Protocol J2W-MC-PYAB (m)

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

NCT04427501

Approval Date: 02-Mar-2021

Title Page

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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: m

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 (m) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 02-Mar-2021 GMT

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (l)	03-February-2021
Amendment (k)	20-January-2021
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 m

Overall Rationale for the Amendment:

This amendment addresses the removal of treatment arms 16 and 17. Treatment arms 16 and 17 were planned to evaluate shorter administration times. This evaluation will now take place in PYAB addendum 3.0 with treatment arms 20 and 21. As a result, references to treatment arms 16 and 17 in the main protocol were removed and the objectives and endpoints for treatment arms 13-14 and 18-19 were separated.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3.2 Schedule of Activities (SoA) 3.0 Objectives and Endpoints 4.1.1 Design Outline 4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria 6.1.2 Temporary Stopping Criteria 8.2.2 Vital Signs 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.4 Statistical Analyses 9.4.2 Primary Endpoints 9.4.3.1 Key Secondary Endpoints 9.4.3.2 Safety 9.4.3.3 Additional Secondary Endpoints 9.4.6 Subgroup Analyses 9.5 Interim Analyses 9.6 Data Monitoring Committee	Treatment arms 16 and 17 and related text were removed.	The evaluation of shorter administration times will now take place in the PYAB 3.0 addendum with treatment arms 20 and 21.
1.1 Synopsis 3.0 Objectives and Endpoints	Treatment arms 13-14 and 18-19 objectives and endpoints were separated and updated.	The treatment arms 13-14 and 18-19 will be analyzed separately. Endpoints updated for the removal of treatment arms 16-17 and also for clarity.
1.1 Synopsis 1.2 Schema 4.1.1 Design Outline	Updated note to indicate that the protocol addenda include treatment arms for this study.	Generalized the statement to avoid future amendments if changes were made in the protocol addenda.
4.3 Justification for Dose	Added new subheadings and specify the subcutaneous dose	For clarification
5.1 Inclusion Criteria	Criterion #5 Replaced “agreements and guidance” with “requirements	Section 10.4 contains reproductive and contraceptive requirements.
9.1 Statistical Hypotheses	Updated hypothesis for treatment arms 13-14 and added hypothesis for 18-19.	Separated objectives and endpoints
9.2 Sample Size Determination	Updated text for treatment arms 13-14 and 18-19	New objectives and endpoints
9.4 Statistical Analyses	Key secondary endpoints of overall clinical status will use data from “multiple” treatment arms instead of “all”.	Updated analysis.
9.4.2 Primary Endpoints	Updated text for treatment arms 13-14 and 18-19	New objectives and endpoints

Section # and Name	Description of Change	Brief Rationale
9.4.3.1 Key Secondary Endpoints	Updated text for treatment arms 13-14 and 18-19	Updated objectives and endpoints
9.4.3.3 Additional Secondary Endpoints	Updated text for treatment arms 13-14 and 18-19	Updated objectives and endpoints
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Phase 2/3 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
Primary	
Characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on SARS-CoV-2 viral load and viral clearance	Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load
Secondary The secondary objectives are to characterize the effect of LY3819253, and LY3819253 in combination with LY3832479, compared to placebo on…	
• safety	• Safety assessments such as AEs and SAEs
• SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤ 8 days of symptoms prior to randomization
• symptom resolution	• Time to symptom resolution

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

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

Treatment arms 7-9

Objectives	Endpoints
Primary	
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 ≥24 hours of acute care) or death from any cause by Day 29.
Key Secondary The key secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on…	
• the reduction of SARS-CoV-2 viral load	• Change from baseline to Day 7 (±2 days)
• Persistently high SARS-CoV-2 viral load	• Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or o a COVID-19 related emergency room visit, or o death from any cause
• sustained symptom resolution	• time to sustained symptom resolution
Additional Secondary	
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• 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
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs

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

Treatment arms 13-14

Objectives	Endpoints
Primary	
Persistently high SARS-CoV-2 viral load for treatment arm 14 compared to treatment arm 13.	Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
Key Secondary	
Reduction of SARS-CoV-2 viral load for treatment arm 14 compared to treatment arm 13.	Change from baseline to Day 7 (±2 days)
Clinical status for treatment arm 14 compared to all high-risk placebo participants in treatment arms 8 and 13.	Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29.
Additional Secondary	
Clinical status for treatment arm 14 compared to all high-risk placebo participants in treatment arms 8 and 13.	Proportion (percentage) of participants who experience these events by Day 29 • COVID-19 related hospitalization (defined as ≥24 hours of acute care), or • a COVID-19 related emergency room visit, or • death from any cause
Treatment arm 13 compared to treatment arm 14 on…	
• sustained symptom resolution	• time to sustained symptom resolution
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• 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
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs, including date and time of events

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

Treatment arms 18-19

Objectives	Endpoints
Primary	
Persistently high SARS-CoV-2 viral load for treatment arm 19 compared to treatment arm 18	Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
Key Secondary	
Reduction of SARS-CoV-2 viral load for treatment arm 19 compared to treatment arm 18	Change from baseline to Day 7 (±2 days)
Overall participant clinical status for treatment arm 19 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29.
Additional Secondary	
Clinical status for treatment arm 19 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience these events by Day 29 • COVID-19 related hospitalization (defined as ≥24 hours of acute care), or • a COVID-19 related emergency room visit, or • death from any cause
Treatment arm 19 compared to treatment arm 18 on…	
• sustained symptom resolution	• time to sustained symptom resolution
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• 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
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs, including date and time of events

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-dose 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, 18-19.

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)

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. Treatment arms 1-9 and 13-14 are participant and investigator blinded. Treatment arms 18-19 are open label.

Number of Participants:

Treatment arms 1-4 and 6

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, 13-14, and 18-19

Participants in treatment arms 7-9, 13-14, and 18-19 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 treatment arms 13 and 14 is approximately 400 participants randomized 2:3, placebo:combination of LY3819253 and LY3832479.

The planned sample size for treatment arms 18 and 19 is approximately 460 participants per treatment arm.

Intervention Groups and Duration:

This table describes the planned treatment arms.

Treatment arms	Dose	Intervention	Route of Administration
1	---	Placebo	Intravenous
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	
18	700 mg + 1400 mg	LY3819253+LY3832479	
19	250 mg + 500 mg	LY3819253+LY3832479	Subcutaneous

NOTE: PYAB protocol addenda also include treatment arms for this study.

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

Participants will receive intervention on Day 1, 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.

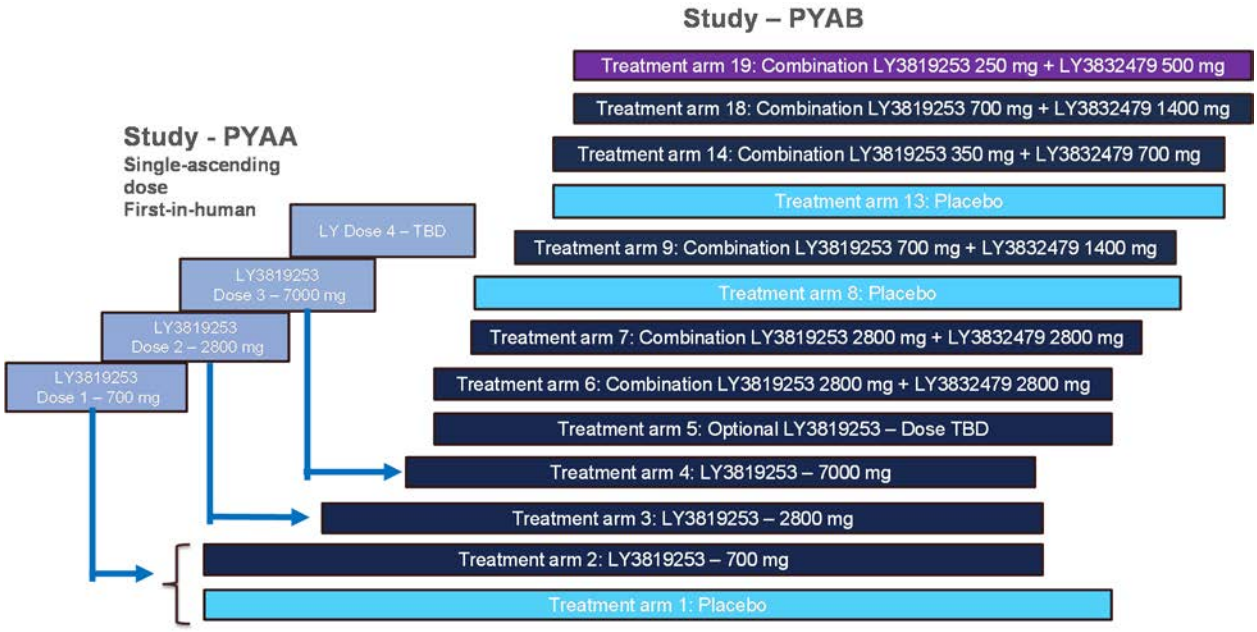
Treatment arms 18-19 are open-label.

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, 13-14, and 18-19.

1.2. Schema



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

NOTE: Treatment arms 1-9, 13-14, and 18 are administered as an intravenous infusion.
Treatment arm 19 is administered as subcutaneous injection.
PYAB protocol addenda also include treatment arms for this study.

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**													ED	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**	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	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**													ED	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**	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	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. **Screening visit only**: SpO2 while breathing room air. Data not collected on CRF. **Day 1** timing: • immediately before the infusion • every 15 minutes during the infusion, as possible, and • every 30 minutes for 2 hours after the infusion. During infusion, only record pulse rate, BP and SpO2. Automation may be used. See Section 8.2.2 for data collected on CRF. **All other study days:** once daily.

Schedule of Activities for Treatment Arms 1-4 and 6																		
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**	**15**	**18**	**22**	**25**	**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	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: • Emergency room visits • hospitalized • ICU admittance, • Extended care facility admittance, and • discharge
Clinical status and concomitant procedures if participant is hospitalized			Daily if hospitalized												X	X			Documentation from hospital records is acceptable. Includes: consciousness status (ACVPU), limitation on activities due to COVID-19, and requirements for • Ongoing hospital medical care • Supplemental oxygen • Non-invasive ventilation or high flow oxygen device • Mechanical ventilation • ECMO, or • Additional organ support (e.g. pressors, renal replacement).

Schedule of Activities for Treatment Arms 1-4 and 6																			
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**	**15**	**18**	**22**	**25**	**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	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
• C-reactive protein (CRP); high - sensitivity • Ferritin • D-dimer • Procalcitonin • Troponin		X		X						X				X	X				Day 1: before IV infusion All other days: sample may occur at any time during the day No sample needed if participant is hospitalized Lilly-designated central laboratory

Schedule of Activities for Treatment Arms 1-4 and 6																			
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**	**15**	**18**	**22**	**25**	**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	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**													ED	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**	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	2	2	2	2	2	2	2	2	4	4	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
Randomization and Dosing																			
Randomization		X																	

Schedule of Activities for Treatment Arms 1-4 and 6																		
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**	**15**	**18**	**22**	**25**	**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	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, 18-19

This SoA is for participants in treatment arms 7 through 9, and 13 and 14, 18 and 19.

Schedule of Activities for Treatment Arms 7-9, 13-14, 18-19																
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, 18-19																
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, 18-19															
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	X	Documentation of hospital-based exam is acceptable. Record SpO2 while participant is at rest. **Screening visit only**: SpO2 while breathing room air. Data not collected on CRF. **IV dose Day 1 timing:** • immediately before administration • every 15 minutes during the infusion, as possible and applicable • if infusion is <15 minutes, immediately following completion of infusion • every 30 minutes for 1 hour after the administration. During infusion, only record pulse rate, BP and SpO2. Automation may be used. **SQ dose Day 1 timing:** • immediately before injection, and • every 30 minutes for 1 hour after the administration. **All other study days:** once daily. See Section 8.2.2 for data collected on CRF.

Schedule of Activities for Treatment Arms 7-9, 13-14, 18-19															
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: • Emergency room visits • hospitalized • ICU admittance, • Extended care facility admittance, and • Discharge
Clinical status and concomitant procedures if participant is hospitalized			Daily if hospitalized							X	X	X	X			Documentation from hospital records is acceptable if hospitalized at any time. Includes: • NEWS 2 Consciousness (ACVPU) • Limitation on activities due to COVID-19 using the Patient Global Assessment for Daily Activities of Physical Function • Concomitant procedures of interest for organ support (e.g., proning, renal support) • Additional organ support (e.g. pressors, renal replacement). Oxygen support and vital signs data should be collected while participant is hospitalized.

Schedule of Activities for Treatment Arms 7-9, 13-14, 18-19																
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																
Laboratory Tests and Sample Collection																
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
• C-reactive protein (CRP); high - sensitivity • Ferritin • D-dimer • Procalcitonin • Troponin		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, 18-19															
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 administration. 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	X	**Day 1** IV infusion: before IV infusion (adults only) and within 30 minutes after the end of infusion . SQ injection: anytime after dosing, preferably as close to the end of the visit as possible. Day 3 sample for SQ dose, treatment arm 19, only. 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, 18-19																
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 sample needed for Day 3 SQ dose. 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

Schedule of Activities for Treatment Arms 7-9, 13-14, 18-19																
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																
Randomization and Dosing																
Randomization		X														
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; IV = intravenous; 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; SQ = subcutaneous; WOCBP = women of child-bearing potential.

2. Introduction

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

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

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

2.1. Study Rationale

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

2.2. Background

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

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

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

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 and Injection Site 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.

There is also potential for injection site reactions (ISRs) with subcutaneous dosing.

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

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

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

3.2. Treatment arms 7-9

Objectives	Endpoints
Primary	
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 ≥24 hours of acute care) or death from any cause by Day 29.
Key Secondary The secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on…	
• the reduction of SARS-CoV-2 viral load	• Change from baseline to Day 7 (±2 days)
• persistently high SARS-CoV-2 viral load	• Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or o a COVID-19 related emergency room visit, or o death from any cause
• sustained symptom resolution	• time to sustained symptom resolution
Additional Secondary	
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• 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
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs

Objectives	Endpoints
Exploratory	
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60 and 85 o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or o death from any cause
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.

3.3. Treatment arms 13-14

Objectives	Endpoints
Primary	
Persistently high SARS-CoV-2 viral load for treatment arm 14 compared to treatment arm 13	Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
Key Secondary	
Reduction of SARS-CoV-2 viral load for treatment arm 14 compared to treatment arm 13	Change from baseline to Day 7 (±2 days)
Clinical status for treatment arm 14 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29.
Additional Secondary	
Clinical status for treatment arm 14 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience these events by Day 29 • COVID-19 related hospitalization (defined as ≥24 hours of acute care), or • a COVID-19 related emergency room visit, or • death from any cause
Treatment arm 13 compared to treatment arm 14 on…	
• sustained symptom resolution	• time to sustained symptom resolution
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• 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
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs, including date and time of events

Objectives	Endpoints
Exploratory	
Treatment arm 14 compared to treatment arms 8 and 13 on overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60 and 85 o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or o death from any cause
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.

3.4. Treatment arms 18-19

Objectives	Endpoints
Primary	
Persistently high SARS-CoV-2 viral load for treatment arm 19 compared to treatment arm 18	Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
Key Secondary	
Reduction of SARS-CoV-2 viral load for treatment arm 19 compared to treatment arm 18	Change from baseline to Day 7 (±2 days)
Overall participant clinical status for treatment arm 19 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29.
Additional Secondary	
Clinical status for treatment arm 19 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience these events by Day 29 • COVID-19 related hospitalization (defined as ≥24 hours of acute care), or • a COVID-19 related emergency room visit, or • death from any cause
Treatment arm 19 compared to treatment arm 18 on…	
• sustained symptom resolution	• time to sustained symptom resolution
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• 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
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs, including date and time of events

Objectives	Endpoints
Exploratory	
Treatment arm 19 compared to treatment arms 8 and 13 on overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60 and 85 o COVID-19 related hospitalization (defined as ≥24 hours of acute care), or o death from any cause
Characterize the pharmacokinetics of LY3819253 in combination with LY3832479	Mean concentration of LY3832479 in presence of LY3819253 on Day 29

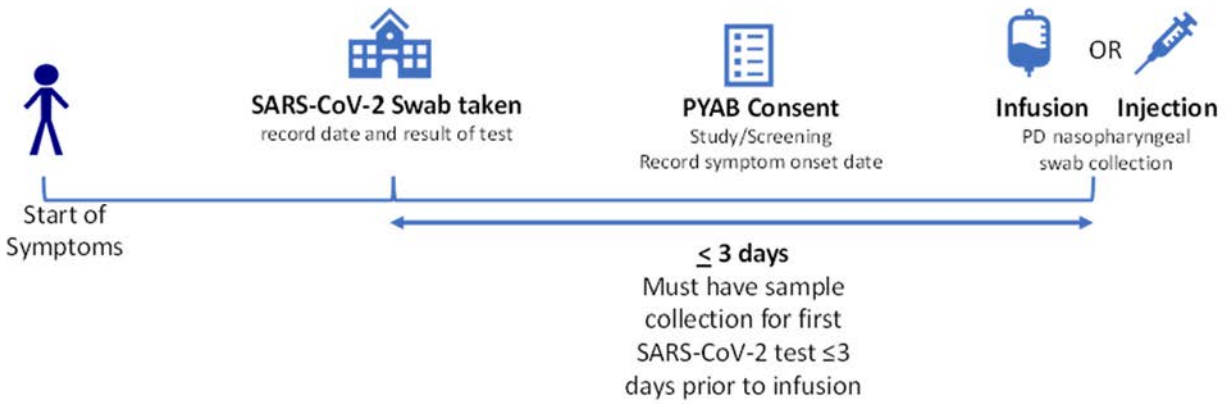
Abbreviations: AE = adverse event; SAE =serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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-dose sample collection.

Treatment Arms

This table describes the planned treatment arms.

Treatment arms	Dose	Intervention	Route of Administration
1	---	Placebo	Intravenous
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	
18	700 mg + 1400 mg	LY3819253+LY3832479	
19	250 mg + 500 mg	LY3819253+LY3832479	Subcutaneous

NOTE: PYAB protocol addenda also include treatment arms for this study.

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.

Treatment arms 18-19 are open-label.

For treatment arm 19, a safety review will occur after approximately 20 participants are dosed and have at least 24 hours of safety data, before continuing dosing subsequent participants. The investigator and the Lilly sponsor team are responsible for determining if safety is acceptable to continue dosing subsequent participants.

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, 18-19.

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.

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

Post-treatment follow-up

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

4.2. Scientific Rationale for Study Design

Overall Design

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

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

Due to emerging data, participants will no longer receive placebo and new potential participants will have the opportunity to receive active intervention.

Treatment arms 18-19 are open-label because of the change in primary endpoint to a more objective evaluation of change in viral load. This also removes the need for a double-dummy design requiring every participant to receive an infusion and subcutaneous injections.

Safety reviews are included for treatment arm 19 to minimize the risk of any unanticipated safety concerns in participants before fully enrolling the treatment arm.

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). 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* IC90 of viral cell-entry neutralization in the lung tissue for at least 28 days in 90% of the participant population. The maximum dose of 7000 mg is selected due to uncertainty in model predicted PK concentrations, viral load reduction and consideration of infusion volume in participants. The dose will not exceed 7000 mg in this study.

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

LY3819253 + LY3832479

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

2800 mg LY3819253 and 2800 mg LY3832479

The dose selection of 2800 mg LY3819253 and 2800 mg LY3832479 is based on PK and PK/PD modeling to have a sustained lung concentration above the *in vitro* IC90 of viral cell-entry neutralization (95th percentile of the estimates) 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 95th 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.

Addition of adolescents

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 ≥ 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 ≥ 40 kg. Thus, adolescent participants will receive the same dose level as the adult participants.

700 mg LY3819253 and 1400 mg LY3832479

In treatment arms 9 and 18, 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 IC50 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 IC90 of viral neutralization for at least 28 days in 90% of the participant population.

350 mg LY3819253 and 700 mg LY3832479

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).

250 mg LY3819253 and 500 mg LY3832479

Treatment arm 19 participants will receive a combination of 250 mg LY3819253 and 500 mg LY3832479. The subcutaneous doses were selected based on PK/PD modeling as described above, in addition to interim PK, viral load, symptoms, clinical outcome and safety data from Study PYAH.

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 ≥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 ≤3 days prior to start of the infusion

Sex

5. Are males or females, including pregnant females
   Reproductive and Contraceptive requirements are 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, 18-19

27. Are ≥18 years of age and satisfy at least one of the following at the time of screening
    - Are pregnant
    - Are ≥ 65 years of age
    - Have a BMI ≥ 35
    - Have chronic kidney disease
    - Have type 1 or type 2 diabetes
    - Have immunosuppressive disease
    - Are currently receiving immunosuppressive treatment, or
    - Are ≥ 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
    - Are pregnant
    - Have a BMI ≥85th percentile for their age and gender based on CDC growth charts, 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 SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥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 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.

Intervention Name	Placebo	LY3819253					LY3832479			
Dose Formulation	0.9% sodium chloride solution	Solution								
Dosage Level(s) (mg)	Not applicable	250	350	700	2800	7000	500	700	1400	2800
Use	placebo	experimental								
IMP and NIMP	IMP	IMP								
Sourcing	Commercially available 0.9% sodium chloride solution	From Lilly								
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately								

Abbreviations: IMP = investigational medicinal product.

Infusion and subcutaneous dose preparation 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.

Subcutaneous injections will be administered in the abdomen. The dose will be administered as 3 injections of 2-mL each. Different quadrants of the abdomen should be used for each injection. Record the package number and location of administration.

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.

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

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

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

6.1.2. Temporary Stopping Criteria

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

Treatment arms 1-9, 13-14

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, and 18.

Treatment arm 19

For the first 20-30 participants administered intervention, dosing will be re-evaluated if these circumstances occur

- 3 or more participants develop AEs that are considered to be related to study treatment OR
- 1 or more participants develop AEs that are considered to be related to study treatment and are serious (SAEs) or graded as severe.

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

Adverse Event-related Information

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

Topic	Location
DAIDS table describing severity of reactions	Section 6.1.1.2
Definition of AEs	Section 10.3.1
Assessment of Intensity/Severity	Section 10.3.3

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, where applicable, 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 (≤8 days versus >8 days) and age at the time of screening (<18 years of age versus ≥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

For the blinded treatment arms, neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study.

This table describes general procedures for unblinding.

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

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.

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

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

8.2.2. Vital Signs

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

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

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, 18

This table outlines Day 1 vital signs data collection on the CRF in relation to the infusion for treatment arms 7-9, 13-14, and 18. 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.

Treatment arm 19

Vital signs data collection on the CRF will occur immediately before the subcutaneous injection, and at 30 minutes after the injection.

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 ≥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 6.1.1
Premedication for infusions	Section 6.1.1.1
Management of infusion reactions	Section 6.1.1.2
DAIDS table describing severity	Section 6.1.1.2
Treatment guidelines for infusion-related reactions	Section 6.1.1.2

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

8.3.8. Injection Site Reactions

For subcutaneous injections, manifestations of a local ISR may include erythema, induration, pain, pruritus, and edema. If an ISR is reported by a participant or site staff, the ISR CRF will be used to capture additional information about this reaction, for example, injection-site pain, degree and area of erythema, induration, pruritis and edema.

8.3.9. 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.

For treatment arm 14, the hypothesis is whether there is a difference in the proportion of participants with persistently high SARS-CoV-2 viral load at Day 7 compared to treatment arm 13.

For treatment arm 19, the hypothesis is non-inferiority in the proportion of participants with persistently high SARS-CoV-2 viral load at Day 7 compared to treatment arm 18.

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 treatment arms 13 and 14 is approximately 400 participants randomized 2:3, placebo:combination of LY3819253 and LY3832479.

Treatment arm 18

The planned sample size for treatment arm 18 is approximately 460 participants.

Treatment arm 19

The planned sample size for treatment arm 19 is approximately 460 participants.

Stratification

Participants will be stratified by

- duration since symptom onset category (≤8 days versus >8 days)
- age at the time of screening (<18 years of age versus ≥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 (± 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 (± 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 for these arms is based on the endpoint of proportion of participants with persistently high SARS-CoV-2 viral load at Day 7. A sample size of approximately 400 participants provides greater than 90% power to demonstrate that LY3819253 in combination with LY3832479 is statistically significantly better than placebo. This sample size calculation assumed a placebo event rate of 30% and a relative reduction of 60% for LY3819253 in combination with LY3832479, which were informed from available data on rates of persistently high SARS-CoV-2 viral load.

Treatment arms 18-19

The primary objective for these treatment arms is to demonstrate non-inferiority (NI) of treatment arm 19 compared to the active comparator treatment arm 18.

An NI boundary of 1.96 will be used, which is smaller than the inverse of the 97.5th percentile of the posterior distribution of the odds ratio (OR) for treatment arm 19 to treatment arm 18 for the Day 7 persistently high viral load endpoint. The posterior distribution of the OR was derived using a Bayesian hierarchical meta-analysis of PYAB data.

The NI margin of 1.96 ensures preservation of at least 50% of treatment arm 19 efficacy, estimated using the observed odds ratio. Additional details regarding the justification of the NI boundary of 1.96 will be provided in the statistical analysis plan (SAP).

The randomization of approximately 920 participants across treatment arms 18 and 19 provides 85% power to establish NI of treatment arm 19 compared to treatment arm 18. If Day 7 persistently high viral load status has an odds ratio of 1 for the comparison of arm 19, the upper bound of the 95% CI of the OR is $\leq$1.96.

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 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,
- 13 and 14, and
- 18 and 19.

Note, for the key secondary endpoints of overall clinical status the analysis will use data from multiple treatment arms.

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 (± 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

The primary endpoint is the overall participant clinical status, measured by the proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥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.

Treatment Arms 13-14

The primary endpoint is the difference in the proportion of participants with persistently high SARS-CoV-2 viral load at Day 7 between treatment arm 14 compared to treatment arm 13.

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

Treatment Arms 18-19

The primary endpoint is noninferiority in the proportion of participants with persistently high SARS-CoV-2 viral load at Day 7 between treatment arm 19 compared to treatment arm 18.

The primary analysis method will be a logistic regression with a primary success criterion of the upper bound of the 95% CI ≤1.96.

Full details will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Key Secondary Endpoints

Treatment arms 7-9

Key secondary endpoints for treatment arms 7-9 include

- Reduction of SARS-CoV-2 viral load measured by change from baseline to Day 7 (±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 ≥ 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.

Treatment arms 13-14 and 18-19

Key secondary endpoints include

- Reduction of SARS-CoV-2 viral load measured by change from baseline to Day 7 (±2 days), and
- Proportion (percentage) of participants who experience COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29

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.

For treatment arms 13-14, 18-19 post-administration observations and AEs will be evaluated.

For treatment arm 19, reported injection site reactions will be further characterized.

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 (± 4 days) in SARS-CoV-2 viral load among participants enrolled with ≤8 days of symptoms prior to randomization
- Time to symptom resolution
    - symptoms are scored as absent
- Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15 and 22
- Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15 and 22
- Time to symptom improvement
    - symptoms scored as moderate or severe at baseline are scored as mild or absent, AND
    - symptoms scored as mild or absent at baseline are scored as absent.
- Change in symptom score (total of ratings) from baseline to Days 7, 11, 15 and 22
- SARS-CoV-2 viral load and viral clearance including:

  - Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, and 22)
  - Time to SARS-CoV-2 clearance
  - SARS-CoV-2 viral load area under the concentration-time curve (AUC) assessed through Day 29
- Proportion (percentage) of participants who experience these events by Days 29, 60 and 85
  - COVID-19 related hospitalization (defined as ≥ 24 hours of acute care)
  - a COVID-19 related emergency room visit, or
  - death.

Treatment Arms 7–9

Additional secondary endpoints for treatment arms 7-9 include

- SARS-CoV-2 viral load reduction change from baseline to
  - Day 3 (+ 1 day)
  - Day 5 (± 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.

Treatment Arms 13–14, 18-19

Treatment arm 14 and treatment arm 19 will be compared to all high-risk placebo participants in pooled treatment arms 8 and 13, for proportion (percentage) of participants who experience these events by Day 29

- COVID-19 related hospitalization (defined as ≥24 hours of acute care), or
- a COVID-19 related emergency room visit, or
- death from any cause.

Additional secondary endpoints will compare

- Treatment arm 13 to treatment arm 14, and
- Treatment arm 19 to treatment arm 18.

The endpoints are

  - time to sustained symptom resolution
  - SARS-CoV-2 viral load reduction change from baseline to

    - Day 3 (+ 1 day)
    - Day 5 (± 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
- high risk status for severe COVID-19 illness (treatment arms 1-4, 6), or
- SARS-CoV-2 vaccine status (treatment arms 13-14, 18-19).

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, 18-19

Unblinded assessments of efficacy will be done separately for treatment arms 7 and 8, 8 and 9, 13 and 14, and 18 and19.

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.

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

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.

Treatment Arms 13-14, 18-19

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

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 reconsenting guidelines as appropriate. Verbal reconsenting 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.

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

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

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

- The following study-specific clinical events related to COVID-19 are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug:
    - Hypoxemia due to COVID-19 requiring supplemental oxygen;
    - Hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices;

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

10.3.2. Definition of SAE

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

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

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording

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

Assessment of Intensity

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

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

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

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

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

SAE Reporting via Paper CRF

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

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

Women

Woman of Childbearing Potential (WOCBP)

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

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

Woman not of Childbearing Potential (WOCBP)

Women in the following categories are not considered WOCBP

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

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

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

3. Postmenopausal female is defined as, women with:
    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 ≥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

Hypersensitivity Tests	Notes Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
LY3819253 and LY3832479 anti-drug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3819253 and LY3832479 concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. Urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Collect a follow-up urine sample after approximately 4 weeks. **Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, collect a urine sample for N-methylhistamine testing.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **NOTE:** The basophil activation test is an in vitro cell based assay that only requires a serum sample. It is a surrogate assay for drug specific IgE but is not specific for IgE.
Complement (C3, C3a and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

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

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

Close Hepatic Monitoring

This table describes when close hepatic monitoring should occur.

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

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

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

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

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

Comprehensive Hepatic Evaluation

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

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

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

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

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

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

Additional Hepatic Data Collection (Hepatic Safety CRF)

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

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

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

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

Hepatic Evaluation Testing

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

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

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

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

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

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

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

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

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

10.8. Appendix 8: Abbreviations

Term	Definition
AC	assessment committee
ADA	anti-drug antibody
ADE	antibody-dependent enhancement
adolescent	Participant 12 to 17 years of age
assent	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.
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
CIOMS	Council for International Organizations of Medical Sciences
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of an intervention.
Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CTA	Clinical trial agreement
DMC	data monitoring committee
ECG	electrocardiogram
FiO2	fraction of inspired oxygen in the air
Enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Intervention	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IWRS	interactive web-response system
Legal representative	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.
NP	Nasopharyngeal
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK/PD	pharmacokinetics/pharmacodynamics
SAE	serious adverse event
SAP	statistical analysis plan
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SpO2	saturation of peripheral oxygen

10.9. Appendix 9: Protocol Amendment History

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

Amendment l: 03 February 2021

Overall Rationale for the Amendment:

This amendment addresses changes in response to emerging data. As a result, participants will no longer receive placebo, the sample size for treatment arms 13 and 14 is reduced, open-label treatment arms 16-19 are added and objectives and endpoints changed.

Treatment arms 16 and 17 will evaluate faster infusion times using sentinel dosing.

Treatment arm 18 will act as the active comparator for treatment arms 14, 16-17 and 19.

Treatment arm 19 will evaluate the efficacy and safety of subcutaneous dosing.

Treatment arms 16-19 will not be blinded because of the change in primary endpoint to a more objective evaluation of change in viral load. This also removes the need for a double-dummy design requiring every participant to receive an infusion and subcutaneous injections.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Removed treatment arms 13-14 from most headers and sub-headings where it was grouped with treatment arms 7-9.	Treatment arm 13-14 was added to new sections with new treatment arms 16-19.
1.1 Synopsis	New Objectives/Endpoints table for treatment arms 13-14, 16-19	Change in primary endpoint to viral load for treatment arms 14, 16-18. Addition of new treatment arms and comparison analysis
1.1 Synopsis	Updated Treatment and Assessment Period	Addition of new treatment arms
1.1 Synopsis	Updated Disclosure Statement	Addition of new open-label treatment arms.
1.1 Synopsis	Updated Number of Participants	Addition of new treatment arms and new objectives and endpoints
1.1 Synopsis	Updated Intervention Groups and Duration table. Added text for new treatment arms.	Addition of new treatment arms
1.1 Synopsis	Updated Data Monitoring Committee treatment arms	Addition of new treatment arms
1.2 Schema	Updated the study schema	Added new treatment arms and associated note
1.3.2 Schedule of Activities	Added treatment arms 16-19 to this SoA	Treatment arms 16-19 will follow this SoA
1.3.2 Schedule of Activities	Vital Sign – updated text to include SQ dosing.	Addition of treatment arm 19

Section # and Name	Description of Change	Brief Rationale
1.3.2 Schedule of Activities	Pharmacokinetic (PK) sample – clarified sample collection timing after the end of IV infusion	Site feedback that this needed clarification.
1.3.2 Schedule of Activities	Pharmacokinetic (PK) sample - added Day 3 sample and sample times for SQ dose.	Needed to complete the PK profile for SQ dose. Addition of SQ dose.
1.3.2 Schedule of Activities	Immunogenicity sample – clarified that no sample is needed to match the Day 3 PK sample for SQ dose.	Day 3 sample not needed to match the Day 3 PK sample
2.3 Benefit/Risk Assessment	Added the risk of injection site reactions (ISRs).	Addition of SQ dose
3.3 Objectives and Endpoints	Added new objectives and endpoints table for treatment arms 13-14, 16-19	Change in primary endpoint to viral load for treatment arms 14, 16 and 17 compared to treatment arm 18. Addition of new treatment arms and comparison analysis
4.1.1 Design Outline	Updated Figure 2 participant flow diagram	Included injections for SQ dosing
4.1.1 Design Outline	Treatment and Assessment Period – updated last bullet from post-infusion to post-dose	Addition of SQ dosing
4.1.1 Design Outline	Updated Treatment arm table	Addition of new treatment arms
4.1.1 Design Outline	Added treatment arms 16-19 will be open-label. Added text and a new table to describe the sentinel dosing for treatment arms 16 and 17.	New treatment arms and primary endpoint. Treatment arms 16 and 17 will evaluate shorter infusion times using sentinel dosing to ensure safety is acceptable.
4.1.1 Design Outline	Added text to describe that treatment arm 18 will be an active comparator, and for the safety review for treatment arm 19	Participants will no longer receive placebo. A safety review will occur for participants in treatment arm 19 receiving SQ dose
4.1.1 Design Outline	Added new treatment arms for visit types	Addition of new treatment arms
4.2 Scientific Rationale for Study Design	Added text for participants no longer receiving placebo and description of open-label treatment arms. Added text for the multiple safety reviews for treatment arms 16-19	Emerging data. Safety reviews to minimize the risk of any unanticipated safety concerns before fully enrolling the treatment arms.
4.3 Justification for Dose	Added treatment arm 18 to the justification of the 700/1400 dose. Added treatment arms 16 and 17 for the 350/700 dose. Added treatment arm 19 for SQ dose.	Addition of new treatment arms.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Added new treatment arms for Criteria #27 and #28.	Addition of new treatment arms
5.1 Inclusion Criteria	Added "are pregnant" to criteria #27 and #28	Emerging data indicate that being pregnant is a risk factor for COVID-19 illness
6.1 Study Intervention(s) Administered	Updated first sentence to broaden scope	Introduction of SQ dosing in addition to IV infusion
6.1 Study Intervention(s) Administered	Updated the Study Intervention table with new dose levels	Addition of new treatment arms
6.1 Study Intervention(s) Administered	Added text for subcutaneous dosing	Addition of treatment arm 19
6.1.2 Temporary Stopping Criteria	Added stopping criteria for treatment arms 16-17 and 19.	These treatment arms will evaluate faster infusion times and SQ dosing.
6.2 Preparation/Handling/ Storage/Accountability	Updated text to accommodate new open-label treatment arms	Addition of new treatment arms.
6.3 Measures to Minimize Bias: Randomization and Blinding	Updated Blinding sub-section to accommodate new open-label treatment arms	Addition of new treatment arms
8.2.2 Vital Signs	Updated text for data collection on the CRF for new treatment arms	Addition of new treatment arms
8.3.8 Injection Site Reactions	New section for SQ dose	Addition of SQ dosing
8.3.9 Product Complaints	Renumbered section to 8.3.9 with addition of new Section 8.3.8 Injection Stie Reactions	
9.1 Statistical Hypotheses	Updated and added text for treatment arms 14, 16-18.	Addition of new treatment arms and new primary objective
9.2 Sample Size Determination	Updated sample size for treatment arms 13 and 14	New strategy for objectives and endpoints and analyses
9.2 Sample Size Determination	Added sample size for new treatment arms 16-19	Addition of new treatment arms
9.2 Sample Size Determination	Removed simulation information for previous treatment arms 13 and 14, and added simulation information for treatment arms 14, 16-19	Addition of new treatment arms
9.3 Populations for Analyses	Removed the row for Modified Efficacy population	No longer needed
9.4 Statistical Analyses	Updated treatment arms for analyses	Addition of new treatment arms
9.4.2 Primary Endpoint	Updated endpoint for treatment arms 14, 16-18	Treatment arm 13 is no longer needed for the primary endpoint. The addition of treatment arms.
9.4.3.1 Key Secondary Endpoints	Updated for new treatment arms	New endpoints per emerging data
9.4.3.2 Safety	Added text for new treatment arms	Post-administration observations and AEs will be evaluated for the new treatment arms.

Section # and Name	Description of Change	Brief Rationale
		Injection site reactions will be characterized.
9.4.3.3 Additional Secondary Endpoints	Added separate section for new treatment arms for clarity as some endpoints are different for the new treatment arms.	New treatment arms and endpoints
9.4.6 Subgroup Analyses	Added SARS-CoV-2 vaccine status	Participants who received a vaccine are allowed in the study
9.5 Interim Analyses	Updated for new treatment arms	Addition of new treatment arms
9.6 Data Monitoring Committee	Updated for new treatment arms	Addition of new treatment arms
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

Amendment k: 20 January 2021

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.

Section # and Name	Description of Change	Brief Rationale
	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

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.
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.

Section # and Name	Description of Change	Brief Rationale
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
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.

Section # and Name	Description of Change	Brief Rationale
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.

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
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 **±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

Section # and Name	Description of Change	Brief Rationale
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

Section # and Name	Description of Change	Brief Rationale
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

Section # and Name	Description of Change	Brief Rationale
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

Section # and Name	Description of Change	Brief Rationale
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 ≥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-approriate” 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

Section # and Name	Description of Change	Brief Rationale
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.

Section # and Name	Description of Change	Brief Rationale
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

Section # and Name	Description of Change	Brief Rationale
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 5th 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.

Section # and Name	Description of Change	Brief Rationale
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.

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

Section # and Name	Description of Change	Brief Rationale
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

Section # and Name	Description of Change	Brief Rationale
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

11. References

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Leo Document ID = 92915380-49a4-4e5f-9cd9-ad0612eb6ee6

Approver: PPD

Approval Date & Time: 02-Mar-2021 04:13:23 GMT

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Approver: PPD

Approval Date & Time: 02-Mar-2021 04:15:23 GMT

Signature meaning: Approved