and added text for treatment arm 11	Addition of new treatments
11 References	Added FDA EUA fact sheet for bamlanivimab	Addition of reference.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

### Amendment f: 20 October 2020

#### Overall Rationale for the Amendment:

This amendment addresses changes requested by the Food and Drug Administration (FDA) for treatment arms 7 and 8. Treatment arms 7 and 8 will now include adolescent participants at higher risk for severe disease and hospitalization, and the primary and secondary endpoints will be updated.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated treatment arms 7 and 8 objectives and endpoints	Per FDA request to capture primary and secondary clinical endpoints until Day 29
1.1 Synopsis	Added child/adolescent assent to the screening procedure	Addition of adolescent participants
1.1 Synopsis	Added text in Number of Participants to say that adult and adolescent participants with at least 1 risk factor are in treatment arms 7 and 8	Addition of adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Added a row for informed assent	For adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Added a row to collect information on vaccines at screening	For adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Updated comments for the SARS-CoV-2 Test Panel	This panel is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Updated comments for pharmacokinetics Day 1 predose sample	Predose sample is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Updated comments for pharmacogenetics sample	This sample is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
2.3 Benefit/Risk Assessment	Added text for adolescents	Addition of adolescent participants
3 Objectives and Endpoints	Updated endpoints for Treatment Arms 7 and 8	Per FDA feedback
4.1.1 Design Outline	Added child/adolescent assent to the screening procedure	Addition of adolescent participants
4.2 Scientific Rationale for Study Design	Added rationale for including adolescent participants	Addition of adolescent participants

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
4.3 Justification for Dose	Added justification for adolescents	Addition of adolescent participants
5.1 Inclusion Criteria	Removed note about new criterion #27	Not applicable any longer
5.1 Inclusion Criteria	Updated Criterion #1 to include participants $\geq 12$ years of age	Addition of adolescent participants
5.1 Inclusion Criteria	Updated Criterion #5 nomenclature for participant sex from "men" and "women" to "male" and "female"	More appropriate terms for adolescent participants
5.1 Inclusion Criteria	Updated Criterion #8 to include assent	Addition of adolescent participants
5.1 Inclusion Criteria	Updated criterion #27 to indicate that it is for participants 18 years of age or older	To distinguish this criterion from the new #28 criterion for adolescents
5.1 Inclusion Criteria	Updated criterion #27 to state "type 1 or type 2" diabetes	Clarification of diabetes description
5.1 Inclusion Criteria	Added criterion #28	Addition of adolescent participants
5.2 Exclusion Criteria	Added criterion #29	Addition of adolescent participants
6.1 Study Intervention(s) Administered	Added that the site must have "age-appropriate" resuscitation equipment	For the adolescent participants
6.3 Measures to Minimize Bias: Randomization	Added stratification by age	Addition of adolescent participants
6.5 Concomitant Therapy	Updated Prior Treatment to add recording vaccines for adolescents	Addition of adolescent participants
8.7 Genetics	Added clarification that sample collection will be collected in adults only	This sample is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
9.1 Statistical Hypotheses	Minor change from "and" to "or"	
9.2 Sample Size Determination	Added stratification by age	Addition of adolescent participants
9.2 Sample Size Determination	Updated justification for Treatment arms 7 and 8	Further clarifications for the sample size justification
9.4.2 Primary Endpoints	Updated according to objectives and endpoints table	Per FDA feedback
9.4.3.2 Additional Secondary Endpoints	Updated according to objectives and endpoints table	Per FDA feedback
9.5 Interim Analyses	Unblinded assessments of efficacy will not be conducted until participants complete Day 29 visit, not Day 22.	correction
10.1.3. Informed Consent Process	Updated for adolescent population	Addition of adolescent participants
10.2 Appendix 2 Clinical Laboratory Tests	Added comments where sample collection is for adults only	Addition of adolescent participants

Section # and Name	Description of Change	Brief Rationale
10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Added women not of child-bearing potential to those participating in the study.	Correction and addition of adolescent participants
10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Added assent to section about male participants with partners who become pregnant	Addition of adolescent participants
10.8 Abbreviations	Added “assent” and “legal representative”	Addition of adolescent participants
11 References	Added references used in new text	Additional references used in body of protocol.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

### Amendment e: 13 October 2020

#### Overall Rationale for the Amendment:

This amendment addresses changes for treatment arms 7 and 8. This population is at higher risk for more severe disease and hospitalization. The sample size is increased, and the objectives and endpoints are updated to support potential marketing applications. The changes for treatment arms 7 and 8 affect sections throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated text to match the body of the protocol for the Objectives and Endpoints	See rationale for Section 3.
1.1 Synopsis	Updated information to match the body of the protocol for the Design Outline	Updated visit type table and added another specifically for treatment arms 7 and 8
1.1 Synopsis	Updated text to match the body of the protocol for the Number of participants.	Increase in sample size for treatment arms 7 and 8. See rationale for Section 9.2.
1.1 Synopsis	Updated Data Monitoring Committee (DMC) information to match the body of the protocol	See rationale for Section 9.6
1.3 Schedule of Activities (SoA)	Removed information pertaining to treatment arms 7 and 8 in the existing SoA	Participants enrolling into treatment arms 7 and 8 will have a different visit and sample schedule than treatment arms 1-4 and 6.
1.3 Schedule of Activities (SoA)	Created a separate SoA for treatment arms 7 and 8	Participants enrolling into treatment arms 7 and 8 will have a different visit and sample schedule.
2.2 Background	Removed information specific to a previous amendment	No longer applicable

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
3 Objectives and Endpoints	Updated the table for treatment arms 7 and 8	Changed the primary endpoints and updated the secondary endpoints based on emerging data
3 Objectives and Endpoints	Added pharmacokinetic endpoint for treatment arms 7 and 8	Will analyze the pharmacokinetics
4.1.1 Design Outline	Removed treatment arms 7 and 8 information from the visit type information table	Treatment arms 7 and 8 will have a different visit structure
4.1.1 Design Outline	Created a separate visit type information table for treatment arms 7 and 8	To match the new SoA specific to treatment arms 7 and 8
4.2 Scientific Rationale for Study Design	Added text for treatments 7 and 8 participant characteristics	Additional rationale for studying the population
5.1 Inclusion Criteria	Updated criterion #27 to include other chronic respiratory diseases	To broaden the population with high risk factors
6.1 Study Intervention(s) Administered	Changed monitoring from 2 hours after completion of the infusion to 1 hour	Based on available safety data
6.1.2 Temporary Stopping Criteria	Added information for DMC's role	An external DMC will review safety for treatment arms 7 and 8
6.3 Measures to Minimize Bias: Randomization and Blinding	Updated the Unblinding (IWRS) table to remove 'case report form'	A case report form is not used to record unblinding.
8.1 Efficacy Assessments	Removed specific endpoint dates	Endpoints are not the same across all treatment arms. Removed text to make more general. The information is also located in other sections of the protocol.
8.2.2 Vital Signs	Added clarifications for treatment arms 1-4 and 6 versus 7 and 8. Added a table for treatment arms 7 and 8.	Treatment arms 7 and 8 have different collection times for Day 1
8.5.1 Bioanalytical	Generalized text for remaining sample usage	To optimize the amount of information from sample collection, samples may be used for exploratory analyses beyond just metabolism or bioanalytical experiments
8.9 Immunogenicity	Generalized text for remaining sample usage	To optimize the amount of information from sample collection, samples may be used for exploratory analyses
9.1 Statistical Hypotheses	Added statistical hypothesis for treatment arms 7 and 8	New information to match the updated primary endpoints
9.2 Sample Size Determination	Updated sample size for treatment arms 7 and 8	Increase in sample size to provide statistical power for updated primary endpoints
9.2 Sample Size Determination	Updated section, moved text within section and added clarifications for treatment arms 1-4 and 6 versus 7 and 8.	Updated sample size rationale for treatments 7 and 8 sample size
9.4 Statistical Analyses	Updated section with new analyses	Aligned analysis plan with updated primary endpoints



Section # and Name	Description of Change	Brief Rationale
9.4.2 Primary Endpoints	Updated treatment arms 7 and 8 primary endpoints	New endpoints based on emerging data
9.4.3.2 Additional Secondary Endpoints	Updated treatment arms 7 and 8 secondary endpoints	Changes made to the primary endpoints dictated a change in secondary endpoints. Day 15 endpoints were removed per the new SoA.
9.4.6 Subgroup Analyses	Added clarifying text	Last bullet only applicable to treatment arms 1-4 and 6
9.5 Interim Analyses	Added clarifying text for treatment arms 7 and 8	Interim analyses will be different compared to treatment arms 1-4 and 6
9.6 Data Monitoring Committee (DMC)	Added clarifying text for treatment arms 7 and 8	The sponsor will form an external DMC to analyze safety data
10.1.3 Informed Consent Process	Added text to re-consenting information	Clarification
10.1.5 Committees Structure	Added clarifying text for treatment arms 7 and 8	The sponsor will form an external DMC to analyze safety data
Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Updated text for collection of information on infants after a woman gives birth	Per FDA feedback on pediatric development of LY3819253
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

#### **Amendment d: 18 September 2020**

##### **Overall Rationale for the Amendment:**

This amendment broadens the definition of patients with COVID-19 who are at a high risk of hospitalization.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Updated inclusion criterion 27.	Broadened definition of patients with COVID-19 at high risk for hospitalization.

#### **Amendment c: 31 August 2020**

##### **Overall Rationale for the Amendment:**

The sponsor is activating the optional treatment arm 7 with the combination of LY3819253 and LY3832479. Treatment arm 7 will consist of a population with risk factors for severe COVID-19 illness. Treatment arm 8 is added to the study as the corresponding placebo control. The primary and key secondary endpoints for treatment arms 7 and 8 are different than treatments 1-4 and 6.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.1 Synopsis	Updated text to match the body of the protocol for the Number of participants.	Updates were made to Section 9.2 to more accurately describe the sample sizes for the different treatment arms.
1.1 Synopsis	Updated text to match the body of the protocol for the Intervention Groups and Duration.	Activation of treatment arm 7 and addition of treatment arm 8.
1.1 Synopsis	Updated text to match the body of the protocol for the Objectives and Endpoints	See rationale for Section 3 below.
1.1 Synopsis	Updated text to match the body of the protocol for the Study Day and Visit Type table	Several study days had different visit types for treatment arms 1-4 and 6 versus treatment arms 7 and 8
1.1 Synopsis	Added text to clarify the corresponding placebo control treatment arm	Treatment arm 1 is the corresponding placebo control for treatment arms 2-4 and 6. Treatment arm 8 is the corresponding placebo control for treatment arm 7.
1.2 Schema	Updated treatment arm 7 information and added treatment arm 8.	Activation of treatment arm 7 and addition of treatment arm 8.
1.3 Schedule of Activities	Added a sentence to beginning paragraph to refer to the study day and visit type table in Section 4.1.1.	The referenced table provides additional clarifications.
1.3 Schedule of Activities	Days 4-6 were separated to accommodate procedures specific to treatment arms 7 and 8	Activation of treatment arm 7 and addition of treatment arm 8.
1.3 Schedule of Activities	Added footnotes in the Study Day row to indicate when telephone visits are allowed for the different treatment arms	Clarification
1.3 Schedule of Activities	Days 18 and 25 are telephone visits for treatment arms 7 and 8 only	Nasopharyngeal swabs and vital signs not collected on these days for treatment arms 7 and 8
1.3 Schedule of Activities	Day 5 is still a telephone visit for treatment arms 1-4 and 6	Clarification
1.3 Schedule of Activities	Updated visit windows for Days 5 and 7	To avoid overlap
1.3 Schedule of Activities	Added Day 5 vital sign collection only for treatment arms 7 and 8	Collection for participants with risk factors for severe disease
1.3 Schedule of Activities	Vital signs not collected on Days 18 and 25 for treatment arms 7 and 8	To accommodate a telephone visit.
1.3 Schedule of Activities	Added a nasopharyngeal (NP) swab on Day 5 only for treatment arms 7 and 8	Collect additional data to inform future clinical development

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.3 Schedule of Activities	NP swabs not collected on Days 18 and 25 for treatment arms 7 and 8	Based on emerging blinded data
1.3 Schedule of Activities	Added an exploratory biomarker sample on Day 5 for treatment arms 7 and 8	To help understand the correlation of emerging immune response to other parameters
3 Objectives and Endpoints	Created separate table for treatment arms 7 and 8	These treatment groups have different endpoints based on emerging data
4.1.1 Design outline	Updated treatment arm 7 information and added treatment arm 8.	Activation of treatment arm 7 and addition of treatment arm 8.
4.1.1 Design outline	Updated the Study Day and Visit Type table	Several study days had different visit types for treatment arms 1-4 and 6 versus treatment arms 7 and 8
4.1.1 Design outline	Added text to clarify the corresponding placebo control treatment arm	Treatment arm 1 is the corresponding placebo control for treatment arms 2-4 and 6. Treatment arm 8 is the corresponding placebo control for treatment arm 7.
4.2 Scientific Rationale for Study Design	Added participant characteristics for treatment arms 7 and 8	Activation of treatment arm 7 and addition of treatment arm 8.
5.1 Inclusion Criteria	Added criterion #27 specifically for treatment arms 7 and 8.	To focus on participants with risk factors for severe COVID-19 illness.
5.2 Exclusion Criteria	Criterion #20, changed “a history of” to “received”	Clarification
6.1 Study Intervention(s) Administered	Removed information that described the optional treatment arm 7.	Treatment arm is now activated and dose levels are described in Section 4.1.1.
6.2 Preparation/Handling/Storage/Accountability	In first sentence, replaced ‘temperature’ with ‘storage’. In 5 <sup>th</sup> paragraph, replaced text to say “The investigator or designee...”	Clarifications
7.1 Discontinuation of Study Intervention	Clarified the days and assessments in SoA if discontinued	Clarification
7.2 Participant Discontinuation/Withdrawal from the Study	Clarifications at the time of discontinuation	Clarification
8.2.5 Procedures of Special Interest	Limitations on activities due to COVID-19 are measured with a patient global assessment for daily activities of physical function	Clarification
9.2 Sample Size Determination	Updates to more accurately describe the sample sizes for the different treatment arms. Added text titles to improve readability.	Addition of treatment arms 7 and 8 and clarification for other treatment arms.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
9.4 Statistical Analyses	Added text for treatment arms 7 and 8.	Clarification
9.4.2 Primary Endpoints	Added endpoint for treatment arms 7 and 8.	Based on preliminary blinded data.
9.4.3.2 Additional Secondary Endpoints	Added a sub-section for treatment arms 7 and 8.	Secondary endpoints for treatments 7 and 8 are based on changes to the study population to include participants with risk factors for severe illness and emerging blinded data.
9.4.6. Subgroup Analyses	Added text for treatment arms 7 and 8.	Clarification
9.5 Interim Analyses	Updated first bullet in first paragraph	Not only applicable for LY3819253-only treatment arms
9.5 Interim Analyses	Clarification of timing for when the Assessment Committee is authorized to evaluate unblinded interim analyses and safety analyses.	Clarification
11 References	Removed irrelevant reference	Correction
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

**Amendment b: 31 July 2020****Overall Rationale for Amendment b:**

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

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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. <ul style="list-style-type: none"> <li>• Rationale</li> <li>• Objectives and endpoints table</li> <li>• Design Outline</li> <li>• Number of participants</li> <li>• Intervention Groups and Duration - moved treatment group table here and updated content.</li> </ul>	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 LY3832479 and 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
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

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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 LY3819253-specific text	For the addition of LY3832479
8.3.7 Infusion-related Reactions	Removed LY3819253-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
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

Section # and Name	Description of Change	Brief Rationale
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

### Amendment a: 19 June 2020

#### 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

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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.
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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Approver: PPD

Approval Date & Time: 20-Jan-2021 22:59:55 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 20-Jan-2021 23:00:25 GMT

Signature meaning: Approved

## Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Original Protocol	30-May-2020

### 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

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
9.4.3.2. Additional Secondary Endpoints	Updated according to changes in Section 3	Consistency across sections.
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

## Protocol Amendment Summary of Changes Table

<b>DOCUMENT HISTORY</b>	
<b>Document</b>	<b>Date</b>
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.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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. <ul style="list-style-type: none"> <li>• Rationale</li> <li>• Objectives and endpoints table</li> <li>• Design Outline</li> <li>• Number of participants</li> <li>• Intervention Groups and Duration - moved treatment group table here and updated content.</li> </ul>	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

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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 LY3832479 and 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
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

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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
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

## **Protocol Amendment Summary of Changes Table**

<b>DOCUMENT HISTORY</b>	
<b>Document</b>	<b>Date</b>
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### **Amendment c**

#### **Overall Rationale for the Amendment:**

The sponsor is activating the optional treatment arm 7 with the combination of LY3819253 and LY3832479. Treatment arm 7 will consist of a population with risk factors for severe COVID-19 illness. Treatment arm 8 is added to the study as the corresponding placebo control. The primary and key secondary endpoints for treatment arms 7 and 8 are different than treatments 1-4 and 6.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.1 Synopsis	Updated text to match the body of the protocol for the Number of participants.	Updates were made to Section 9.2 to more accurately describe the sample sizes for the different treatment arms.
1.1 Synopsis	Updated text to match the body of the protocol for the Intervention Groups and Duration.	Activation of treatment arm 7 and addition of treatment arm 8.
1.1 Synopsis	Updated text to match the body of the protocol for the Objectives and Endpoints	See rationale for Section 3 below.
1.1 Synopsis	Updated text to match the body of the protocol for the Study Day and Visit Type table	Several study days had different visit types for treatment arms 1-4 and 6 versus treatment arms 7 and 8
1.1 Synopsis	Added text to clarify the corresponding placebo control treatment arm	Treatment arm 1 is the corresponding placebo control for treatment arms 2-4 and 6. Treatment arm 8 is the corresponding placebo control for treatment arm 7.
1.2 Schema	Updated treatment arm 7 information and added treatment arm 8.	Activation of treatment arm 7 and addition of treatment arm 8.
1.3 Schedule of Activities	Added a sentence to beginning paragraph to refer to the study day and visit type table in Section 4.1.1.	The referenced table provides additional clarifications.
1.3 Schedule of Activities	Days 4-6 were separated to accommodate procedures specific to treatment arms 7 and 8	Activation of treatment arm 7 and addition of treatment arm 8.
1.3 Schedule of Activities	Added footnotes in the Study Day row to indicate when telephone visits are allowed for the different treatment arms	Clarification
1.3 Schedule of Activities	Days 18 and 25 are telephone visits for treatment arms 7 and 8 only	Nasopharyngeal swabs and vital signs not collected on these days for treatment arms 7 and 8
1.3 Schedule of Activities	Day 5 is still a telephone visit for treatment arms 1-4 and 6	Clarification
1.3 Schedule of Activities	Updated visit windows for Days 5 and 7	To avoid overlap
1.3 Schedule of Activities	Added Day 5 vital sign collection only for treatment arms 7 and 8	Collection for participants with risk factors for severe disease
1.3 Schedule of Activities	Vital signs not collected on Days 18 and 25 for treatment arms 7 and 8	To accommodate a telephone visit.
1.3 Schedule of Activities	Added a nasopharyngeal (NP) swab on Day 5 only for treatment arms 7 and 8	Collect additional data to inform future clinical development
1.3 Schedule of Activities	NP swabs not collected on Days 18 and 25 for treatment arms 7 and 8	Based on emerging blinded data



<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.3 Schedule of Activities	Added an exploratory biomarker sample on Day 5 for treatment arms 7 and 8	To help understand the correlation of emerging immune response to other parameters
3 Objectives and Endpoints	Created separate table for treatment arms 7 and 8	These treatment groups have different endpoints based on emerging data
4.1.1 Design outline	Updated treatment arm 7 information and added treatment arm 8.	Activation of treatment arm 7 and addition of treatment arm 8.
4.1.1 Design outline	Updated the Study Day and Visit Type table	Several study days had different visit types for treatment arms 1-4 and 6 versus treatment arms 7 and 8
4.1.1 Design outline	Added text to clarify the corresponding placebo control treatment arm	Treatment arm 1 is the corresponding placebo control for treatment arms 2-4 and 6. Treatment arm 8 is the corresponding placebo control for treatment arm 7.
4.2 Scientific Rationale for Study Design	Added participant characteristics for treatment arms 7 and 8	Activation of treatment arm 7 and addition of treatment arm 8.
5.1 Inclusion Criteria	Added criterion #27 specifically for treatment arms 7 and 8.	To focus on participants with risk factors for severe COVID-19 illness.
5.2 Exclusion Criteria	Criterion #20, changed “a history of” to “received”	Clarification
6.1 Study Intervention(s) Administered	Removed information that described the optional treatment arm 7.	Treatment arm is now activated and dose levels are described in Section 4.1.1.
6.2 Preparation/Handling/Storage/Accountability	In first sentence, replaced ‘temperature’ with ‘storage’. In 5 <sup>th</sup> paragraph, replaced text to say “The investigator or designee...”	Clarifications
7.1 Discontinuation of Study Intervention	Clarified the days and assessments in SoA if discontinued	Clarification
7.2 Participant Discontinuation/Withdrawal from the Study	Clarifications at the time of discontinuation	Clarification
8.2.5 Procedures of Special Interest	Limitations on activities due to COVID-19 are measured with a patient global assessment for daily activities of physical function	Clarification
9.2 Sample Size Determination	Updates to more accurately describe the sample sizes for the different treatment arms. Added text titles to improve readability.	Addition of treatment arms 7 and 8 and clarification for other treatment arms.
9.4 Statistical Analyses	Added text for treatment arms 7 and 8.	Clarification
9.4.2 Primary Endpoints	Added endpoint for treatment arms 7 and 8.	Based on preliminary blinded data.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
9.4.3.2 Additional Secondary Endpoints	Added a sub-section for treatment arms 7 and 8.	Secondary endpoints for treatments 7 and 8 are based on changes to the study population to include participants with risk factors for severe illness and emerging blinded data.
9.4.6. Subgroup Analyses	Added text for treatment arms 7 and 8.	Clarification
9.5 Interim Analyses	Updated first bullet in first paragraph	Not only applicable for LY3819253-only treatment arms
9.5 Interim Analyses	Clarification of timing for when the Assessment Committee is authorized to evaluate unblinded interim analyses and safety analyses.	Clarification
11 References	Removed irrelevant reference	Correction
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

## Protocol Amendment Summary of Changes Table

<b>DOCUMENT HISTORY</b>	
<b>Document</b>	<b>Date</b>
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment d

#### Overall Rationale for the Amendment:

This amendment broadens the definition of patients with COVID-19 who are at a high risk of hospitalization.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
5.1 Inclusion Criteria	Updated inclusion criterion 27.	Broadened definition of patients with COVID-19 at high risk for hospitalization.

## Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment (d)	18-September-2020
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment e

#### Overall Rationale for the Amendment:

This amendment addresses changes for treatment arms 7 and 8. This population is at higher risk for more severe disease and hospitalization. The sample size is increased, and the objectives and endpoints are updated to support potential marketing applications. The changes for treatment arms 7 and 8 affect sections throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated text to match the body of the protocol for the Objectives and Endpoints	See rationale for Section 3.
1.1 Synopsis	Updated information to match the body of the protocol for the Design Outline	Updated visit type table and added another specifically for treatment arms 7 and 8
1.1 Synopsis	Updated text to match the body of the protocol for the Number of participants.	Increase in sample size for treatment arms 7 and 8. See rationale for Section 9.2.
1.1 Synopsis	Updated Data Monitoring Committee (DMC) information to match the body of the protocol	See rationale for Section 9.6
1.3 Schedule of Activities (SoA)	Removed information pertaining to treatment arms 7 and 8 in the existing SoA	Participants enrolling into treatment arms 7 and 8 will have a different visit and sample schedule than treatment arms 1-4 and 6.
1.3 Schedule of Activities (SoA)	Created a separate SoA for treatment arms 7 and 8	Participants enrolling into treatment arms 7 and 8 will have a different visit and sample schedule.
2.2 Background	Removed information specific to a previous amendment	No longer applicable
3 Objectives and Endpoints	Updated the table for treatment arms 7 and 8	Changed the primary endpoints and updated the secondary endpoints based on emerging data
3 Objectives and Endpoints	Added pharmacokinetic endpoint for treatment arms 7 and 8	Will analyze the pharmacokinetics
4.1.1 Design Outline	Removed treatment arms 7 and 8 information from the visit type information table	Treatment arms 7 and 8 will have a different visit structure

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
4.1.1 Design Outline	Created a separate visit type information table for treatment arms 7 and 8	To match the new SoA specific to treatment arms 7 and 8
4.2 Scientific Rationale for Study Design	Added text for treatments 7 and 8 participant characteristics	Additional rationale for studying the population
5.1 Inclusion Criteria	Updated criterion #27 to include other chronic respiratory diseases	To broaden the population with high risk factors
6.1 Study Intervention(s) Administered	Changed monitoring from 2 hours after completion of the infusion to 1 hour	Based on available safety data
6.1.2 Temporary Stopping Criteria	Added information for DMC's role	An external DMC will review safety for treatment arms 7 and 8
6.3 Measures to Minimize Bias: Randomization and Blinding	Updated the Unblinding (IWRS) table to remove 'case report form'	A case report form is not used to record unblinding.
8.1 Efficacy Assessments	Removed specific endpoint dates	Endpoints are not the same across all treatment arms. Removed text to make more general. The information is also located in other sections of the protocol.
8.2.2 Vital Signs	Added clarifications for treatment arms 1-4 and 6 versus 7 and 8. Added a table for treatment arms 7 and 8.	Treatment arms 7 and 8 have different collection times for Day 1
8.5.1 Bioanalytical	Generalized text for remaining sample usage	To optimize the amount of information from sample collection, samples may be used for exploratory analyses beyond just metabolism or bioanalytical experiments
8.9 Immunogenicity	Generalized text for remaining sample usage	To optimize the amount of information from sample collection, samples may be used for exploratory analyses
9.1 Statistical Hypotheses	Added statistical hypothesis for treatment arms 7 and 8	New information to match the updated primary endpoints
9.2 Sample Size Determination	Updated sample size for treatment arms 7 and 8	Increase in sample size to provide statistical power for updated primary endpoints
9.2 Sample Size Determination	Updated section, moved text within section and added clarifications for treatment arms 1-4 and 6 versus 7 and 8.	Updated sample size rationale for treatments 7 and 8 sample size
9.4 Statistical Analyses	Updated section with new analyses	Aligned analysis plan with updated primary endpoints
9.4.2 Primary Endpoints	Updated treatment arms 7 and 8 primary endpoints	New endpoints based on emerging data
9.4.3.2 Additional Secondary Endpoints	Updated treatment arms 7 and 8 secondary endpoints	Changes made to the primary endpoints dictated a change in secondary endpoints. Day 15 endpoints were removed per the new SoA.
9.4.6 Subgroup Analyses	Added clarifying text	Last bullet only applicable to treatment arms 1-4 and 6
9.5 Interim Analyses	Added clarifying text for treatment arms 7 and 8	Interim analyses will be different compared to treatment arms 1-4 and 6

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
9.6 Data Monitoring Committee (DMC)	Added clarifying text for treatment arms 7 and 8	The sponsor will form an external DMC to analyze safety data
10.1.3 Informed Consent Process	Added text to re-consenting information	Clarification
10.1.5 Committees Structure	Added clarifying text for treatment arms 7 and 8	The sponsor will form an external DMC to analyze safety data
Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Updated text for collection of information on infants after a woman gives birth	Per FDA feedback on pediatric development of LY3819253
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

## Protocol Amendment Summary of Changes Table

<b>DOCUMENT HISTORY</b>	
<b>Document</b>	<b>Date</b>
Amendment (e)	13-October-2020
Amendment (d)	18-September-2020
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment f

#### Overall Rationale for the Amendment:

This amendment addresses changes requested by the Food and Drug Administration (FDA) for treatment arms 7 and 8. Treatment arms 7 and 8 will now include adolescent participants at higher risk for severe disease and hospitalization, and the primary and secondary endpoints will be updated.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.1 Synopsis	Updated treatment arms 7 and 8 objectives and endpoints	Per FDA request to capture primary and secondary clinical endpoints until Day 29
1.1 Synopsis	Added child/adolescent assent to the screening procedure	Addition of adolescent participants
1.1 Synopsis	Added text in Number of Participants to say that adult and adolescent participants with at least 1 risk factor are in treatment arms 7 and 8	Addition of adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Added a row for informed assent	For adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Added a row to collect information on vaccines at screening	For adolescent participants

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Updated comments for the SARS-CoV-2 Test Panel	This panel is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Updated comments for pharmacokinetics Day 1 predose sample	Predose sample is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
1.3.2 Schedule of Activities for Treatment Arms 7 and 8	Updated comments for pharmacogenetics sample	This sample is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
2.3 Benefit/Risk Assessment	Added text for adolescents	Addition of adolescent participants
3 Objectives and Endpoints	Updated endpoints for Treatment Arms 7 and 8	Per FDA feedback
4.1.1 Design Outline	Added child/adolescent assent to the screening procedure	Addition of adolescent participants
4.2 Scientific Rationale for Study Design	Added rationale for including adolescent participants	Addition of adolescent participants
4.3 Justification for Dose	Added justification for adolescents	Addition of adolescent participants
5.1 Inclusion Criteria	Removed note about new criterion #27	Not applicable any longer
5.1 Inclusion Criteria	Updated Criterion #1 to include participants $\geq 12$ years of age	Addition of adolescent participants
5.1 Inclusion Criteria	Updated Criterion #5 nomenclature for participant sex from “men” and “women” to “male” and “female”	More appropriate terms for adolescent participants
5.1 Inclusion Criteria	Updated Criterion #8 to include assent	Addition of adolescent participants
5.1 Inclusion Criteria	Updated criterion #27 to indicate that it is for participants 18 years of age or older	To distinguish this criterion from the new #28 criterion for adolescents
5.1 Inclusion Criteria	Updated criterion #27 to state “type 1 or type 2” diabetes	Clarification of diabetes description
5.1 Inclusion Criteria	Added criterion #28	Addition of adolescent participants
5.2 Exclusion Criteria	Added criterion #29	Addition of adolescent participants
6.1 Study Intervention(s) Administered	Added that the site must have “age-appropriate” resuscitation equipment	For the adolescent participants
6.3 Measures to Minimize Bias: Randomization	Added stratification by age	Addition of adolescent participants
6.5 Concomitant Therapy	Updated Prior Treatment to add recording vaccines for adolescents	Addition of adolescent participants
8.7 Genetics	Added clarification that sample collection will be collected in adults only	This sample is for adults only to reduce invasive procedures and blood volume collection in adolescent participants
9.1 Statistical Hypotheses	Minor change from “and” to “or”	
9.2 Sample Size Determination	Added stratification by age	Addition of adolescent participants

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
9.2 Sample Size Determination	Updated justification for Treatment arms 7 and 8	Further clarifications for the sample size justification
9.4.2 Primary Endpoints	Updated according to objectives and endpoints table	Per FDA feedback
9.4.3.2 Additional Secondary Endpoints	Updated according to objectives and endpoints table	Per FDA feedback
9.5 Interim Analyses	Unblinded assessments of efficacy will not be conducted until participants complete Day 29 visit, not Day 22.	correction
10.1.3. Informed Consent Process	Updated for adolescent population	Addition of adolescent participants
10.2 Appendix 2 Clinical Laboratory Tests	Added comments where sample collection is for adults only	Addition of adolescent participants
10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Added women not of child-bearing potential to those participating in the study.	Correction and addition of adolescent participants
10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Added assent to section about male participants with partners who become pregnant	Addition of adolescent participants
10.8 Abbreviations	Added “assent” and “legal representative”	Addition of adolescent participants
11 References	Added references used in new text	Additional references used in body of protocol.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

## Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment (f)	20-October-2020
Amendment (e)	13-October-2020
Amendment (d)	18-September-2020
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment g

#### Overall Rationale for the Amendment:

This amendment addresses the addition of treatment arms 9-11. Treatment arm 9 will explore a lower dose level of the combination of LY3819253 and LY3832479. Treatment arm 10 will provide a bridge to the existing placebo arms. Treatment arm 11 is an open-label sub-study comprised of two cohorts to evaluate a faster IV infusion rate of the combination of LY3819253 and LY3832479.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Added Objectives and Endpoints tables for treatment arms 9-11	Addition of new treatments
1.1 Synopsis	Updated sub-headings under Design Outline to remove “double-blind”	Addition of the open-label treatment arm 11
1.1 Synopsis	Updated Disclosure Statement for treatment arms 7-11	Addition of new treatments
1.1 Synopsis	Added Number of Participants for treatment arms 9-11	Addition of new treatments
1.1 Synopsis	Added information for treatment arms 9-11 to Intervention Groups and Duration	Addition of new treatments
1.1 Synopsis	Updated text under Data Monitoring Committee	Addition of new treatments
1.2 Schema	Updated existing figure and added figure for treatment arm 11	Addition of new treatments
1.3.2. Schedule of Activities	Updated to include the new treatments	New treatments will use the same SoA as treatment arms 7-8
2.3 Benefit/Risk	Added sub-headings for clarification of information. Added the potential benefit/risks associated with an increased rate of infusion	Treatment arm 11 will use a faster infusion rate than the other treatment arms



<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
3 Objectives and Endpoints	Added new sub-headings for the separate tables for the different treatment arms	Easier document navigation
3 Objectives and Endpoints	The table for treatment arms 7-8 is now applicable for treatment arms 7-10. Added clarifying text for secondary objectives in this table to describe differences between treatment arms 7-8 versus 9-10	Treatment arms 9-10 will have basically the same objectives and endpoints, but will need more flexibility for the secondary objectives.
3 Objectives and Endpoints	Added a new table for treatment arm 11	Addition of new treatment
4.1.1 Design Outline	Added sub-headings for clarification	Addition of new treatments
4.1.1 Design Outline	Updated sub-headings to remove “double-blind”	Addition of the open-label treatment arm 11
4.1.1 Design Outline	Added information for treatment arms 9-11 in treatment arm table and text	Addition of new treatments
4.1.1 Design Outline	Added information for treatment arms 9-11 for visit types	Addition of new treatments
4.2 Scientific Rationale for Study Design	Added rationale for the addition of treatment arm 11	This treatment arm is an open-label sub-study to evaluate a faster infusion rate.
4.2 Scientific Rationale for Study Design	Updated participant characteristics to add new treatment arms	Addition of new treatments
4.3 Justification for Dose	Section was updated to include the new treatment information	Addition of new treatments
5.1 Inclusion Criteria	Added sub-headings for criteria #27 and #28	Addition of new treatments
6.1 Study Intervention(s) Administered	Added new dose level for LY3832479	Addition of new treatments
6.1.2 Temporary Stopping Criteria	Added sub-headings for treatment arms 1-10 and criteria for treatment arm 11	Addition of new treatments and the 2 cohorts in treatment arm 11
6.3 Measures to Minimize Bias: Randomization and Blinding	Added sub-headings for treatment arms 1-11 and indicate that treatment arm 11 is open label	Addition of new treatment
8.2.2 Vital Signs	Added new treatment arms to table outlining Day 1 vital signs data collection and added the 90 and 120 minute collection to the treatment arms 7-11 table	Addition of new treatments
9.1 Statistical Hypotheses	Added information for treatment arms 9-10	Addition of new treatments
9.2 Sample Size Determination	Added sample size for new treatment arms	Addition of new treatments

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
	Added text to clarify stratification is not applicable for treatment arm 11.	
9.2 Sample Size Determination	Added information for treatment arm 11 under stratification	Stratification is not applicable to treatment arm 11.
9.4 Statistical Analyses	Added information for treatment arms 9-11	Addition of new treatments
9.4.2 Primary Endpoints	Added information for new treatment arms	Addition of new treatments
9.4.3.2 Additional Secondary Endpoints	Updates made to include treatment arms 9-10 and added text for treatment arm 11	Addition of new treatments
9.4.3.3 Pharmacokinetic Analyses	Removed reference to noncompartmental analysis and replaced with descriptive summary.	Number of study participants with evaluable PK concentration data has increased.
9.4.6 Subgroup Analyses	Updates made to include treatment arms 9-10 and added text for treatment arm 11	Addition of new treatments
9.5 Interim Analyses	Updates made to include treatment arms 9-10, added text to explain that unblinded assessments will be done separately for treatment arms 7 and 8, and 9 and 10, and added text for treatment arm 11	Addition of new treatments
9.6 Data Monitoring Committee (DMC)	Updates made to include treatment arms 9-10 and added text for treatment arm 11	Addition of new treatments
11 References	Added FDA EUA fact sheet for bamlanivimab	Addition of reference.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

**Amendment (h) Not applicable. Not approved or submitted to regulatory agencies or independent review boards.**

## Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment (h)	Not applicable. Not approved or submitted to regulatory agencies or independent review boards.
Amendment (g)	17 November 2020
Amendment (f)	20-October-2020
Amendment (e)	13-October-2020
Amendment (d)	18-September-2020
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment i

#### Overall Rationale for the Amendment:

This amendment addresses changes in response to discussions with the FDA to enable independent confirmation of the safety and efficacy of LY3819253 in combination with LY3832479 for the treatment of COVID-19. The decision was made to remove treatment arms 10 and 11, and change the primary objective, statistical methods and sample size for treatment arms 7-9.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated Phase 2 to Phase 2/3	Per FDA feedback to more accurately describe study
1.1 Synopsis	Updated protocol title to Phase 2/3	Per FDA feedback to more accurately describe study
1.1 Synopsis	Updated Objectives and Endpoints table for treatment arms 7-9 to reflect changes in Section 3.	Removed treatment arm 10, updated the primary objective for treatment arms 7-9, moved reduction in viral load from primary to first secondary endpoint, and added Day 29 to symptom resolution and symptom improvement endpoints.
1.1 Synopsis	Removed treatment arm 11 objectives and endpoints table	Treatment arm 11 is removed from this study
1.1 Synopsis	Updated Overall Design to say Phase 2/3	Per FDA feedback to more accurately describe study
1.1 Synopsis	Updated visit type table	Treatment arms 10 and 11 are removed from this study
1.1 Synopsis	Updated Disclosure Statement	Treatment arms 10 and 11 are removed from this study
1.1 Synopsis	Updated Number of Participants	Treatment arms 10 and 11 are removed from this study and the sample size increased for treatment arms 7-9
1.1 Synopsis	Removed treatment arms 10 and 11 and updated placebo control information in Intervention Groups and Duration	Treatment arms 10 and 11 are removed from this study

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.1 Synopsis	Removed treatment arms 10 and 11 from Data Monitoring Committee	Treatment arms 10 and 11 are removed from this study
1.2 Schema	Updated existing figure for treatment arms 1-9 and removed treatment arm 11 figure	Treatment arms 10 and 11 are removed from this study
1.3.2. Schedule of Activities	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
1.3.2. Schedule of Activities	Changed visit window for Study Day 11 to -2/+3 from $\pm 3$	In order to avoid overlapping visits with study day 7 and more flexibility with study day 11 visit
2.3 Benefit/Risk Assessment	Removed text for Risks and Benefits Associated with Faster Rates of Infusion and removed text related to treatment arm 11	Removed treatment arm 11
3.2 Objectives and Endpoints	Updated table for treatment arms 7-9.	Removed treatment arm 10, updated the primary objective for treatment arms 7-9, moved reduction in viral load from primary to first secondary endpoint, and added Day 29 to symptom resolution and symptom improvement endpoints.
3 Objectives and Endpoints	Removed treatment arm 11 objectives and endpoints table	Treatment arm 11 is removed from this study
4.1 Overall Design	Updated Overall Design to say Phase 2/3	Per FDA feedback to more accurately describe study
4.1.1 Design Outline	Removed treatment arms 10 and 11 from Treatment Arm table and text	Treatment arms 10 and 11 are removed from this study
4.1.1 Design Outline	Updated text to describe that treatment arm 8 will be the corresponding placebo control for treatment arms 7 and 9	Will increase the sample size for 8 and enroll with both treatment arms 7 and 9.
4.1.1 Design Outline	Removed information for treatment arms 10 and 11 for visit types	Treatment arms 10 and 11 are removed from this study
4.2 Scientific Rationale for Study Design	Removed rationale for treatment arm 11 and updated text to remove reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
4.3 Justification for Dose	Removed references to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
5.1 Inclusion Criteria	Removed reference to treatment arms 10 and 11 for inclusion criteria #27 and #28	Treatment arms 10 and 11 are removed from this study
5.1 Inclusion Criteria	Added "have chronic kidney disease" to criterion #28	Medical decision
6.1.1.2 Management of Infusion Reactions	Added footnote and source back to table describing the severity of reactions according to Division of Allergy and Infectious Diseases (DAIDS)	This information was inadvertently removed in a previous version of the protocol

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
6.1.2 Temporary Stopping Criteria	Removed reference to treatment arms 10 and 11 and removed specific stopping criteria for treatment arm 11	Treatment arms 10 and 11 are removed from this study
6.3 Measures to Minimize Bias: Randomization and Blinding	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
8.2.2 Vital Signs	Removed reference to treatment arms 10 and 11 for vital signs data collection table	Treatment arms 10 and 11 are removed from this study
9.1 Statistical Hypotheses	Removed reference to treatment arms 10 and 11 and updated hypothesis for treatment arm 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes for the primary objective and endpoint.
9.2 Sample Size Determination	Removed reference to treatment arms 10 and 11 and updated sample size information for treatment arms 7 - 9	Change in strategy per discussions with FDA
9.4 Statistical Analyses	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes in analyses
9.4.2 Primary Endpoints	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes in analyses
9.4.3.2 Additional Secondary Endpoints	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect the move of viral load from primary to secondary endpoint, and the addition of Day 29 to symptom improvement and symptom resolution endpoints
9.4.6 Subgroup Analyses	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
9.5 Interim Analyses	Removed reference to treatment arms 10 and 11 and updated information for treatment arms 7 - 9	Treatment arms 10 and 11 are removed from this study, and updates reflect changes in analyses
9.6 Data Monitoring Committee (DMC)	Removed reference to treatment arms 10 and 11	Treatment arms 10 and 11 are removed from this study
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described



## Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment (i)	30-November-2020
Amendment (h)	Not applicable. Not approved or submitted to regulatory agencies or independent review boards.
Amendment (g)	17-November-2020
Amendment (f)	20-October-2020
Amendment (e)	13-October-2020
Amendment (d)	18-September-2020
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment j

#### Overall Rationale for the Amendment:

This amendment addresses changes in response to emerging data, discussions with the FDA and the addition of treatment arms 13 and 14. Treatment arms 10-12 were skipped due to internal programming capabilities.

Section # and Name	Description of Change	Brief Rationale
Throughout protocol	Added treatment arms 13-14 identifiers where applicable	Addition of treatment arms 13 and 14
1.1 Synopsis	Updated treatment arms 7-9 Objectives and Endpoint table. This table is now also applicable for treatment arms 13-14.	Alignment with FDA feedback and emerging data. Identified key secondary objectives, updated other secondary endpoints.
1.1 Synopsis	Updated Disclosure Statement to accommodate all treatment arms	Statement applies to all treatment arms
1.1 Synopsis	Updated Number of Participants for treatment arms 7-9 and 13-14	Correction of sample size for 7-9 and addition of treatment arms 13 and 14
1.1 Synopsis	Updated Intervention Groups and Duration table with new treatment arms. Added information about placebo control for treatment arms 13 and 14.	Addition of treatment arms 13 and 14.
1.1 Synopsis	Updated Data Monitoring Committee to include treatment arms 13 and 14	Addition of treatment arms 13 and 14.
1.2 Schema	Updated Schema and Figure title	Addition of treatment arms 13 and 14.
1.3.2 Schedule of Activities (SoA) for 7-9	Will use this SoA for treatment arms 7-9, 13-14	Addition of treatment arms 13 and 14.



<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.3.2 Schedule of Activities (SoA) for 7-9, 13-14	Clarified collection of prior “non-COVID” vaccine treatments for adolescents	clarification
1.3.2 Schedule of Activities (SoA) for 7-9, 13-14	Updated vital signs and Oxygen Support timing for Day 1 for an infusion that is <15 minutes	Addition of treatment arms 13 and 14.
1.3.2 Schedule of Activities (SoA) for 7-9, 13-14	Added clarification that pregnancy testing is not applicable for females pregnant at screening	Pregnant females are eligible in this study.
2.3 Benefit/Risk Assessment	Updated the risk associated with administration of LY3819253	From emerging clinical data
2.3 Benefit/Risk Assessment	Added benefit/risk information for the pregnant population	Pregnant females are eligible in this study.
3.2 Objectives and Endpoints for Treatment arms 7-9, 13-14	Added treatment arms 13-14. Identified key secondary objectives, updated other secondary and exploratory endpoints.	Addition of treatment arms 13 and 14. Alignment with FDA feedback and emerging data.
4.1.1 Design Outline	Updated treatment arm table with new treatment arms. Added information about placebo control for treatment arms 13 and 14.	Addition of treatment arms 13 and 14.
4.2 Scientific Rationale for Study Design	Added information for pregnant participants	Pregnant females are eligible in this study
4.3 Justification for Dose	Added information for new treatment arms	Addition of treatment arms 13 and 14.
5.1 Inclusion Criteria	Updated Criterion #5 to include pregnant females	Pregnant females are eligible in this study
5.1 Inclusion Criteria	Added “requires daily medication for control” to Criterion #28	Per the Emergency Use Authorization (EUA) for adolescents
5.2 Exclusion Criteria	Added “or have received a SARS-CoV-2 vaccine” to Criterion #21	Clarification of criterion because of the availability of the vaccine.
5.2 Exclusion Criteria	Removed “pregnant or” from Criterion #24	Pregnant females are eligible in this study
6.1 Study Intervention(s) Administered	Added new dose levels to Study Intervention table	Addition of treatment arm 14.
6.1 Study Intervention(s) Administered	Replaced “pharmacy preparation instructions” for “pharmacy manual”	Correction. Infusion information may be found in the pharmacy preparation instructions.
6.1.1.2. Management of Infusion Reactions	Removed duplicate text about premedication for infusions	This information is located in Section 6.1.1.1. and was inadvertently repeated in Section 6.1.1.2.
7.2 Participant Discontinuation/Withdrawal from Study	Removed “if the participant becomes pregnant during the study” from the bulleted list	Pregnant females are eligible in this study

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
8.2.2 Vital Signs	Updated Treatment arms 7-9, 13-14 table for Day 1 data collection for an infusion that is <15 minutes	Addition of treatment arms 13 and 14.
8.2.3 Clinical Laboratory Assessments	Removed text from Pregnancy testing sub-section "Participants who are pregnant will be discontinued from the study"	Pregnant females are eligible in this study
8.3.5 Pregnancy	Removed text from section so that it is aligned with Section 10.4, Appendix 4.	Correction
8.3.6 Hypersensitivity Reactions	Removed text about the risk of systemic hypersensitivity reactions	The risks are outlined in Section 2.3. Benefit/Risk Assessment
9.1 Statistical Hypotheses	Updated text according to changes to primary endpoint and added text for new treatment arms	Alignment with FDA feedback and emerging data. Addition of treatment arms 13 and 14.
9.2 Sample Size Determination	Added sub-headers for clarity. Updated sample size for treatment arms 7-9. Added sample size and randomization for treatment arms 13-14.	Statistician decision and addition of treatment arms 13 and 14.
9.4 Statistical Analyses	Added treatment arms 13 and 14	Addition of treatment arms 13 and 14.
9.4.2 Primary Endpoints	Updated text according to changes to primary endpoint and for new treatment arms	Alignment with FDA feedback and emerging data. Addition of treatment arms 13 and 14.
9.4.3.1 Key Secondary Endpoints	New Section	Alignment with FDA feedback and emerging data.
9.4.3.2 Safety	This section is renumbered	Section moved down due to new Key Secondary Endpoints section
9.4.3.3 Additional Secondary Endpoints	This section is renumbered. Updated endpoints for treatment arms 7-9 and added arms 13 and 14	Renumbered due to new Key Secondary Endpoints section. Alignment with FDA feedback and emerging data.
9.4.3.4 Pharmacokinetic Analyses	This section is renumbered.	Renumbered due to new Key Secondary Endpoints section.
9.4.6 Subgroup Analyses	Removed incorrect text	Correction
9.5 Interim Analyses	Added sub-headers and updated text for treatment arms 7-9. Added text for new treatment arms	Updates made for clarification and addition of treatment arms 13 and 14.
9.6 Data Monitoring Committee	Added treatment arms 13-14 to Treatment Arms 7-9 sub-header and updated first sentence under this header	Removed text that was not applicable to these treatment arms.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Updated text for the inclusion of pregnant females	Pregnant females are eligible in this study
11 References	Added Chen et.al.2020 reference	Source for information in Section 2.3
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

## Protocol Amendment Summary of Changes Table

<b>DOCUMENT HISTORY</b>	
<b>Document</b>	<b>Date</b>
Amendment (j)	07-January-2021
Amendment (i)	30-November-2020
Amendment (h)	Not applicable. Not approved or submitted to regulatory agencies or independent review boards.
Amendment (g)	17-November-2020
Amendment (f)	20-October-2020
Amendment (e)	13-October-2020
Amendment (d)	18-September-2020
Amendment (c)	31-August-2020
Amendment (b)	31-July-2020
Amendment (a)	19-June-2020
Original Protocol	30-May-2020

### Amendment k

#### Overall Rationale for the Amendment:

This amendment allows participants in the study who have received the SARS-CoV-2 vaccine. SARS-CoV-2 vaccines are now available to the public and those who received a vaccine or have participated in a SARS-CoV-2 vaccine study are allowed in the study.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
Section 1.3.2 Schedule of Activities for Treatment Arms 7-9,13-14	Updated Prior treatments of special interest to allow the SARS-CoV-2 vaccine	The SARS-CoV-2 vaccine is now allowed
2.3 Benefit/Risk Assessment	Updated risk information for LY3819253	Emerging data
4.2 Scientific Rationale for Study Design	Added a sub-section for participants who have received the SARS-CoV-2 vaccine	Vaccines are now available to the public and those who received a vaccine are allowed in the study
5.2 Exclusion Criteria	Criterion #21 is removed	SARS-CoV-2 vaccines are now available to the public and those who received a vaccine or have participated in a SARS- CoV-2 vaccine study are allowed in the study

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
6.5 Concomitant Therapy	Added vaccines to prior treatment list that should be recorded. Added “non-SARS-CoV-2” to clarify what vaccines are recorded for adolescents.	Need a record of those who received a SARS-Cov-2 vaccine.  Need a record of non-SARS-CoV-2 vaccines that adolescents received 90 days prior to signing informed consent.
9.2 Sample Size	Added clarification that there is no set sample size for participants with prior vaccine use. Added stratification factor for whether a participant received a vaccine or not prior to screening	Those who received a SARS-CoV-2 vaccine are allowed in the study.
9.3 Populations for Analyses	Added the Modified Efficacy population to table	To distinguish a population for analysis that will not include those that received a SARS-CoV-2 vaccine.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

**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**

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**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

Section	Page
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 .....	1
2. Table of Contents .....	2
3. Revision History .....	8
4. Study Objectives .....	9
4.1. Primary Objective .....	9
4.2. Secondary Objectives .....	9
4.3. Exploratory Objectives .....	10
5. Study Design .....	11
5.1. Summary of Study Design .....	11
5.1.1. Design Outline .....	11
5.1.2. Screening .....	11
5.1.3. Double-blind Treatment and Assessment Period .....	11
5.1.4. Posttreatment Follow-up .....	12
5.2. Determination of Sample Size .....	12
5.3. Method of Assignment to Treatment .....	12
5.3.1. Randomization .....	12
5.3.2. Blinding .....	13
6. A Priori Statistical Methods .....	14
6.1. General Considerations .....	14
6.1.1. Analysis Populations .....	14
6.1.2. Definition of Study Baseline .....	15
6.1.3. Study Time Intervals .....	15
6.1.4. Analysis Methods .....	16
6.2. Adjustments for Covariates .....	17
6.3. Handling of Dropouts or Missing Data .....	18
6.3.1. Non-Responder Imputation (NRI) .....	18
6.3.2. Last Observation Carried Forward (LOCF) .....	18
6.3.3. Mixed-effects Model Repeated Measures (MMRM) .....	18
6.3.4. Highest Disease States Imputation (HDSI) .....	18
6.4. Multicenter Studies .....	19
6.5. Multiple Comparisons/Multiplicity .....	19
6.6. Participant Disposition .....	19

6.7.	Participant Characteristics .....	20
6.8.	Treatment Compliance .....	20
6.9.	Prior Medication and Concomitant Therapy .....	21
6.10.	Efficacy Analyses .....	21
6.10.1.	Primary Outcome and Methodology.....	21
6.10.2.	Additional Analyses of the Primary Outcome.....	22
6.10.2.1.	Dose Response Modeling .....	22
6.10.2.2.	Bayesian Modeling.....	23
6.10.3.	Secondary Efficacy Analyses .....	23
6.10.3.1.	SARS-CoV-2 Viral Load Among Participants Enrolled with $\leq 8$ Days of Symptoms Prior to Randomization.....	23
6.10.3.2.	SARS-CoV-2 Viral Load AUC.....	23
6.10.3.3.	SARS-CoV-2 Clearance at Days 7, 11, 15, and 22.....	24
6.10.3.4.	Time to SARS-CoV-2 Clearance .....	24
6.10.3.5.	Symptom Resolution .....	24
6.10.3.6.	Time to Symptom Resolution .....	24
6.10.3.7.	Symptom Improvement .....	25
6.10.3.8.	Time to Symptom Improvement .....	25
6.10.3.9.	COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 29).....	25
6.10.3.10.	Change in Symptom Questionnaire Score.....	26
6.11.	Health Outcomes/Quality-of-Life Analyses.....	26
6.11.1.	Symptoms and Overall Clinical Status Participant Questionnaire .....	26
6.12.	Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods.....	27
6.12.1.	General PK Parameter Rules .....	28
6.12.2.	Individual PK Parameter Rules.....	29
6.12.3.	Individual Concentration versus Time Profiles .....	29
6.12.4.	Average Concentration versus Time Profiles.....	29
6.12.5.	Treatment of Outliers during Pharmacokinetic Analysis.....	30
6.12.5.1.	Data within an Individual Profile .....	30
6.12.5.2.	Data Between Individual Profiles.....	30
6.12.5.3.	Reporting of Excluded Values .....	31
6.12.6.	Pharmacokinetic Statistical Methodology.....	31
6.13.	Safety Analyses.....	32
6.13.1.	Baseline and Postbaseline Definitions for Safety Groups.....	32
6.13.2.	Extent of Exposure.....	33
6.13.3.	Adverse Events .....	33

6.13.4. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events ..... 34

6.13.5. Hospitalization, Clinical Events, Clinical Status, and Environmental Risk Factors ..... 35

6.13.6. Clinical Laboratory Evaluation..... 35

6.13.7. Vital Signs and Other Physical Findings..... 35

6.13.8. Electrocardiograms ..... 37

6.13.9. Immunogenicity ..... 37

6.14. Subgroup Analyses..... 37

6.15. Protocol Violations..... 39

6.16. Interim Analyses and Data Monitoring..... 39

6.16.1. Interim Analyses ..... 39

6.16.2. Data Monitoring Committee/Assessment Committee ..... 41

6.17. Planned Exploratory Analyses..... 41

6.17.1. Protocol-Defined Exploratory Endpoints..... 41

6.17.1.1. Viral Resistance..... 41

6.17.1.2. SpO2 AUC Assessed through Day 29..... 41

6.17.1.3. Symptom Questionnaire AUC assessed through Day 29 ..... 41

6.17.1.4. Worst NIAID Score..... 42

6.17.2. Additional Exploratory Analyses not Defined in the Protocol..... 42

6.17.2.1. Clinical Worsening based on the NIAID Scale..... 42

6.17.2.2. National Early Warning Score ..... 42

6.17.2.3. NEWS2 Consciousness Level..... 42

6.17.2.4. NIAID/NEWS2 Overall Improvement..... 42

6.17.2.5. Time to Hospitalization ..... 42

6.17.2.6. Duration of Hospitalization..... 43

6.17.2.7. Time to Admission to ICU..... 43

6.17.2.8. Proportions of Participants Hospitalized, Admitted to the ICU, Requiring Mechanical Ventilation..... 43

6.17.2.9. Days since Symptom Onset Cutpoint Analysis ..... 43

6.18. Annual Report Analyses..... 43

6.19. Clinical Trial Registry Analyses..... 44

7. References ..... 45

8. Appendices ..... 46



**Table of Contents**

<b>Table</b>	<b>Page</b>
Table PYAB.4.1. Secondary Objectives of Study J2W-MC-PYAB .....	9
Table PYAB.4.2. Exploratory Objectives of Study J2W-MC-PYAB .....	10
Table PYAB.5.1. Treatment Arms of Study J2W-MC-PYAB.....	12
Table PYAB.5.2. Unblinding Procedures for Study J2W-MC-PYAB .....	13
Table PYAB.6.1. Analysis Populations .....	14
Table PYAB.6.2. Definition of Study Period Time Intervals.....	16
Table PYAB.6.3. Tables and Figures Related to Demographics and Other Characteristics of Study Population .....	16
Table PYAB.6.4. Tables and Figures Related to Disposition .....	19
Table PYAB.6.5. Tables and Figures Related to Demographics and Other Characteristics of Study Population .....	20
Table PYAB.6.6. Summary Tables Related to Concomitant Medications .....	21
Table PYAB.6.7. Symptom and Clinical Status Questionnaire Scores .....	27
Table PYAB.6.8. Pharmacokinetic Parameters .....	28
Table PYAB.6.9. Baseline and Postbaseline Definitions for Safety Groups Initial Controlled Periods of Individual Studies Controlled Integrated Analysis Sets .....	32
Table PYAB.6.10. Additional Types of Adverse Events to be Summarized .....	34
Table PYAB.6.11. Tables and Figures Produced to Support Vital Signs and Physical Characteristics .....	36
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 .....	37
Table PYAB.6.13. Concomitant Medications of Interest Subgroup.....	39

**Table of Contents**

**Figure**

**Page**

Figure PYAB.5.1. Overview of participant flow from time of SARS-CoV-2 symptoms  
to IV infusion. .... 11

**Table of Contents**

<b>Appendix</b>		<b>Page</b>
Appendix 1.	NEWS2 Scoring Scale .....	47
Appendix 2.	NIAID Scoring Scale .....	49

### 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 ( $\pm 4$  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
<b>Secondary</b>	
Characterize the effect of LY3819253 compared to placebo on safety	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load among participants with $\leq 8$ days since symptom onset	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm 4</math> days) in SARS-CoV-2 viral load among participants enrolled with <math>\leq 8</math> days of symptoms prior to randomization</li> </ul>
Characterize the effect of LY3819253 compared to placebo on symptom resolution	<ul style="list-style-type: none"> <li>Time to symptom resolution</li> <li>Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15, and 22</li> <li>Change in symptom score (total of ratings) from baseline to Days 7, 11, 15, and 22</li> </ul>
Characterize the effect of LY3819253 compared to placebo on symptom improvement	<ul style="list-style-type: none"> <li>Time to symptom improvement</li> <li>Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15, and 22</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SARS-CoV-2 viral load and viral clearance	<ul style="list-style-type: none"> <li>Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 15, and 22)</li> <li>Time to SARS-CoV-2 clearance</li> <li>SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed through Day 29</li> </ul>

**Secondary Objectives of Study J2W-MC-PYAB**

<b>Objectives</b>	<b>Endpoints</b>
Characterize the pharmacokinetics of LY3819253	<ul style="list-style-type: none"> <li>• LY3819253 mean concentration on Day 29</li> </ul>
Characterize the effect of LY3819253 compared to placebo on overall participant clinical status	<ul style="list-style-type: none"> <li>• Proportion (percentage) of participants who experience these events by Day 29               <ul style="list-style-type: none"> <li>○ COVID-19-related hospitalization (defined as <math>\geq 24</math> hours of acute care)</li> <li>○ a COVID-19-related emergency room visit, or</li> <li>○ death</li> </ul> </li> </ul>

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

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

<b>Objectives</b>	<b>Endpoints</b>
<b>Exploratory</b>	
Characterize emergence of viral resistance to LY3819253	<ul style="list-style-type: none"> <li>• Comparison from baseline to the last evaluable timepoint up to Day 29</li> </ul>
Characterize the effect of LY3819253 compared to placebo on SpO2 over time	<ul style="list-style-type: none"> <li>• SpO2 AUC assessed through Day 29</li> </ul>
Characterize the effect of LY3819253 compared to placebo on symptom severity	<ul style="list-style-type: none"> <li>• Symptom severity as assessed by mean AUC through Day 29 of symptom questionnaire</li> </ul>
Characterize the effect of LY3819253 compared to placebo on improvement on the NIAID Ordinal Scale	<ul style="list-style-type: none"> <li>• Comparison of the mean worst daily NIAID ordinal scale values at Days 7, 11, 15, and 22</li> </ul>

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

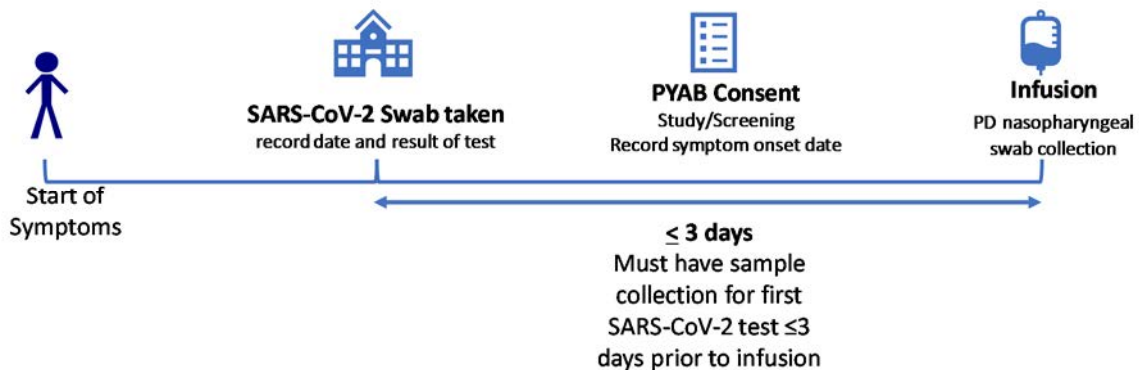
Additional exploratory objectives not previously defined in the protocol are described in [Section 6.17.2](#).

## 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 ( $\leq 8$  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 ( $\pm 4$  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 ( $\pm 4$  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 ( $\leq 8$  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**

<p>Unblinding (IWRS)</p>	<ul style="list-style-type: none"> <li>• 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</li> <li>• In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants’ intervention assignment is warranted</li> <li>• 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</li> <li>• If a participant’s intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance</li> <li>• The date and reason that the blind was broken must be recorded in the source documentation and case report form</li> </ul>
--------------------------	--

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	<p><b>Definition:</b> All participants who signed informed consent.</p> <p><b>Purpose:</b> Used for disposition analysis.</p> <p><b>Treatment Groups:</b> None</p> <p><b>Inferential Comparisons:</b> None</p>
Efficacy	<p><b>Definition:</b> 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).</p> <p><b>Purpose:</b> Used for efficacy and health outcomes analyses.</p> <p><b>Treatment Groups (Short Label):</b> 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), LY total, and placebo (Pbo)</p> <p><b>Inferential Comparisons:</b> Each LY dose versus placebo</p>

**Analysis Populations**

<b>Population</b>	<b>Description</b>
Safety	<p><b>Definition:</b> All participants randomly assigned and who received any amount of study intervention. Participants will be analyzed according to the intervention they actually received.</p> <p><b>Purpose:</b> Used for safety analyses.</p> <p><b>Treatment Groups (Short Label):</b> 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), LY total, and placebo (Pbo)</p> <p><b>Inferential Comparisons:</b> LY total versus placebo</p>
Pharmacokinetic	<p><b>Definition:</b> 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.</p> <p><b>Purpose:</b> Used for PK analyses.</p> <p><b>Treatment Groups (Short Label):</b> 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), and placebo (Pbo)</p> <p><b>Inferential Comparisons:</b> Each LY dose versus placebo</p>

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:

$$\text{Length of interval (days)} = \text{End Date} - \text{Interval Start Date} + 1$$

To convert any time length from days to weeks, the following formula will be used:

$$\text{Length of interval (weeks)} = \text{Length of interval (days)} / 7$$

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**

<b>Study Period</b>	<b>Interval Start Definition</b>	<b>Interval End Definition</b>
<b>Screening:</b> 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.
<b>Treatment and Assessment Period:</b> 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.
<b>Post-Treatment Follow-Up:</b> 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**

<b>Method</b>	<b>Analysis</b>
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 ( $\leq 8$  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 ( $\leq 8$  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 ( $\leq 8$  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 ( $\leq 8$  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 ( $\leq 8$  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 <ul style="list-style-type: none"> <li>• study discontinuation and</li> <li>• study treatment period discontinuation</li> </ul> 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	<p><b>Variables to be included:</b></p> <ul style="list-style-type: none"> <li>• Age</li> <li>• Age groups (&lt;65, ≥65 and &lt;75, ≥75 and &lt;85, ≥85, ≥65, and ≥75 years)</li> <li>• Sex</li> <li>• Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)</li> <li>• Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)</li> <li>• Height</li> <li>• Weight</li> <li>• Body mass index, and</li> <li>• Days since COVID-19 symptom onset.</li> <li>• High-risk status for severe COVID-19 illness</li> </ul> <p><b>Statistics to be included:</b></p> <p>Continuous: Mean, standard deviation, min, max, median, and first quartile and third quartile</p> <p>Categorical: n and percent (denominator for percentages will be the number of participants with nonmissing values)</p> <p>A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets)</p> <p>No inferential statistics</p>
Medical History and Preexisting conditions	<p>Number and percentage of participants with medical history events and preexisting conditions using MedDRA PT nested within SOC</p> <ul style="list-style-type: none"> <li>• Ordered by decreasing frequency within SOC on the LY total arm</li> </ul> <p>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).</p>
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 <ul style="list-style-type: none"> <li>Ordered by decreasing frequency</li> </ul> No inferential statistics
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication <ul style="list-style-type: none"> <li>Ordered by decreasing frequency</li> </ul> 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  $(45-Ct)/\log_2 10$ , or  $(45-Ct)/3.321928$ .

### 6.10.1. Primary Outcome and Methodology

Primary endpoint is the change from baseline to Day 11 ( $\pm 4$  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 ( $\leq 8$  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 be 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 ( $\pm 4$  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  $d$ ,  $y = \{y_1, \dots, y_n\}$  be the observed data, and  $m \in \{1, \dots, M\}$  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

$$p(\mu(d) | y) = \sum_{m=1}^M p(\mu(d) | y, m) p(m | y)$$

$$p(m | y) = \frac{p(y | m)p(m)}{\sum_{m^*} p(y | m^*)p(m^*)}$$

where  $p(\mu(d) | y, m)$  is the posterior mean dose response curve from model  $m$ ,  $p(m | y)$  is the posterior weight of model  $m$ ,  $p(y | m)$  is the marginal likelihood of the data under model  $m$ , and  $p(m)$  is the prior weight assigned to model  $m$ . In cases where  $p(y | m)$  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

$\mu$ : a constant common to all observations

$\alpha$ : a fixed coefficient on the covariate log base 10 baseline viral load

$\alpha_i$ : a parameter corresponding to treatment i

$\beta_k$ : a parameter corresponding to day k

$(\alpha\beta)_{ik}$ : an interaction parameter corresponding to treatment i and day k

$\varepsilon_{ij}, \varepsilon_{ijk}$ : random error for between- and within-subject variability

prior  $\mu, \alpha, \alpha_i, \beta_k, (\alpha\beta)_{ik} \sim N(0, 100)$

$\varepsilon_{ij} \sim N(0, \sigma_1), \varepsilon_{ijk} \sim N(0, \sigma_2)$

$\sigma_1, \sigma_2 \sim uniform(0, 100) \text{ or } igamma(0.01, 0.01)$

### 6.10.3. Secondary Efficacy Analyses

#### 6.10.3.1. SARS-CoV-2 Viral Load Among Participants Enrolled with $\leq 8$ 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  $\leq 8$  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 ( $\leq 8$  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 ( $\leq 8$  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  $\geq 24$  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 ( $t_{1/2}$ ), AUC from time 0 to infinity ( $AUC[0-\infty]$ ),  $AUC(0-D29)$ , 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 <sup>a</sup>	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 <sub>last</sub> )	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 <sub>last</sub> -∞)	%	Percentage of AUC(0-∞) extrapolated
t <sub>last</sub>		Time of the last observed drug concentration
C <sub>max</sub>	µg/mL	Maximum observed drug concentration
C <sub>D29</sub>	µg/mL	Observed drug concentration on Day 29
t <sub>max</sub>	h	Time of maximum observed drug concentration
t <sub>½</sub>	h	Half-life associated with the terminal rate constant ( $\lambda_z$ ) in non-compartmental analysis
CL	L/h	Total body clearance of drug calculated
V <sub>z</sub>	L	Volume of distribution during the terminal phase
V <sub>ss</sub>	L	Volume of distribution at steady state

<sup>a</sup> 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<sub>max</sub>) will be reported from observed values. If C<sub>max</sub> occurs at more than 1 time point, t<sub>max</sub> will be assigned to the first occurrence of C<sub>max</sub>.
- 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<sub>max</sub> and then the logarithmic trapezoidal method will be used after t<sub>max</sub>. 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<sub>max</sub>.



- 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- $\infty$ ) 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  $t_{1/2}$  is estimated over a time window of <2 half-lives, the values will be flagged in the data listings. Any  $t_{1/2}$  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  $\pm 10\%$ , 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  $\pm 10\%$ . 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  $n \geq 6$ , 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  $\pm 3 \times \text{SD}$  of the remaining log-transformed values.
- d. If the extreme value is within the range of arithmetic mean  $\pm 3 \times \text{SD}$ , 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  $\pm 3 \times \text{SD}$ , 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  $n \geq 6$  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  $\pm 3 \times \text{SD}$  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- $\infty$ ) 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**

<b>Analysis Type</b>	<b>Baseline</b>	<b>Postbaseline</b>
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	<ul style="list-style-type: none"> <li>• Includes participants who have both a baseline and a postbaseline measurement from a planned visit.</li> <li>• Unplanned measurements will be excluded.</li> <li>• Last baseline will be used.</li> <li>• Descriptive summary statistics will be included in a table below the box plot.</li> <li>• No inferential statistics.</li> </ul>
Box plots for change from baseline values by visit	<ul style="list-style-type: none"> <li>• Includes participants who have both a baseline and a postbaseline planned measurement.</li> <li>• Unplanned measurements will be excluded.</li> <li>• Last baseline will be used.</li> <li>• Descriptive summary statistics will be included in a table below the box plot.</li> <li>• 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.</li> </ul>
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	<ul style="list-style-type: none"> <li>• Each study individually and studies combined will be displayed.</li> <li>• Includes participants who have both a baseline and postbaseline observation.</li> <li>• Unplanned measurements will be included.</li> <li>• Lines indicating the reference limits will be included.</li> <li>• <b>Max vs Max:</b> Maximum baseline versus maximum postbaseline.</li> <li>• <b>Min vs Min:</b> Minimum baseline versus minimum postbaseline.</li> </ul>
Summary tables for shifts to high/low	<ul style="list-style-type: none"> <li>• Limits provided by the central lab service will be used to define low and high.</li> <li>• <b>Normal/high to low:</b> Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low.                         <ul style="list-style-type: none"> <li>○ Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 postbaseline result.</li> </ul> </li> <li>• <b>Normal/low to high:</b> Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high.                         <ul style="list-style-type: none"> <li>○ Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period.</li> </ul> </li> <li>• Statistical comparisons will be included.</li> </ul>

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.

### 6.13.8. 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<sup>2</sup>, ≥25 to <30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup> to <40 kg/m<sup>2</sup>, and ≥40 kg/m<sup>2</sup>)
- 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:

$$P(\Delta_{LY700mg} - \Delta_{placebo} > -0.3) > 0.8$$

or

$$P(\Delta_{LY7,000mg} - \Delta_{LY700mg} < -0.3) > 0.85$$

- Enrolling up to 100 additional participants to a new or existing dose arm to better characterize the dose-response relationship if:

$$P(\Delta_{LY700mg} - \Delta_{placebo} < -0.3) > 0.85$$

Note:  $\Delta$  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. SpO<sub>2</sub> 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<sub>2</sub> 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, SpO<sub>2</sub> AUC(0-D29) data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, SpO<sub>2</sub> 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 ( $\leq 8$  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 ( $\leq 8$  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 ( $\pm 4$  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](http://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

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## Appendix 1. NEWS2 Scoring Scale

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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 <sub>2</sub> Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO <sub>2</sub> 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; SpO<sub>2</sub> = oxygen saturation.

Figure APP.1.2. NEWS2 Scoring Clinical Risk Thresholds

NEWS 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.

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## Appendix 2. NIAID Scoring Scale

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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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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

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## 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

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17-December-2020

Statistical Analysis Plan Version 6 electronically signed and approved by Lilly  
on date provided below.

Approval Date: 13-Jan-2021 GMT

## 2. Table of Contents

Section	Page
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 .....	1
2. Table of Contents.....	2
3. Revision History .....	9
4. Study Objectives .....	16
4.1. Primary Objective .....	16
4.2. Secondary Objectives .....	16
4.3. Exploratory Objectives.....	19
5. Study Design.....	20
5.1. Summary of Study Design.....	20
5.1.1. Design Outline .....	20
5.1.2. Screening .....	20
5.1.3. Double-Blind Treatment and Assessment Period.....	20
5.1.4. Posttreatment Follow-up .....	21
5.2. Determination of Sample Size .....	21
5.3. Method of Assignment to Treatment .....	23
5.3.1. Randomization .....	23
5.3.2. Blinding.....	24
6. A Priori Statistical Methods .....	25
6.1. General Considerations .....	25
6.1.1. Analysis Populations.....	25
6.1.2. Definition of Study Baseline .....	27
6.1.3. Study Time Intervals.....	28
6.1.4. Analysis Methods.....	28
6.2. Adjustments for Covariates .....	30
6.3. Handling of Dropouts or Missing Data .....	30
6.3.1. Non-Responder Imputation .....	30
6.3.2. Modified Non-Responder Imputation.....	30
6.3.3. Mixed-Effects Model Repeated Measures .....	31
6.3.4. Highest Disease States Imputation) .....	31
6.3.5. Modified Last Observation Carried Forward .....	31
6.4. Multicenter Studies .....	31
6.5. Multiple Comparisons/Multiplicity.....	32



6.6.	Participant Disposition .....	32
6.7.	Participant Characteristics .....	33
6.8.	Treatment Compliance .....	35
6.9.	Prior Medication and Concomitant Therapy .....	35
6.10.	Efficacy Analyses .....	35
6.10.1.	Primary Outcome and Methodology.....	36
6.10.2.	Additional Analyses of the Primary Outcome.....	37
6.10.2.1.	Dose Response Modeling for Treatment Arms 1-4, and 6 .....	37
6.10.2.2.	Bayesian Modeling.....	38
6.10.3.	Secondary Efficacy Analyses .....	39
6.10.3.1.	SARS-CoV-2 Viral Load Among Participants Enrolled with $\leq 8$ Days of Symptoms Prior to Randomization.....	39
6.10.3.2.	SARS-CoV-2 Viral Load AUC.....	39
6.10.3.3.	SARS-CoV-2 Clearance at Days 7, 11, 15, and 22.....	40
6.10.3.4.	Time to SARS-CoV-2 Clearance .....	40
6.10.3.5.	Symptom Resolution .....	40
6.10.3.6.	Time to Symptom Resolution .....	41
6.10.3.7.	Symptom Improvement .....	41
6.10.3.8.	Time to Symptom Improvement .....	41
6.10.3.9.	COVID-19-Related Deterioration (COVID-19-Related Hospitalization, Emergency Room Visit, or Death from Any Cause by Day 29, 60, and 85).....	42
6.10.3.10.	Change in Symptom Questionnaire Score .....	42
6.10.3.11.	Secondary Efficacy Analyses for Treatment Arms 7-9, 13-14.....	42
6.10.3.11.1.	SARS-CoV-2 Viral Load $>5.27$ on Day 7 (+2 Days).....	42
6.10.3.11.2.	SARS-CoV-2 Viral Load for Day 3, 5, and 7 .....	43
6.10.3.11.3.	SARS-CoV-2 Viral Load AUC from Day 1 to Day 7 .....	43
6.10.3.11.4.	Time to SARS-CoV-2 Clearance .....	44
6.10.3.11.5.	Time to Sustained Symptom Resolution.....	44
6.10.3.11.6.	Time to Sustained Complete Symptom Resolution.....	44
6.10.3.11.7.	Time to Complete Symptom Resolution.....	44
6.10.3.11.8.	Proportion of Participants with Symptom Resolution on Days 2-11 .....	44
6.10.3.11.9.	Time to Symptom Resolution.....	44
6.10.3.11.10.	Proportion of Participants with Symptom Improvement on Days 2-11 .....	45
6.10.3.11.11.	Time to Symptom Improvement .....	45
6.10.4.	Symptoms and Overall Clinical Status Participant Questionnaire .....	45

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods.....46

6.12. Safety Analyses.....46

    6.12.1. Baseline and Postbaseline Definitions for Safety Groups.....47

    6.12.2. Extent of Exposure.....47

    6.12.3. Adverse Events .....47

    6.12.4. Deaths, Other Serious Adverse Events, and Other Notable  
Adverse Events .....49

    6.12.5. Hospitalization, Clinical Events, Clinical Status, and  
Environmental Risk Factors .....49

    6.12.6. Clinical Laboratory Evaluation.....50

    6.12.7. Vital Signs and Other Physical Findings.....50

    6.12.8. Electrocardiograms .....52

    6.12.9. Immunogenicity .....52

6.13. Subgroup Analyses.....52

6.14. Protocol Violations.....55

6.15. Interim Analyses and Data Monitoring.....56

    6.15.1. Interim Analyses .....56

    6.15.2. Data Monitoring Committee/Assessment Committee .....58

6.16. Planned Exploratory Analyses.....59

    6.16.1. Protocol-Defined Exploratory Endpoints.....59

        6.16.1.1. Viral Resistance.....59

        6.16.1.2. SpO<sub>2</sub> AUC Assessed through Day 29.....59

        6.16.1.3. Symptom Questionnaire AUC through Day 29 .....59

        6.16.1.4. Worst NIAID Score.....60

        6.16.1.5. COVID-19-Related Clinical Status (COVID-19-Related  
Hospitalization or Death From Any Cause) by Days 60  
and 85.....60

    6.16.2. Additional Exploratory Analyses not Defined in the Protocol.....60

        6.16.2.1. Clinical Worsening Based on the NIAID Scale .....60

        6.16.2.2. National Early Warning Score .....60

        6.16.2.3. NEWS2 Consciousness Level.....60

        6.16.2.4. NIAID/NEWS2 Overall Improvement .....60

        6.16.2.5. Time to Hospitalization .....61

        6.16.2.6. Duration of Hospitalization.....61

        6.16.2.7. Time to Admission to ICU.....61

        6.16.2.8. Proportions of Participants Hospitalized, Admitted to the  
ICU, Requiring Mechanical Ventilation.....61

        6.16.2.9. Days Since Symptom Onset Cutpoint Analysis.....62

        6.16.2.10. SpO<sub>2</sub> Measurements of Interest .....62

6.16.2.11. Viral Load Plots..... 62

6.16.2.12. Proportion of Participants with Symptom Resolution on  
Days 22 and 29 ..... 62

6.16.2.13. Proportion of Participants with Symptom Improvement  
on Days 22 and 29 ..... 62

6.17. Annual Report Analyses..... 62

6.18. Clinical Trial Registry Analyses ..... 63

7. References ..... 64

8. Appendices ..... 65

## Table of Contents

<b>Table</b>		<b>Page</b>
Table PYAB.4.1.	Secondary Objectives of Study J2W-MC-PYAB .....	16
Table PYAB.4.2.	Exploratory Objectives of Study J2W-MC-PYAB .....	19
Table PYAB.5.1.	Treatment Arms of Study J2W-MC-PYAB.....	21
Table PYAB.5.2.	Unblinding Procedures for Study J2W-MC-PYAB .....	24
Table PYAB.6.1.	Analysis Populations .....	26
Table PYAB.6.2.	Definition of Study Period Time Intervals .....	28
Table PYAB.6.3.	Tables and Figures Related to Demographics and Other Characteristics of Study Population.....	29
Table PYAB.6.4.	Tables and Figures Related to Disposition .....	33
Table PYAB.6.5.	Tables and Figures Related to Demographics and Other Characteristics of Study Population.....	34
Table PYAB.6.6.	Summary Tables Related to Concomitant Medications.....	35
Table PYAB.6.7.	Symptom and Clinical Status Questionnaire Scores .....	46
Table PYAB.6.8.	Baseline and Postbaseline Definitions for Safety Groups Initial Controlled Periods of Individual Studies Controlled Integrated Analysis Sets .....	47
Table PYAB.6.9.	Additional Types of Adverse Events to be Summarized .....	48
Table PYAB.6.10.	Tables and Figures Produced to Support Vital Signs and Physical Characteristics .....	51
Table PYAB.6.11.	Categorical Criteria for Abnormal Treatment- Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes in Adults.....	52
Table PYAB.6.12.	Concomitant Medications of Interest Subgroup .....	54

**Table of Contents**

<b>Figure</b>		<b>Page</b>
Figure PYAB.5.1.	Overview of participant flow from time of SARS-CoV-2 symptoms to IV infusion. ....	20

**Table of Contents**

<b>Appendix</b>		<b>Page</b>
Appendix 1.	NEWS2 Scoring Scale.....	66
Appendix 2.	NIAID Scoring Scale.....	68

### 3. Revision History

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

DOCUMENT HISTORY	
Document	Date
Version 6	See approval date on cover page
Version 5	17-Dec-2020
Version 4	18-Sep-2020
Version 3	08-Sep-2020
Version 2	31-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 <sub>2</sub> , 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	Added text	To add more details for candidate models for

Section # and Name	Description of Change	Brief Rationale
Modeling		dose response.
6.10.3.2 SARS-CoV-2 Viral Load AUC	Added text	AUC0-11(day)
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 <sub>2</sub> , respiratory rate, FiO <sub>2</sub>
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 <sub>2</sub> 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 SpO <sub>2</sub> endpoint using different cutoffs

### Overall Rationale for the Revision on Version 2:

New treatment arms 7 and 8 are added to this study with the combination of LY3819253 and LY3832479 and placebo.

Section # and Name	Description of Change	Brief Rationale
4.1 Primary Objective	Added primary endpoint for treatment arms 7 and 8	Addition of new treatment arms
4.2 Secondary Objectives	Added secondary endpoints for treatment arms 7 and 8	Addition of new treatment arms
5.1.3 Double-Blind	Added treatment arms 7 and 8	Addition of new treatment arms



Section # and Name	Description of Change	Brief Rationale
Treatment and Assessment Period		
5.2 Determination of Sample Size	Added text for the sample size for treatment arms 7 and 8	Addition of new treatment arms
6.1 General Considerations	Added text for treatment arms 7 and 8. Added text.	Addition of new treatment arms. Clarification of text.
6.7 Participant Characteristics	Added text for treatment arms 7 and 8. Clarified the definition of high-risk status for treatment arms 1-4 and 6.	Addition of inclusion criterion #27 for treatment arms 7 and 8
6.10 Efficacy Analysis	Added text	Addition of new treatment arms
6.10.1 Primary Outcome and Methodology	Added text for primary endpoint and methodology for treatment arms 7 and 8	Addition of new treatment arms
6.10.2.3. Sensitivity Analysis for Treatment Arms 7 and 8	Added a section for the sensitivity analysis for the primary endpoint for treatment arms 7 and 8	Addition of new treatment arms
6.10.3.3 SARS-CoV-2 Clearance at Days 7, 11, 15, and 22	Added text.	Clarification of text.
6.10.3.5 Symptom Resolution	Added text.	Clarification of text. Added data collection modality subgroup analysis.
6.10.3.7 Symptom Improvement	Added text.	Clarification of text. Added data collection modality subgroup analysis.
6.10.3.9 COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 29, 60, and 85)	Added text.	Clarification of text.
6.10.3.11 Additional Secondary Efficacy Analyses for Treatment Arms 7 and 8	Added a section for the additional secondary efficacy endpoints for treatment arms 7 and 8	Addition of new treatment arms
6.12 Safety Analyses	Removed text.	Clarification of text.
6.13 Subgroup Analyses	Added text for treatment arms 7 and 8	Change in inclusion criteria for treatment arms 7 and 8
6.15.1 Interim Analyses	Added text for interim analyses planned for treatment arms 7 and 8	Addition of new treatment arms
6.16.1.3 Symptom Questionnaire AUC through Day 29	Updated text.	Clarification of text.
6.16.2.8 Proportions of Participants Hospitalized, Admitted to the ICU, Requiring Mechanical Ventilation	Added text.	Clarification of text.
6.6.2.11 Viral Load Plots	Added text	Added exploratory viral load plots

Section # and Name	Description of Change	Brief Rationale
Appendix 1. NEWS2 Scoring Scale	Added text.	Added text to clarify how missing consciousness data will be handled in the analysis.

### Overall Rationale for the Revision on Version 3:

Clarifications to the analysis population used to analyze coronavirus disease 2019 (COVID-19)-related deterioration and hospitalization events. Clarifications on the analysis population and analyses with respect to patients with missing baseline efficacy assessments.

Section # and Name	Description of Change	Brief Rationale
6.1.1 Analysis Populations	<ul style="list-style-type: none"> <li>Clarified definition of the efficacy population to be consistent with what is defined in the protocol.</li> <li>Clarified use of safety population to include deterioration and hospitalization events in the population table.</li> </ul>	Alignment with protocol. Clarification of text.
6.1.4 Analysis Methods	Clarified that patients with missing baseline measures will be excluded from the corresponding analyses of change from baseline.	Clarification of text describing methodology.
6.3.3 Mixed-Effects Model Repeated Measures (MMRM)	Clarified that patients with missing baseline measures will be excluded from the corresponding analyses of change from baseline.	Clarification of text describing methodology.
6.10.3.9 COVID-19-Related Deterioration	Clarified that the safety population will be utilized to analyze COVID-19-related deterioration.	Clarification of text.
6.10.3.11 Additional Secondary Efficacy Analyses for Treatment Arms 7 and 8	Clarified that the safety population will be utilized to analyze COVID-19-related deterioration.	Clarification of text.
6.16.2 Additional Exploratory Analyses not Defined in the Protocol	Clarified that the analyses of hospitalization events will utilize the safety population.	Clarification of text.

### Overall Rationale for the Revision on Version 4:

New primary endpoints were defined for treatment arms 7 through 9.

Section # and Name	Description of Change	Brief Rationale
4.1 Primary Objective	Added the co-primary endpoint of the proportion of participants who experience a COVID-19 hospitalization or death	Alignment with protocol amendment f.
4.2 Secondary Objectives	Clarified secondary endpoints and made modifications to secondary endpoints, clarified the key secondary endpoints.	Alignment with protocol amendments f-i. Modified to Phase 3 endpoints.
4.3 Exploratory Objectives	Clarified exploratory endpoints.	Alignment with protocol amendments f-j.
5.1.3 Double-Blind Treatment and	Added treatment arm 9.	Alignment with protocol

Section # and Name	Description of Change	Brief Rationale
Assessment Period		amendment i.
5.2 Determination of Sample Size	Added sample size for treatment arm 9.	Alignment with protocol amendment i.
5.3.1 Randomization	Added randomization for treatment arms 7-9	Alignment with protocol amendments f-i.
5.3.2 Blinding	Clarified text	Alignment with protocol amendment i.
6.1. General Considerations	Added descriptive statistics for adolescent versus adult participants. Clarified that BMI criteria for high-risk status is $\geq 30$ .	Inclusion of adolescent participants in the protocol amendment f-i.
6.1.1 Analysis Populations	Add treatment arm 9.	Alignment with protocol amendment i.
6.1.4 Analysis Methods	Added Bayesian methodology and added that multiplicity adjustments will be done for treatment arms 7-9	Alignment with protocol amendment i.
6.3.2 Last Observation Carried Forward (LOCF)	Removed section	Not needed
6.3.2 Modified Non-Responder Imputation (mNRI)	Added section	Clarified this is used in viral clearance analyses
6.3.5 Modified Last Observation Carried Forward	Clarified that this imputation is not used in change from baseline symptom score analyses.	Clarification
6.5 Multiple Comparisons/Multiplicity	Added that multiplicity is done from treatment arms 7-9	Added for Phase 3 endpoints.
6.7 Participant Characteristics	Clarified analyses for adolescents.	Inclusion of adolescent participants in the protocol amendment f.
6.10 Efficacy Analyses	Removed duplicated text	Removed duplicated text
6.10.1 Primary Outcome and Methodology	Added analysis methodology for treatment arms 7-9.	Alignment with protocol amendment f-i.
6.10.2.1 Dose Response Modeling for Treatment Arms 1-4 and 6	Clarified this is only for treatment arms 1-4 and 6	Clarification
6.10.2.2 Bayesian Modeling	Added text for treatment arms 7-9	Alignment with protocol amendment i.
6.10.3.11 Secondary Efficacy Analyses for Treatment Arms 7-9	Updated section to align with the secondary objectives for treatment arms 7-9	Alignment with protocol amendment f-i.
6.11 Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods	Removed content related to noncompartmental analysis methods	Descriptive analysis will be reported
6.12 Safety Analyses	Clarified text	Clarified text
6.13 Subgroup Analyses	<ul style="list-style-type: none"> <li>Clarified analyses for adolescents.</li> <li>Clarified analyses for treatment arms 7-9</li> </ul>	Alignment with protocol amendment f-i.
6.15.1 Interim Analyses	Updated text for Treatment arms 7-9	Alignment with protocol amendment f-i.
6.15.2 Data Monitoring Committee/Assessment Committee	Updated text for Treatment arms 7 and 8	Alignment with protocol amendment f-i.
6.16.2.11 Viral Load Plots	Clarified text	Clarified text

Section # and Name	Description of Change	Brief Rationale
6.16.2.12 Proportion of Participants with Symptom Resolution on Days 22 and 29	Added Section	Moved to exploratory analyses
6.16.2.13 Proportion of Participants with Symptom Improvement on Days 22 and 29	Added Section	Moved to exploratory analyses

### Overall Rationale for the Revision on Version 5:

New treatment arms 13 and 14 added per protocol amendment (j).

Section # and Name	Description of Change	Brief Rationale
4.1 Primary Objective	Added objective for treatment arms 13 and 14	Protocol amendment (j)
	Clarified that death includes death from all causes	Clarification
4.2 Secondary Objectives	Added objectives for treatment arms 13 and 14	Protocol amendment (j)
	Clarified that death includes death from all causes	Clarification
4.3 Exploratory Objectives	Added objectives for treatment arms 13 and 14	Protocol amendment (j)
	Clarified that death includes death from all causes	Clarification
5.1.3 Double-Blind Treatment and Assessment Period	Added treatment arms 13 and 14	Protocol amendment (j)
5.2 Determination of Sample Size	Added treatment arms 13 and 14	Protocol amendment (j)
6.1 General Considerations	Added treatment arms 13 and 14	Protocol amendment (j)
	Added analyses for pregnant women	Protocol amendment (j) now allows pregnant women to participate in the study
6.1.1 Analysis Populations	Added descriptions for treatment arms 13 and 14	Protocol amendment (j)
	Added a per-protocol population	Additional sensitivity analyses
6.5 Multiple Comparisons/Multiplicity	Clarified that death includes death from all causes	Clarification
6.7 Participant Characteristics	Added treatment arms 13 and 14	Protocol amendment (j)
	Added analyses for pregnant women	Protocol amendment (j) now allows pregnant women to participate in the

Section # and Name	Description of Change	Brief Rationale
		study
6.10 Efficacy Analyses	Added analysis details for treatment arms 13 and 14	Protocol amendment (j)
6.10.1 Primary Outcome and Methodology	Added analysis details for treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification
6.10.2.2 Bayesian Modeling	Added treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification
6.10.3.9 COVID-19-Related Deterioration (COVID-19-Related Hospitalization, Emergency Room, or Death from Any Cause by Day 29, 60, and 85)	Clarified that death includes death from all causes	Clarification
6.10.3.11 Secondary Efficacy Analyses for Treatment Arms 7-9, 13-14	Added treatment arms 13 and 14	Protocol amendment (j)
6.10.3.11.4 Time to SARS-CoV-2 Clearance	Added treatment arms 13 and 14	Protocol amendment (j)
6.13 Subgroup Analyses	Added treatment arms 13 and 14  Added analyses for pregnant women	Protocol amendment (j)  Protocol amendment (j) now allows pregnant women to participate in the study
6.15.1 Interim Analyses	Added treatment arms 13 and 14  PK/PD and unblinding sections were added	Protocol amendment (j)  Clarification
6.15.2 Data Monitoring Committee/Assessment Committee	Added treatment arms 13 and 14	Protocol amendment (j)
6.16.1.5 COVID-19-Related Clinical Status (COVID-19-Related Hospitalization or Death from any cause) by Day 60 and 85	Added treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification

## 4. Study Objectives

### 4.1. Primary Objective

#### Treatment Arms 1-4, and 6

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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 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 ( $\pm 4$  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.

#### Treatment Arms 7-9, 13-14

The primary objective is to characterize the effect of LY2819253 in combination with LY3832479 compared to placebo on overall participant clinical status. The primary endpoint is the proportion of participants who experience COVID-19 related hospitalization (defined as  $\geq 24$  hours of acute care) or death from any cause by Day 29.

### 4.2. Secondary Objectives

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

Objectives	Endpoints
<b>Secondary for Treatment Arms 1-4 and 6</b> Characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on:	
<ul style="list-style-type: none"> <li>safety</li> </ul>	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral load among participants with <math>\leq 8</math> days since symptom onset</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline to Day 11 (<math>\pm 4</math> days) in SARS-CoV-2 viral load among participants enrolled with <math>\leq 8</math> days of symptoms prior to randomization</li> </ul>
<ul style="list-style-type: none"> <li>symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>Time to symptom resolution</li> <li>Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15, and 22</li> <li>Change in symptom score (total of ratings) from baseline to Days 7, 11, 15, and 22</li> </ul>

**Secondary Objectives of Study J2W-MC-PYAB**

Objectives	Endpoints
<ul style="list-style-type: none"> <li>• symptom improvement</li> </ul>	<ul style="list-style-type: none"> <li>• Time to symptom improvement</li> <li>• Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15, and 22</li> </ul>
<ul style="list-style-type: none"> <li>• SARS-CoV-2 viral load and viral clearance</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, and 22)</li> <li>• Time to SARS-CoV-2 clearance</li> <li>• SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29</li> </ul>
<ul style="list-style-type: none"> <li>• overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion (percentage) of participants who experience these events by Day 29                             <ul style="list-style-type: none"> <li>○ COVID-19-related hospitalization (defined as <math>\geq 24</math> hours of acute care)</li> <li>○ a COVID-19-related emergency room visit, or</li> <li>○ death.</li> </ul> </li> </ul>
<p><b>Additional Secondary for Treatment Arms 1-4 and 6</b></p>	
<p>Characterize the pharmacokinetics of LY3819253 and LY3819253 in combination with LY3832479</p>	<ul style="list-style-type: none"> <li>• Mean concentration of LY3819253 alone and in the presence of LY3832479 on Day 29</li> <li>• Mean concentration of LY3832479 in presence of LY3819253 on Day 29</li> </ul>
<p><b>Key Secondary for Treatment Arms 7-9, 13-14</b></p> <p><b>The key secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on:</b></p>	
<ul style="list-style-type: none"> <li>• the reduction of SARS-CoV-2 viral load</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline to Day 7 (<math>\pm 2</math> days)</li> </ul>
<ul style="list-style-type: none"> <li>• persistently high SARS-CoV-2 viral load</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)</li> </ul>
<ul style="list-style-type: none"> <li>• overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion (percentage) of participants who experience these events by Day 29                             <ul style="list-style-type: none"> <li>○ COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care), or</li> <li>○ COVID-19 related emergency room visit, or</li> <li>○ death from any cause.</li> </ul> </li> </ul>

**Secondary Objectives of Study J2W-MC-PYAB**

Objectives	Endpoints
<ul style="list-style-type: none"> <li>Sustained symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>Time to sustained symptom resolution</li> </ul>
<p><b>Other Secondary for Treatment Arms 7-9, 13-14</b></p> <p><b>The secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on:</b></p>	
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral load reduction</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline to                             <ul style="list-style-type: none"> <li>Day 3 (+1 day)</li> <li>Day 5 (±2 days)</li> </ul> </li> <li>SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7</li> </ul>
<ul style="list-style-type: none"> <li>SARS-CoV-2 viral clearance</li> </ul>	<ul style="list-style-type: none"> <li>Time to SARS-CoV-2 clearance</li> </ul>
<ul style="list-style-type: none"> <li>symptom resolution</li> </ul>	<ul style="list-style-type: none"> <li>Time to sustained complete symptom resolution</li> <li>Time to complete symptom resolution</li> <li>Time to symptom resolution</li> <li>Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11</li> </ul>
<ul style="list-style-type: none"> <li>symptom improvement</li> </ul>	<ul style="list-style-type: none"> <li>Time to symptom improvement</li> <li>Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11</li> </ul>
<ul style="list-style-type: none"> <li>safety</li> </ul>	<ul style="list-style-type: none"> <li>Safety assessments such as AEs and SAEs</li> </ul>

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.



### 4.3. Exploratory Objectives

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

Objectives	Endpoints
<b>Exploratory for Treatment Arms 1-4 and 6</b>	
Characterize emergence of viral resistance to LY3819253 and LY3819253 in combination with LY3832479	<ul style="list-style-type: none"> <li>Comparison from baseline to the last evaluable time point up to Day 29</li> </ul>
Characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on:	
<ul style="list-style-type: none"> <li>SpO<sub>2</sub> over time</li> </ul>	<ul style="list-style-type: none"> <li>SpO<sub>2</sub> AUC assessed through Day 29</li> </ul>
<ul style="list-style-type: none"> <li>symptom severity</li> </ul>	<ul style="list-style-type: none"> <li>Symptom severity as assessed by mean AUC through Day 29 of symptom questionnaire</li> </ul>
<ul style="list-style-type: none"> <li>overall improvement on the NIAID Ordinal Scale</li> </ul>	<ul style="list-style-type: none"> <li>Comparison of the mean worst daily NIAID ordinal scale values at Days 7, 11, 15, and 22</li> </ul>
<b>Exploratory for Treatment Arms 7-9, 13-14</b>	
<ul style="list-style-type: none"> <li>Overall participant clinical status</li> </ul>	<ul style="list-style-type: none"> <li>Proportion (percentage) of participants who experience these events by Days 22, 60, and 85               <ul style="list-style-type: none"> <li>COVID-19 related hospitalization (defined as <math>\geq 24</math> hours of acute care)</li> <li>death from any cause</li> </ul> </li> </ul>
Characterize the pharmacokinetics of LY3819253 in combination with LY3832479	<ul style="list-style-type: none"> <li>Mean concentration of LY3832479 in presence of LY3819253 on Day 29</li> </ul>

Abbreviations: AUC = area under the response-time curve; COVID-19 = coronavirus disease 2019; NIAID = National Institute of Allergy and Infectious Diseases; SpO<sub>2</sub> = saturation of peripheral oxygen.

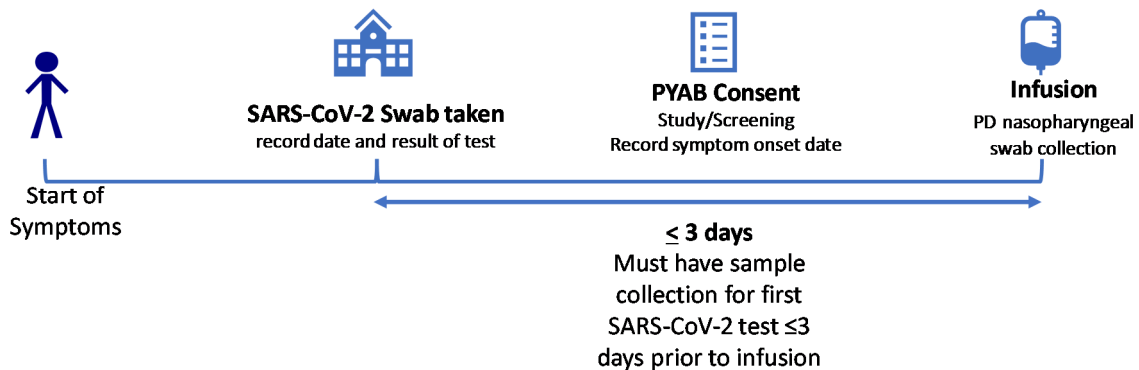
Additional exploratory objectives not previously defined in the protocol are described in Section [6.16.2](#).

## 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; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

**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
Optional 5	To Be Determined	LY3819253
6	2800 mg + 2800 mg	LY3819253+LY3832479
7	2800 mg + 2800 mg	LY3819253+LY3832479
8	---	placebo
9	700 mg + 1400 mg	LY3819253+LY3832479
13	---	placebo
14	350 mg + 700 mg	LY3819253+LY3832479

An optional LY3819253 treatment arm 5 may be added based on interim analysis results.

An optional LY3819253-only treatment arm 5 may be added based on interim analysis results.

Treatment arm 1 is the corresponding placebo control for treatment arms 2 through 4 and 6.

Treatment arm 8 is the corresponding placebo control for treatment arms 7 and 9.

Treatment arm 13 is the concurrent placebo control for treatment arm 14.

#### **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**

### **Sample Size**

#### *Treatment arms 1-4 and 6*

The initial planned sample size is approximately 500 participants allocated across 5 treatment arms (treatment arms 1 through 4 and 6). Additional placebo participants may be enrolled to ensure up to 50 concurrent placebo controls for treatment arm 6.

Up to 100 additional participants may be introduced for optional treatment arm 5. See Protocol Section 9.5 for interim analysis details.

*Treatment arms 7-9*

Participants in treatment arms 7 through 9 are adults and adolescents with at least 1 risk factor for developing severe COVID-19 illness. There is no set sample size for the adolescent participants.

The planned sample size for the primary comparison of treatment arms 7 and 8 is approximately 1000 participants equally randomized to placebo or the combination of LY3819253 and LY3832479.

The planned sample size for treatment arm 9 is approximately 500 participants. Since treatment arm 9 begins enrollment after treatment arm 7, additional participants will be enrolled in treatment arm 8 to ensure at least a 33% increase in placebo participants and adequate placebo control for the primary comparison of treatment arms 8 and 9. Randomization is planned to be 1:2 (treatment arm 8:treatment arm 9) allocation ratio. Therefore, it is anticipated that the analyses for treatment arms 8 and 9 will utilize approximately 750 placebo patients in treatment arm 8 versus approximately 500 for treatment arm 9.

*Treatment arms 13 and 14*

Participants in treatment arms 13 and 14 are adults and adolescents with at least 1 risk factor for developing severe COVID-19 illness. There is no set sample size for the adolescent participants.

The planned sample size for the primary comparison of treatment arms 13 and 14 is approximately 1000 participants randomized 2:3, placebo:combination of LY3819253 and LY3832479.

**Stratification**

Participants will be stratified by duration since symptom onset category ( $\leq 8$  days versus  $> 8$  days) and age at the time of screening ( $< 18$  years of age versus  $\geq 18$  years of age).

**Treatment Arms 1 Through 4 and 6***Simulations*

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 of interest 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 ( $\pm 4$  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.

### **Treatment Arms 7 Through 9**

Sample size justification is based on the endpoint of proportion of participants experiencing COVID-related hospitalization or death from any cause. A sample size of approximately 500 adult participants per treatment arm provides greater than 90% power to demonstrate that LY3819253 in combination with LY3832479 is statistically significantly better than placebo, defined as odds ratio  $<1$  in the proportion of participants experiencing a COVID-related hospitalization or death from any cause. This sample size calculation assumes a placebo event rate of 8.7% and a relative reduction of 60% for LY3819253 in combination with LY3832479, which were informed from available data on hospitalization or death events.

### **Treatment arms 13-14**

Sample size justification is based on the endpoint of proportion of participants experiencing COVID-related hospitalization or death from any cause. A sample size of approximately 1000 adult participants randomized 2:3 provides greater than 90% power to demonstrate that LY3819253 in combination with LY3832479 is statistically significantly better than placebo, defined as odds ratio  $<1$  in the proportion of participants experiencing a COVID-related hospitalization or death from any cause. This sample size calculation assumes a placebo event rate of 8.7% and a relative reduction of 60% for LY3819253 in combination with LY3832479, which were informed from available data on hospitalization or death events.

## **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 ( $\leq 8$  days versus  $>8$  days) and age at the time of screening ( $<18$  years of age versus  $\geq 18$  years of age).

For treatment arms 1 through 4 and 6, 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 additional placebo participants are enrolled, then the allocation ratio may change accordingly. See Protocol Section 9.5 for details.

For treatment arms 7 and 8, all eligible participants will be initially randomized using a 1:1 allocation ratio. Given the staggered start of treatment arm 9, all eligible participants will be randomized in a 1:2 (treatment arm 8:treatment arm 9) allocation ratio. Periodic adjustments to the allocation ratio may be made.

**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**

<p>Unblinding (IWRS)</p>	<ul style="list-style-type: none"> <li>• 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</li> <li>• In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants’ intervention assignment is warranted</li> <li>• 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</li> <li>• If a participant’s intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind even if consultation occurred in advance</li> <li>• The date and reason that the blind was broken must be recorded in the source documentation</li> </ul>
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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 (eg, 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 (ie, 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.

Analyses will be performed separately for treatment arms

- 1-4 and 6,
- 7 and concurrently enrolled 8,
- 8 and 9, and
- 13 and 14.

For treatment arms 7-9 and 13-14, subgroup analyses ( $\geq 12$  and  $< 18$  years old versus  $\geq 18$  years old) will be performed on all analyses and include descriptive statistics only. For treatment arms 13-14, subgroup analyses will be performed on all female participants who are pregnant at baseline and will include descriptive statistics only.

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	<p><b>Definition:</b> All participants who signed informed consent.</p> <p><b>Purpose:</b> Used for disposition analysis.</p> <p><b>Treatment Groups:</b> None</p> <p><b>Inferential Comparisons:</b> None</p>
Efficacy	<p><b>Definition:</b> 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).</p> <p><b>Purpose:</b> Used for efficacy and pharmacodynamic variables analyses.</p> <p><b>Treatment Groups (Short Label):</b></p> <p><i>Treatment arms 1-4 and 6:</i></p> <p>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).</p> <p><i>Treatment arms 7-9, 13-14:</i></p> <p>2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 350 mg LY 3819253 and 700 mg LY3832479 (350/700 LY/LY2), LY total, and placebo (Pbo).</p> <p>Additional optional combination arms may be added if decided.</p> <p><b>Inferential Comparisons:</b> Each LY dose versus placebo</p>
Safety	<p><b>Definition:</b> All participants randomly assigned and who received any amount of study intervention. Participants will be analyzed according to the intervention they actually received.</p> <p><b>Purpose:</b> Used for safety analyses, analyses of COVID-19-related deterioration and hospitalization events.</p> <p><b>Treatment Groups (Short Label):</b></p> <p><i>Treatment arms 1-4 and 6:</i></p> <p>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).</p> <p><i>Treatment arms 7-9, 13-14:</i></p> <p>2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 350 mg LY 3819253 and 700 mg LY3832479 (350/700 LY/LY2), LY total, and placebo (Pbo).</p> <p>Additional optional combination arms may be added if decided.</p> <p><b>Inferential Comparisons:</b> LY total versus placebo</p>
Pharmacokinetic and PK/PD (exposure-response)	<p><b>Definition:</b> All randomized participants who received study intervention and have at least 1 postdose PK sample. Participants will be analyzed according to</p>



Population	Description
relationships)	<p>the intervention they received.</p> <p><b>Purpose:</b> Used for PK analyses.</p> <p><b>Treatment Groups (Short Label):</b></p> <p><i>Treatment arms 1-4 and 6:</i></p> <p>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).</p> <p><i>Treatment arms 7-9, 13-14:</i></p> <p>2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 350 mg LY 3819253 and 700 mg LY3832479 (350/700 LY/LY2), LY total, and placebo (Pbo).</p> <p>Additional optional combination arm may be added if decided.</p> <p><b>Inferential Comparisons:</b> Each LY dose versus placebo</p>
Per-Protocol	<p><b>Definition:</b> All participants in the efficacy population who do not meet any of the following criteria:</p> <ul style="list-style-type: none"> <li>• received medication other than the medication the participant was randomized to receive;</li> <li>• did not meet an inclusion criterion; or</li> <li>• met an exclusion criterion.</li> </ul> <p><b>Purpose:</b> Used for sensitivity analyses for the primary and key secondary endpoints.</p> <p><b>Treatment Groups (Short Label):</b></p> <p><i>Treatment arms 7-9, 13-14:</i></p> <p>2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 350 mg LY 3819253 and 700 mg LY3832479 (350/700 LY/LY2), LY total, and placebo (Pbo).</p> <p>Additional optional combination arms may be added if decided.</p> <p><b>Inferential Comparisons:</b> Each LY dose versus placebo</p>

Abbreviations: COVID-19 = coronavirus disease 2019; 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:

$$\text{Length of interval (days)} = \text{End Date} - \text{Interval Start Date} + 1$$

To convert any time length from days to weeks, the following formula will be used:

$$\text{Length of interval (weeks)} = \text{Length of interval (days)} / 7$$

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.

Unless otherwise specified, treatment effects using frequentist approaches will be conducted using 2-sided tests at an alpha level of 0.05. When Bayesian methods are used for analyses, posterior mean, posterior standard deviation, credible intervals, and posterior probability of the effect of interest will be summarized.

No adjustment for multiplicity will be performed for treatment arms 1 through 6. For treatment arms 7 through 9, a multiple testing procedure that controls the familywise error rate at the 1-sided 0.025 level will be applied to the primary and key secondary endpoints.

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 pharmacokinetic/pharmacodynamic (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 (eg, 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 ( $\leq 8$  days versus  $> 8$  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 ( $\leq 8$  days versus  $> 8$  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 ( $\leq 8$  days versus  $> 8$  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. If the sample size is less than 5 in any treatment arm an exact test (ie, Fisher's exact) will be conducted instead of using a logistic regression.

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 ( $\leq 8$  days versus  $> 8$  days), will be reported. Time for all analyses will be described in units of days.

For all change from baseline analyses, patients who do not have a valid baseline measure will be excluded.

## 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 ( $\leq 8$  days versus  $> 8$  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

For analysis of categorical efficacy and pharmacodynamic variables, missing data will be imputed using a non-responder imputation (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. Modified Non-Responder Imputation

For analysis of viral clearance (yes/no), missing data will be imputed using modified non-responder imputation (mNRI). Specifically for patients that have missing postbaseline data for RT-PCR testing for SARS-CoV-2 (based on nasopharyngeal swab sampling) then viral clearance status will be imputed as follows:

- If a participant has previously achieved viral clearance (ie, the participant previously had 2 consecutive negative tests), then viral clearance will be imputed as "Yes."

- If a participant has not previously achieved viral clearance (ie, the participant does not have 2 consecutive previous negative tests), then viral clearance will be imputed as “No.”

After imputation, data from all participants will be included in the analyses. The application of mNRI to viral clearance helps ensure that the maximum number of randomized participants are represented in the analysis.

### **6.3.3. *Mixed-Effects Model Repeated Measures***

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.

For all change from baseline analyses, patients who do not have a valid baseline measure will be excluded from the model.

### **6.3.4. *Highest Disease States Imputation***

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, with the exception of change in symptom score, 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

### Treatment Arms 1-4, and 6

As this is a Phase 2 (nonconfirmatory) dose-finding study; no adjustments for multiple comparisons will be made.

### Treatment Arms 7-9, 13-14

A hierarchical multiple comparisons procedure, which will control type I error in the primary endpoint analysis, will be implemented. All primary and key secondary endpoints within a dose will be tested in a sequential manner at a 1-sided 0.025 significance level. The following is a list of the primary and key secondary outcomes to be tested for each dose:

- Primary (Test 1) - proportion of participants who experience COVID-19 related hospitalization (defined as  $\geq 24$  hours of acute care) or death from any cause by Day 29 (primary objective)
- Key Secondary (Test 2) – change from baseline to Day 7 ( $\pm 2$  days) in viral load
- Key Secondary (Test 3) – proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
- Key Secondary (Test 4) – proportion of participants who experience these events by Day 29:
  - COVID-19 related hospitalization (defined as  $\geq 24$  hours of acute care)
  - COVID-19 related emergency room visit, or
  - Death from any cause
- Key Secondary (Test 5) - time to sustained symptom resolution (defined as 2 consecutive assessments a score of 0 in all of the following symptoms: shortness of breath, feeling feverish, body aches and pain, sore throat, chills, and headache; and a score of 0 or 1 in both cough and fatigue symptoms).

## 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 (ie, 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 <ul style="list-style-type: none"> <li>• study discontinuation and</li> <li>• study treatment period discontinuation</li> </ul> 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 (ie, 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	<p><b>Variables to be included:</b></p> <ul style="list-style-type: none"> <li>• Age</li> <li>• Age groups (&lt;65, ≥65 years old), (&lt;35, ≥35 to &lt;45, ≥45 to &lt;55, ≥55 to &lt;65, ≥65 years old), and (&lt;65, ≥65 to &lt;75, ≥75 to &lt;85, ≥85 years old)</li> <li>• Sex</li> <li>• Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)</li> <li>• Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)</li> <li>• Height</li> <li>• Weight</li> <li>• Body mass index (BMI), and</li> <li>• Days since COVID-19 symptom onset.</li> <li>• Days since COVID-19 symptom onset (≤8 days, &gt;8 days)</li> <li>• SpO<sub>2</sub></li> <li>• SpO<sub>2</sub> category (&lt;96%, ≥96%)</li> <li>• COVID-19 disease severity category</li> <li>• High-risk status for severe COVID-19 illness (Age ≥ 55 or BMI ≥ 30 or a medical history event of interest)</li> </ul> <p><b>Statistics to be included:</b></p> <p>Continuous: Mean, standard deviation, min, max, median, and first quartile and third quartile</p> <p>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</p> <p>For treatment arms 7-9, the age groups are defined as:</p> <ul style="list-style-type: none"> <li>• Age groups (&lt;65, ≥65 years old), (≥12 to &lt;18, ≥18 to &lt;35, ≥35 to &lt;45, ≥45 to &lt;55, ≥55 to &lt;65, ≥65 years old), (&lt;65, ≥65 to &lt;75, ≥75 to &lt;85, ≥85 years old), and (≥12 to &lt;18, ≥18 years old)</li> </ul> <p>High-Risk status will not be summarized for treatment arms 7-9.</p> <p>For treatment arms 13-14, the following additional group is defined as:</p> <ul style="list-style-type: none"> <li>• If female, pregnant (yes/no)</li> </ul>
Medical History and Preexisting conditions	<p>Number and percentage of participants with medical history events and preexisting conditions using MedDRA PT nested within SOC</p> <ul style="list-style-type: none"> <li>• Ordered by decreasing frequency within SOC on the LY total arm</li> </ul> <p>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).</p>
Prior Therapy of Interest	<p>Number and percentage of participants with prior medication of interest will be displayed as “Prior medications”</p>
Listing demographics	<p>--</p>

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 <ul style="list-style-type: none"> <li>Ordered by decreasing frequency</li> </ul> No inferential statistics
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication <ul style="list-style-type: none"> <li>Ordered by decreasing frequency</li> </ul> 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  $(45-Ct)/\log_2 10$ , or  $(45-Ct)/3.321928$ .

**For Treatment Arms 7-9, 13-14**

In addition to the considerations above, treatment arms 7-9 and 13-14 will also include a normalization step for any sample with a positive SARS-CoV-2 test result. The viral load Ct value described in the previous steps will be subtracted by  $(RP\ Ct - 26.17)$ , where RP Ct is a measure for the amount of material in the sample and 26.17 is a historical average value of RP Ct for this assay, used here to center the RP Ct values.

**6.10.1. Primary Outcome and Methodology****Treatment Arms 1-4, and 6**

Primary endpoint is the change from baseline to Day 11 ( $\pm 4$  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 versus 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 through Day 15), will be used for the Day 11 value. If no measurements are available, the Day 11 viral load will be treated as MAR in the analysis.

**Treatment Arms 7-9, 13-14**

For treatment arm 7, the hypothesis is whether there is a difference in the proportion of participants who experience a COVID-related hospitalization or death from any cause compared to concurrently enrolled placebo data from treatment arm 8.

For treatment arm 9, the hypothesis is whether there is a difference in the proportion of participants who experience a COVID-related hospitalization or death from any cause compared to all placebo data from treatment arm 8.

For treatment arm 14, the hypothesis is whether there is a difference in the proportion of participants who experience a COVID-related hospitalization or death from any cause compared to all placebo data from treatment arm 13.

The primary endpoint for treatment arms 7-9 and 13-14 is the overall participant clinical status, measured by the proportion (percentage) of participants who experience these events by Day 29:

- COVID-19-related hospitalization (defined as  $\geq 24$  hours of acute care), or
- Death from any cause

The proportion of participants that experience COVID-19-related hospitalization or death from any cause by Day 29 will be summarized by treatment arm in frequency tables and listed.

In addition, the number of participants that experience COVID-19-related hospitalization or death from any cause by Day 29 will be analyzed using logistic regression to compare LY3819253 and LY3819253 in combination with LY3832479 versus concurrently enrolled placebo for treatment arm 8 and versus all placebo data for treatment group 9.

The primary analysis method will be a logistic regression with a primary success criterion of one-sided alpha level 0.025. The safety population will be utilized to analyze COVID-19-related deterioration.

Based on the ‘Hospitalization Events’ electronic case report form page, a COVID-19-related hospitalization event is defined as a event with:

- ‘Reason for Health Care Visit’ of ‘Primary Study Condition’

AND

- a ‘Health Care Service Type’ of:
  - ‘General Ward’ or ‘ICU’

OR

- ‘Emergency Room’ with a duration of  $\geq 24$  hours.

### **6.10.2. Additional Analyses of the Primary Outcome**

#### **6.10.2.1. Dose Response Modeling for Treatment Arms 1-4, and 6**

A Bayesian model averaging approach may be explored to estimate the dose-response relationship with change from baseline to Day 11 ( $\pm 4$  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  $d$ ,  $y = \{y_1, \dots, y_n\}$  be the observed data, and  $m \in \{1, \dots, M\}$  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

$$p(\mu(d) | y) = \sum_{m=1}^M p(\mu(d) | y, m) p(m | y)$$

$$p(m | y) = \frac{p(y | m)p(m)}{\sum_{m^*} p(y | m^*)p(m^*)}$$

where  $p(\mu(d) | y, m)$  is the posterior mean dose response curve from model  $m$ ,  $p(m | y)$  is the posterior weight of model  $m$ ,  $p(y | m)$  is the marginal likelihood of the data under model  $m$ , and  $p(m)$  is the prior weight assigned to model  $m$ . In cases where  $p(y | m)$  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 Treatment Arms 1-4, and 6

A Bayesian linear mixed-effect model will be fitted to evaluate the success criteria by the Lilly statistics group with the model listed below:

$$y_{ijk} = \mu + \alpha \times \text{base} + \alpha_i + \beta_k + (\alpha\beta)_{ik} + \varepsilon_{ij} + \varepsilon_{ijk}$$

Where  $y_{ijk}$ : the change from baseline in log 10 scale for treatment  $i$ , subject  $j$  at day  $k$

$\mu$ : a constant common to all observations

$\alpha$ : a fixed coefficient on the covariate log base 10 baseline viral load

$\alpha_i$ : a parameter corresponding to treatment  $i$

$\beta_k$ : a parameter corresponding to day  $k$

$(\alpha\beta)_{ik}$ : an interaction parameter corresponding to treatment  $i$  and day  $k$

$\varepsilon_{ij}$ ,  $\varepsilon_{ijk}$ : random error for between- and within-subject variability

prior  $\mu$ ,  $\alpha$ ,  $\alpha_i$ ,  $\beta_k$ ,  $(\alpha\beta)_{ik} \sim N(0, 100)$

$\varepsilon_{ij} \sim N(0, \sigma_1)$ ,  $\varepsilon_{ijk} \sim N(0, \sigma_2)$

$\sigma_1, \sigma_2 \sim \text{uniform}(0, 100)$  or  $\text{igamma}(0.01, 0.01)$

### Treatment Arms 7-9, 13-14

A Bayesian logistic regression model will be fitted to evaluate the success criteria by the Lilly statistics group. Let  $y_i$  be the number of events for arm  $i = 1$  (placebo), 2 (treatment). Let  $n_i$  be the total number of participants in each arm and  $p_i$  be the rates for each arm  $i$ . A logistic regression model is specified as follows:

$$y_i \sim \text{Binomial}(n_i, p_i)$$

with

$$\text{logit}(p_i) = \alpha + \beta (i - 1)$$

where  $\alpha$  is the log odds of the placebo rate and  $\beta$  is the log odds ratio of the treatment relative to the control.

A mixture prior will be used for the log odds ratio  $\beta$  for hospitalization/death:

$$\pi(\beta) = w \times N(-1.44, 0.69^2) + (1 - w) \times N(0, 1^2)$$

The informative component on the log odds ratio was formed using pooled treatment and pooled placebo high risk patients (as defined by inclusion criteria #27) from arms 1-4, and 6. The  $N(0, 1^2)$  component is weakly informative over the range of log odds ratios. The mixture weight  $w$  is set to 0.5 to represent an equally weighted mixture.

A weakly informative prior is placed on the log odds of the placebo arm,

$$\alpha \sim N(0, 2^2)$$

The decision rule for hospitalization/death will be based on the probability odds ratio ( $OR = \exp(\beta)$ ), is less than one

$$P(OR < 1 | y, n).$$

Which will be estimated by computing the percent of the posterior samples of odds ratio which are less than one. If this probability is greater than 0.975, this will be considered a desired level of evidence for success. The safety population will be utilized to analyze the proportion of participants who experience a COVID-related hospitalization or death from any cause.

### **6.10.3. Secondary Efficacy Analyses**

#### **6.10.3.1. SARS-CoV-2 Viral Load Among Participants Enrolled with $\leq 8$ 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  $\leq 8$  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 6.10.2.2, 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 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

#### **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 ( $\leq 8$  days versus  $> 8$  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 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

Symptom questionnaire data may be collected either through direct data capture (by phone call or in person) or through a paper diary. Symptom resolution may also be analyzed by subgroups for modality.

#### **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 ( $\leq 8$  days versus  $>8$  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 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

Symptom questionnaire data may be collected either through direct data capture (by phone call or in person) or through a paper diary. Symptom improvement may also be analyzed by subgroups for modality.

#### **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 (COVID-19-Related Hospitalization, Emergency Room Visit, or Death from Any Cause 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  $\geq 24$  hours of acute care)
- a COVID-19-related emergency room visit, or
- death from any cause

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 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

Proportion (percentage) of participants who experience deterioration by Days 60 and 85 will also be analyzed.

The safety population will be utilized to analyze COVID-19-related deterioration.

#### **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.

#### **6.10.3.11. Secondary Efficacy Analyses for Treatment Arms 7-9, 13-14**

The following will be conducted for treatment arms 7-9 and 13-14:

##### **6.10.3.11.1. SARS-CoV-2 Viral Load >5.27 on Day 7 (+2 Days)**

The proportion of participants with SARS-CoV-2 viral load greater than 5.27 (PHVL) on Day 7 (+2 days), corresponding to CT value of 27.5 based on nasopharyngeal swab sampling for RT-PCR testing for SARS-CoV-2 will be statistically analyzed using a logistic regression with a Firth penalized likelihood (Firth 1993). The model will contain a covariate for treatment arm (7 versus 8 and 9 versus 8). 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.



If Day 7 ( $\pm 2$  days) SARS-CoV-2 viral load is missing, it will be imputed using the first available measurement after Day 7. If no measurements are available, the viral load will be treated as MAR in the analysis.

The proportion of participants with PHVL on Day 7 (+2 days) will also be analyzed on the subset of participants enrolled with  $\leq 8$  days of symptoms prior to randomization using similar methodology, as described above.

### Bayesian Analyses

A Bayesian logistic regression model will be fitted to evaluate the success criteria by the Lilly statistics group. Let  $y_i$  be the number of events for arm  $i = 1$  (placebo), 2 (treatment). Let  $n_i$  be the total number of participants in each arm and  $p_i$  be the rates for each arm  $i$ . A logistic regression model is specified as follows:

$$y_i \sim \text{Binomial}(n_i, p_i)$$

with

$$\text{logit}(p_i) = \alpha + \beta (i - 1)$$

where  $\alpha$  is the log odds of the placebo rate and  $\beta$  is the log odds ratio of the treatment relative to the control.

Weakly informative distributions are used for PHVL:

$$\alpha \sim N(0, 2^2), \beta \sim N(0, 1^2).$$

The decision rule for PHVL will be based on the probability odds ratio ( $OR = \exp(\beta)$ ), is less than one

$$P(OR < 1 | y, n).$$

Which will be estimated by computing the percent of the posterior samples of OR which are less than one. If this probability is greater than 0.95, this will be considered a desired level of evidence for success. The efficacy population will be utilized to analyze the proportion of participants with PHVL.

#### **6.10.3.11.2. SARS-CoV-2 Viral Load for Day 3, 5, and 7**

Change from baseline to Day 3 (+1 day), Day 5 ( $\pm 2$  days), and Day 7 ( $\pm 2$  days) in SARS-CoV-2 viral load will be analyzed in a similar manner as described in Section 6.10.1 (Treatment Arms 1-4, and 6).

#### **6.10.3.11.3. SARS-CoV-2 Viral Load AUC from Day 1 to Day 7**

Similar to the methodology described in Section 6.10.3.2, the AUC from Day 1 predose to Day 7 (AUC[0-D7]) 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-D7) values will be calculated when Day 1 predose and/or Day 7 values are missing, or if more than 1 value is missing in the profile.

**6.10.3.11.4. Time to SARS-CoV-2 Clearance**

Similar methodology, as described in Section 6.10.3.4 will be utilized for treatment arms 7-9 and 13-14.

**6.10.3.11.5. Time to Sustained Symptom Resolution**

Sustained symptom resolution is defined as 2 consecutive assessments with a score of 0 for shortness of breath, feeling feverish, body aches and pains, sore throat, chills, and headache; and a score of 0 or 1 for cough and fatigue on the symptom questionnaire. Time to sustained symptom resolution is defined (in days) as:

*(First study day when sustained symptom resolution status is changed to “Yes” – Infusion Date + 1)*

Similar methodology, as described in Section 6.10.3.6, will be utilized to analyze time to sustained symptom resolution.

**6.10.3.11.6. Time to Sustained Complete Symptom Resolution**

Sustained complete symptom resolution is defined as 2 consecutive assessments with all symptoms (shortness of breath, feeling feverish, body aches and pains, sore throat, chills, headache, cough, and fatigue) on the symptom questionnaire scored as 0. Time to complete sustained complete symptom resolution is defined (in days) as:

*(First study day when sustained complete symptom resolution status is changed to “Yes” – Infusion Date + 1)*

Similar methodology, as described in Section 6.10.3.6, will be utilized to analyze time to sustained complete symptom resolution.

**6.10.3.11.7. Time to Complete Symptom Resolution**

Complete symptom resolution is defined as all symptoms (shortness of breath, feeling feverish, body aches and pains, sore throat, chills, headache, cough, and fatigue) on the symptom questionnaire scored as 0. Time to complete symptom resolution is defined (in days) as:

*(First study day when complete symptom resolution status is changed to “Yes” – Infusion Date + 1)*

Similar methodology, as described in Section 6.10.3.6, will be utilized to analyze time to complete symptom resolution.

**6.10.3.11.8. Proportion of Participants with Symptom Resolution on Days 2-11**

Symptom resolution is defined as a score of 0 for shortness of breath, feeling feverish, body aches and pains, sore throat, chills, and headache; and a score of 0 or 1 for cough and fatigue on the symptom questionnaire.

Similar methodology, as described in Section 6.10.3.5, will be utilized to analyze proportion of participants with symptom resolution on Days 2 through 11.

**6.10.3.11.9. 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)*

Similar methodology, as described in Section 6.10.3.6, will be utilized to analyze time to symptom resolution.

#### **6.10.3.11.10. Proportion of Participants with Symptom Improvement on Days 2-11**

Symptom improvement is defined as a patient experiencing both:

- Symptoms on the symptom questionnaire scored as 2 or 3 at baseline are subsequently scored as 0 or 1, AND
- Symptoms on the symptom questionnaire scored as 0 or 1 at baseline are subsequently scored as 0.

Similar methodology, as described in Section 6.10.3.7, will be utilized to analyze proportion of participants with symptom resolution on Days 2 through 11.

#### **6.10.3.11.11. Time to Symptom Improvement**

Time to symptom improvement is defined as:

*(First study day when symptom improvement status is changed to “Yes” – Infusion Date + 1)*

Similar methodology, as described in Section 6.10.3.8, will be utilized to analyze time to symptom improvement.

### **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 outpatient participants 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 [6.10.2.2](#).

## 6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic and PD analyses are the responsibility of the Eli Lilly and Company PK/PD group.

A summary of LY3819253 and LY3832479 concentration-time data will be reported in the clinical study report. Population PK model-based analyses, exploratory exposure-response analyses (a.k.a., population PK/PD modeling) of safety, pharmacology and efficacy may be performed.

## 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
- continuous measurements:

- p-value based on ANCOVA:
  - model containing terms for treatment,
  - factor of symptom onset ( $\leq 8$  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.6.8 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.6.8. 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.6.9](#).

**Table PYAB.6.9. 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
- serious adverse events, 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), and
- 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.6.10](#). The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, weight, peripheral oxygen saturation (SpO<sub>2</sub>), respiratory rate, fraction of inspired oxygen (FiO<sub>2</sub>), and temperature if data warrant.

The criteria for identifying subjects with treatment-emergent abnormalities are based on [Table PYAB.6.11](#).

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.6.10](#) 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.6.10. Tables and Figures Produced to Support Vital Signs and Physical Characteristics**

Analysis Type	Analysis Details
Box plots for observed values by visit	<ul style="list-style-type: none"> <li>• Includes participants who have both a baseline and a postbaseline measurement from a planned visit.</li> <li>• Unplanned measurements will be excluded.</li> <li>• Last baseline will be used.</li> <li>• Descriptive summary statistics will be included in a table below the box plot.</li> <li>• No inferential statistics.</li> </ul>
Box plots for change from baseline values by visit	<ul style="list-style-type: none"> <li>• Includes participants who have both a baseline and a postbaseline planned measurement.</li> <li>• Unplanned measurements will be excluded.</li> <li>• Last baseline will be used.</li> <li>• Descriptive summary statistics will be included in a table below the box plot.</li> <li>• 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.</li> </ul>
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	<ul style="list-style-type: none"> <li>• Each study individually and studies combined will be displayed.</li> <li>• Includes participants who have both a baseline and postbaseline observation.</li> <li>• Unplanned measurements will be included.</li> <li>• Lines indicating the reference limits will be included.</li> <li>• <b>Max versus Max:</b> Maximum baseline versus maximum postbaseline.</li> <li>• <b>Min versus Min:</b> Minimum baseline versus minimum postbaseline.</li> </ul>
Summary tables for shifts to high/low	<ul style="list-style-type: none"> <li>• Limits provided by the central lab service will be used to define low and high.</li> <li>• <b>Normal/high to low:</b> Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low.                             <ul style="list-style-type: none"> <li>○ Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 postbaseline result.</li> </ul> </li> <li>• <b>Normal/low to high:</b> Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high.                             <ul style="list-style-type: none"> <li>○ Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period.</li> </ul> </li> <li>• Statistical comparisons will be included.</li> </ul>

Abbreviations: ANCOVA = analysis of covariance; Max = maximum; Min = minimum.

**Table PYAB.6.11. 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)	$\leq 90$ and decrease from baseline $\geq 20$	$\geq 140$ and increase from baseline $\geq 20$
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	$\leq 50$ and decrease from baseline $\geq 10$	$\geq 90$ and increase from baseline $\geq 10$
Pulse (bpm) (Supine or sitting)	$< 50$ and decrease from baseline $\geq 15$	$> 100$ and increase from baseline $\geq 15$
Temperature	$< 96^{\circ}\text{F}$ ( $< 35.6^{\circ}\text{C}$ ) and decrease $\geq 2^{\circ}\text{F}$ ( $\geq 1.1^{\circ}\text{C}$ ) from baseline	$\geq 101^{\circ}\text{F}$ ( $\geq 38.3^{\circ}\text{C}$ ) and increase $\geq 2^{\circ}\text{F}$ ( $\geq 1.1^{\circ}\text{C}$ ) 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 body mass index (BMI) (<25 kg/m<sup>2</sup>, ≥25 to <30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup> to <40 kg/m<sup>2</sup>, and ≥40 kg/m<sup>2</sup>)
- 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  $\geq$  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.6.12](#).

**Table PYAB.6.12. Concomitant Medications of Interest Subgroup**

Drug name	ATC Code	Who Drug Preferred Term
Remdesivir	---	REMDESIVIR
Kaletra	J05AR	KALETRA
Lopinavir	J05AR	LOPINAVIR
Hydroxychloroquine	P01BA	HYDROXYCHLOROQUINE
Chloroquine	P01BA	CHLOROQUINE
Baricitinib	L04AA	BARICITINIB
Heparin	B01AB	HEPARIN
Fondaparinux	B01AX	FONDAPARINUX
Argatroban	B01AE	ARGATROBAN
Dexamethasone	H02AB	DEXAMETHASONE

Abbreviation: ATC = anatomical therapeutic chemical.

### Treatment Arms 7-9, 13-14

Subgroup analyses ( $\geq 12$  and  $< 18$  years old versus  $\geq 18$  years old) will be performed on all analyses and include descriptive statistics only.

Subgroup analyses for female participants who are pregnant at baseline will be performed on all analyses and include descriptive statistics only for treatment arms 13-14.

Subgroups for baseline age and baseline BMI will be defined as:

- baseline age groups
  - $\geq 12$  to  $< 18$ ,  $\geq 18$  to  $< 35$ ,  $\geq 35$  to  $< 45$ ,  $\geq 45$  to  $< 55$ ,  $\geq 55$  to  $< 65$ ,  $\geq 65$  years old
  - $< 65$ ,  $\geq 65$  years old
  - $< 65$ ,  $\geq 65$  to  $< 75$ ,  $\geq 75$  to  $< 85$ ,  $\geq 85$  years old; and
  - $\geq 12$  to  $< 18$ ,  $\geq 18$  years old

- baseline BMI groups
  - Group 1:
    - age <18 years old and
      - BMI <85th percentile for their age and gender based on Centers for Disease Control and Prevention (CDC) growth charts
      - BMI ≥85th percentile for their age and gender based on CDC growth charts
    - age ≥18 years old and
      - BMI <35 kg/m<sup>2</sup>
      - BMI ≥35 kg/m<sup>2</sup>, and
  - Group 2:
    - age <18 years old and
      - BMI <70th percentile for their age and gender based on CDC growth charts
      - BMI ≥70th to <80th percentile for their age and gender based on CDC growth charts
      - BMI ≥80th to <90th percentile for their age and gender based on CDC growth charts
      - BMI ≥90th percentile for their age and gender based on CDC growth charts
    - age ≥18 years old and
      - BMI <25 kg/m<sup>2</sup>
      - BMI ≥25 to <30 kg/m<sup>2</sup>
      - BMI ≥30 to <40 kg/m<sup>2</sup>, and
      - BMI ≥40 kg/m<sup>2</sup>

Subgroup analyses for high-risk status will not be performed for treatment arms 7-9 and 13-14. Other subgroup analyses will be conducted only if there is sufficient sample size within the subgroups for treatment arms 7-9 and 13-14.

## 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 any 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:

$$P(\Delta_{LY700mg} - \Delta_{placebo} > -0.3) > 0.8$$

or

$$P(\Delta_{LY7,000mg} - \Delta_{LY700mg} < -0.3) > 0.85$$

- Enrolling up to 100 additional participants to a new or existing dose arm to better characterize the dose-response relationship if:

$$P(\Delta_{LY700mg} - \Delta_{placebo} < -0.3) > 0.85$$

Note:  $\Delta$  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 [6.10.2.2](#).

### **Combination Therapy with LY3819253 and LY3832479 (Treatment Arm 6, 7, and/or 8)**

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.

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.

#### ***Treatment Arm 6***

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.

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.

#### ***Treatment Arms 7-9, 13-14***

Unblinded assessments of efficacy will be done separately for treatment arms 7-8; 8-9; and 13-14.

#### ***Treatment Arms 7 and 8***

Assessments will begin when all participants for treatment arm 7 and concurrently enrolled treatment arm 8 complete the Day 29 visit. Equal allocation to treatment arms 7 and 8 is planned.

#### ***Treatment Arms 8 and 9***

Assessments will begin when all participants for treatment arm 8 and participants from treatment arm 9 complete the Day 29 visit.

Additional participants will be enrolled in treatment arm 8 to ensure at least a 33% increase in placebo participants and adequate placebo control for the primary comparison of treatment arms 8 and 9.

#### *Treatment Arms 13 and 14*

Assessments will begin when all participants from treatment arms 13 and 14 complete the Day 29 visit.

#### **Safety Reviews**

Safety reviews will occur as specified in the Data Monitoring Committee (DMC) charter.

#### **PK/PD**

A limited number of pre-identified individuals may gain access to unblinded data, as specified in the blinding and unblinding plan prior to the primary lock, in order to initiate the population PK/PD model development processes. Following the database lock, the sponsor will be unblinded to analyze and report the data.

#### **Unblinding**

Unblinding details are specified in a separate blinding and unblinding plan.

#### **6.15.2. Data Monitoring Committee/Assessment Committee**

To minimize any bias introduced into the analysis of the study results, analysis plans will be finalized and approved prior to the interim analyses.

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.

Unblinding details are specified in a separate unblinding plan document.

#### **Treatment Arms 1-4, and 6**

The sponsor will form an AC to analyze the interim study data. 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.

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

#### **Treatment Arms 7-9, 13-14**

An external DMC will analyze the interim study data. The primary goal of the DMC is to assess the continuing safety of study participants.

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



## 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, SpO<sub>2</sub> 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 Questionnaire AUC 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 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 Questionnaire AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, baseline symptom total score 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.

#### **6.16.1.5. COVID-19-Related Clinical Status (COVID-19-Related Hospitalization or Death From Any Cause) by Days 60 and 85**

Similar methodology, as described in Section 6.10.1, will be utilized for treatment arms 7-9 and 13-14.

### ***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. Analyses of hospitalization events will be performed utilizing the safety population.

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 ( $\leq 8$  days versus  $>8$  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 ( $\leq 8$  days versus  $>8$  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 through Days 7, 11, 15, and 22.

If an event (hospitalization, ICU, or Mechanical Ventilation) occurs, the participant will be defined as having had the event for all subsequent timepoints evaluated. For example, if a participant experiences a hospitalization on day 8, their hospitalization status would be defined as:

- ‘No’ for the evaluation of Hospitalization through Day 7, and

- ‘Yes’ for Hospitalization through Days 11, 15, and 22.

No imputation will be used as these endpoints are based on running records, that is, an event is only reported if they are observed.

#### **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 ( $\pm 4$  days) in SARS-CoV-2 viral load between treatment with LY3819253, LY3819253/LY3832479, and placebo.

#### **6.16.2.10. SpO<sub>2</sub> Measurements of Interest**

The proportion of participants experiencing an SpO<sub>2</sub> measurement of interest ( $<96\%$ ,  $\geq 96\%$ ), ( $<92\%$ ,  $\geq 92\%$ ) 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<sub>2</sub> as a covariate in the model. Missing values will be considered to be missing completely at random (MCAR).

#### **6.16.2.11. Viral Load Plots**

The 7th octile (87.5th percentile) for the observed viral load data will be plotted across Day 1, Day 3, Day 5, Day 7, and Day 11 for all treatment arms. Additionally, the 4th (median), 5th (62.5th percentile), and 6th (75th percentile) octiles will be plotted separately.

The 4th, 5th, 6th, and 7th octile for viral load data adjusted for days from symptom onset at baseline will be plotted across Day 1, Day 3, Day 5, Day 7, and Day 11 for all treatment arms. Viral load participant data will be adjusted by multiplying the participants number of days from symptom onset at baseline by 0.158 (estimated mean daily decrease in viral load) and then adding the result to all of the participants non-zero viral load measurements. Note, that if the observed viral load is zero, it will not be adjusted.

#### **6.16.2.12. Proportion of Participants with Symptom Resolution on Days 22 and 29**

Similar methodology, as described in Section 6.10.3.11.8, will be utilized to analyze proportion of participants with symptom resolution on Days 22 and 29.

#### **6.16.2.13. Proportion of Participants with Symptom Improvement on Days 22 and 29**

Similar methodology, as described in Section 6.10.3.11.10, will be utilized to analyze proportion of participants with symptom improvement on Days 22 and 29.

### **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](http://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).
- Adverse event reporting is consistent with other document disclosures (eg, 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:

- respiration rate
- oxygen saturation
- systolic blood pressure (BP)
- pulse rate
- level of consciousness or new confusion, and
- temperature.

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO <sub>2</sub> Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO <sub>2</sub> 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; SpO<sub>2</sub> = oxygen saturation.

**Figure APP.1.1. NEWS2 scoring.**



NEWS 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.

**Figure APP.1.2. NEWS2 scoring clinical risk thresholds.**

Consciousness is only collected for participants who are inpatients, therefore, if there is a missing scoring for consciousness then it will be imputed as 0 (Alert).

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## Appendix 2. NIAID Scoring Scale

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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: COVID-19 = coronavirus disease 2019; NIAID = National Institute of Allergy and Infectious Diseases.

Leo Document ID = 5a039303-191f-4b91-97a6-640c63a9ba1c

Approver: PPD

Approval Date & Time: 13-Jan-2021 17:37:38 GMT

Signature meaning: Approved

## Revision History

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

<b>DOCUMENT HISTORY</b>	
<b>Document</b>	<b>Date</b>
Version 6	See approval date on cover page
Version 5	17-Dec-2020
Version 4	18-Sep-2020
Version 3	08-Sep-2020
Version 2	31-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.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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 <sub>2</sub> , 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)

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
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 <sub>2</sub> , respiratory rate, FiO <sub>2</sub>
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 <sub>2</sub> 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 SpO <sub>2</sub> endpoint using different cutoffs

### **Overall Rationale for the Revision on Version 2:**

New treatment arms 7 and 8 are added to this study with the combination of LY3819253 and LY3832479 and placebo.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
4.1 Primary Objective	Added primary endpoint for treatment arms 7 and 8	Addition of new treatment arms
4.2 Secondary Objectives	Added secondary endpoints for treatment arms 7 and 8	Addition of new treatment arms
5.1.3 Double-Blind Treatment and Assessment Period	Added treatment arms 7 and 8	Addition of new treatment arms
5.2 Determination of Sample Size	Added text for the sample size for treatment arms 7 and 8	Addition of new treatment arms
6.1 General Considerations	Added text for treatment arms 7 and 8. Added text.	Addition of new treatment arms. Clarification of text.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
6.7 Participant Characteristics	Added text for treatment arms 7 and 8. Clarified the definition of high-risk status for treatment arms 1-4 and 6.	Addition of inclusion criterion #27 for treatment arms 7 and 8
6.10 Efficacy Analysis	Added text	Addition of new treatment arms
6.10.1 Primary Outcome and Methodology	Added text for primary endpoint and methodology for treatment arms 7 and 8	Addition of new treatment arms
6.10.2.3. Sensitivity Analysis for Treatment Arms 7 and 8	Added a section for the sensitivity analysis for the primary endpoint for treatment arms 7 and 8	Addition of new treatment arms
6.10.3.3 SARS-CoV-2 Clearance at Days 7, 11, 15, and 22	Added text.	Clarification of text.
6.10.3.5 Symptom Resolution	Added text.	Clarification of text. Added data collection modality subgroup analysis.
6.10.3.7 Symptom Improvement	Added text.	Clarification of text. Added data collection modality subgroup analysis.
6.10.3.9 COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 29, 60, and 85	Added text.	Clarification of text.
6.10.3.11 Additional Secondary Efficacy Analyses for Treatment Arms 7 and 8	Added a section for the additional secondary efficacy endpoints for treatment arms 7 and 8	Addition of new treatment arms
6.12 Safety Analyses	Removed text.	Clarification of text.
6.13 Subgroup Analyses	Added text for treatment arms 7 and 8	Change in inclusion criteria for treatment arms 7 and 8
6.15.1 Interim Analyses	Added text for interim analyses planned for treatment arms 7 and 8	Addition of new treatment arms
6.16.1.3 Symptom Questionnaire AUC through Day 29	Updated text.	Clarification of text.
6.16.2.8 Proportions of Participants Hospitalized, Admitted to the ICU, Requiring Mechanical Ventilation	Added text.	Clarification of text.
6.6.2.11 Viral Load Plots	Added text	Added exploratory viral load plots
Appendix 1. NEWS2 Scoring Scale	Added text.	Added text to clarify how missing consciousness data will be handled in the analysis.

### **Overall Rationale for the Revision on Version 3:**

Clarifications to the analysis population used to analyze coronavirus disease 2019 (COVID-19)-related deterioration and hospitalization events. Clarifications on the analysis population and analyses with respect to patients with missing baseline efficacy assessments.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
6.1.1 Analysis Populations	<ul style="list-style-type: none"> <li>Clarified definition of the efficacy population to be consistent with what is defined in the protocol.</li> <li>Clarified use of safety population to include deterioration and hospitalization events in the population table.</li> </ul>	Alignment with protocol. Clarification of text.
6.1.4 Analysis Methods	Clarified that patients with missing baseline measures will be excluded from the corresponding analyses of change from baseline.	Clarification of text describing methodology.
6.3.3 Mixed-Effects Model Repeated Measures (MMRM)	Clarified that patients with missing baseline measures will be excluded from the corresponding analyses of change from baseline.	Clarification of text describing methodology.
6.10.3.9 COVID-19-Related Deterioration	Clarified that the safety population will be utilized to analyze COVID-19-related deterioration.	Clarification of text.
6.10.3.11 Additional Secondary Efficacy Analyses for Treatment Arms 7 and 8	Clarified that the safety population will be utilized to analyze COVID-19-related deterioration.	Clarification of text.
6.16.2 Additional Exploratory Analyses not Defined in the Protocol	Clarified that the analyses of hospitalization events will utilize the safety population.	Clarification of text.

#### **Overall Rationale for the Revision on Version 4:**

New primary endpoints were defined for treatment arms 7 through 9.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
4.1 Primary Objective	Added the co-primary endpoint of the proportion of participants who experience a COVID-19 hospitalization or death	Alignment with protocol amendment f.
4.2 Secondary Objectives	Clarified secondary endpoints and made modifications to secondary endpoints, clarified the key secondary endpoints.	Alignment with protocol amendments f-i. Modified to Phase 3 endpoints.
4.3 Exploratory Objectives	Clarified exploratory endpoints.	Alignment with protocol amendments f-j.
5.1.3 Double-Blind Treatment and Assessment Period	Added treatment arm 9.	Alignment with protocol amendment i.
5.2 Determination of Sample Size	Added sample size for treatment arm 9.	Alignment with protocol amendment i.
5.3.1 Randomization	Added randomization for treatment arms 7-9	Alignment with protocol amendments f-i.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
5.3.2 Blinding	Clarified text	Alignment with protocol amendment i.
6.1. General Considerations	Added descriptive statistics for adolescent versus adult participants. Clarified that BMI criteria for high-risk status is $\geq 30$ .	Inclusion of adolescent participants in the protocol amendment f-i.
6.1.1 Analysis Populations	Add treatment arm 9.	Alignment with protocol amendment i.
6.1.4 Analysis Methods	Added Bayesian methodology and added that multiplicity adjustments will be done for treatment arms 7-9	Alignment with protocol amendment i.
6.3.2 Last Observation Carried Forward (LOCF)	Removed section	Not needed
6.3.2 Modified Non-Responder Imputation (mNRI)	Added section	Clarified this is used in viral clearance analyses
6.3.5 Modified Last Observation Carried Forward	Clarified that this imputation is not used in change from baseline symptom score analyses.	Clarification
6.5 Multiple Comparisons/Multiplicity	Added that multiplicity is done from treatment arms 7-9	Added for Phase 3 endpoints.
6.7 Participant Characteristics	Clarified analyses for adolescents.	Inclusion of adolescent participants in the protocol amendment f.
6.10 Efficacy Analyses	Removed duplicated text	Removed duplicated text
6.10.1 Primary Outcome and Methodology	Added analysis methodology for treatment arms 7-9.	Alignment with protocol amendment f-i.
6.10.2.1 Dose Response Modeling for Treatment Arms 1-4 and 6	Clarified this is only for treatment arms 1-4 and 6	Clarification
6.10.2.2 Bayesian Modeling	Added text for treatment arms 7-9	Alignment with protocol amendment i.
6.10.3.11 Secondary Efficacy Analyses for Treatment Arms 7-9	Updated section to align with the secondary objectives for treatment arms 7-9	Alignment with protocol amendment f-i.
6.11 Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods	Removed content related to noncompartmental analysis methods	Descriptive analysis will be reported
6.12 Safety Analyses	Clarified text	Clarified text
6.13 Subgroup Analyses	<ul style="list-style-type: none"> <li>Clarified analyses for adolescents.</li> <li>Clarified analyses for treatment arms 7-9</li> </ul>	Alignment with protocol amendment f-i.
6.15.1 Interim Analyses	Updated text for Treatment arms 7-9	Alignment with protocol amendment f-i.
6.15.2 Data Monitoring Committee/Assessment Committee	Updated text for Treatment arms 7 and 8	Alignment with protocol amendment f-i.
6.16.2.11 Viral Load Plots	Clarified text	Clarified text
6.16.2.12 Proportion of Participants with Symptom Resolution on Days 22 and 29	Added Section	Moved to exploratory analyses
6.16.2.13 Proportion of Participants with Symptom Improvement on Days 22 and 29	Added Section	Moved to exploratory analyses



## Overall Rationale for the Revision on Version 5:

New treatment arms 13 and 14 added per protocol amendment (j).

Section # and Name	Description of Change	Brief Rationale
4.1 Primary Objective	Added objective for treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification
4.2 Secondary Objectives	Added objectives for treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification
4.3 Exploratory Objectives	Added objectives for treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification
5.1.3 Double-Blind Treatment and Assessment Period	Added treatment arms 13 and 14	Protocol amendment (j)
5.2 Determination of Sample Size	Added treatment arms 13 and 14	Protocol amendment (j)
6.1 General Considerations	Added treatment arms 13 and 14  Added analyses for pregnant women	Protocol amendment (j)  Protocol amendment (j) now allows pregnant women to participate in the study
6.1.1 Analysis Populations	Added descriptions for treatment arms 13 and 14  Added a per-protocol population	Protocol amendment (j)  Additional sensitivity analyses
6.5 Multiple Comparisons/Multiplicity	Clarified that death includes death from all causes	Clarification
6.7 Participant Characteristics	Added treatment arms 13 and 14  Added analyses for pregnant women	Protocol amendment (j)  Protocol amendment (j) now allows pregnant women to participate in the study
6.10 Efficacy Analyses	Added analysis details for treatment arms 13 and 14	Protocol amendment (j)
6.10.1 Primary Outcome and Methodology	Added analysis details for treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification
6.10.2.2 Bayesian Modeling	Added treatment arms 13 and 14	Protocol amendment (j)

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
	Clarified that death includes death from all causes	Clarification
6.10.3.9 COVID-19-Related Deterioration (COVID-19-Related Hospitalization, Emergency Room, or Death from Any Cause by Day 29, 60, and 85)	Clarified that death includes death from all causes	Clarification
6.10.3.11 Secondary Efficacy Analyses for Treatment Arms 7-9, 13-14	Added treatment arms 13 and 14	Protocol amendment (j)
6.10.3.11.4 Time to SARS-CoV-2 Clearance	Added treatment arms 13 and 14	Protocol amendment (j)
6.13 Subgroup Analyses	Added treatment arms 13 and 14  Added analyses for pregnant women	Protocol amendment (j)  Protocol amendment (j) now allows pregnant women to participate in the study
6.15.1 Interim Analyses	Added treatment arms 13 and 14  PK/PD and unblinding sections were added	Protocol amendment (j)  Clarification
6.15.2 Data Monitoring Committee/Assessment Committee	Added treatment arms 13 and 14	Protocol amendment (j)
6.16.1.5 COVID-19-Related Clinical Status (COVID-19-Related Hospitalization or Death from any cause) by Day 60 and 85	Added treatment arms 13 and 14  Clarified that death includes death from all causes	Protocol amendment (j)  Clarification