Protocol: J2X-MC-PYAD(d)

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of LY3819253 Alone and in Combination With LY3832479 in Preventing SARS-CoV-2 Infection and COVID-19 in Skilled Nursing and Assisted Living Facility Residents and Staff; a NIAID and Lilly Collaborative Study

NCT04497987

Approval Date: 22-Jan-2021

Title Page

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Protocol Number: J2X-MC-PYAD; CoVPN #3501

Amendment Number: d

Compound: LY3819253

Study Phase: 3

Short Title: A Study to Evaluate LY3819253 alone and in combination with LY3832479 for the Prevention of SARS-CoV-2 infection and COVID-19; a NIAID and Lilly Collaborative Study

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 150440

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

Approval Date: 22-Jan-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (c)	04 Dec 2020
Amendment (b)	06 Nov 2020
Amendment (a)	27 Oct 2020
Original Protocol	28 Jun 2020

Amendment d

Overall Rationale for the Amendment:

This amendment will allow participants with COVID-19 to enroll in Part 3 (treatment only) of Study PYAD who have recovered from prior COVID-19 infection, or have received prior administration of convalescent plasma, monoclonal antibody, or vaccine for SARS-CoV-2. Inclusion will allow for collection of data to explore safety of treatment of LY3819253 alone or in combination with LY3832479 in any of these participant populations.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1 Part 1 and Prevention Cohort of Part 2	Updated "Prior treatments of special interest" to collect prior use of SARS-CoV-2 vaccine.	The SARS-CoV-2 vaccine is now allowed.
Section 1.3.2 Part 2 Treatment Cohort and Part 3		
2.2 Background	Added background on PYAB interim results.	Emerging data.
2.3 Benefit/Risk Assessment	Updated risk information for LY3819253.	Emerging data.
4.2 Scientific Rationale for Study Design	Added rationale for participants who have received the SARS-CoV-2 vaccine. Added language for Part 3 to reflect that participants who were in independent living situations at the facilities could be enrolled.	Vaccines are now available to the public and those who received a vaccine are allowed in the study. Clarification.
5.2 Exclusion Criteria	Updated Criteria 7, 8, 9, 11, 12, and 13.	This amendment will allow participants with COVID-19 to enroll in Part 3 (treatment only) of the study having recovered from prior COVID-19 infection, or having received prior administration of convalescent plasma, monoclonal antibody, or vaccine for COVID-19. Inclusion will allow for collection of data to explore safety of treatment of LY3819253 alone or in combination with LY3832479 in any of these participant populations.

Section # and Name	Description of Change	Brief Rationale
6.3 Measures to Minimize Bias: Randomization and Blinding	Added stratification factor for whether a participant received a vaccine or not prior to screening	The SARS-CoV-2 vaccine is now allowed
11 References	Added Chen et al. 2020 reference	Source for information in Section 2.3

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of LY3819253 alone and in combination with LY3832479 in Preventing SARS-CoV-2 infection and COVID-19 in Skilled Nursing and Assisted Living Facility Residents and Staff; a NIAID and Lilly Collaborative Study

Short Title: A Study to Evaluate LY3819253 alone and in combination with LY3832479 for the Prevention of SARS-CoV-2 infection and COVID-19; a NIAID and Lilly Collaborative Study

Rationale:

The efficient community spread of SARS-CoV-2 has resulted in the current pandemic of Coronavirus Disease – 2019 (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. Of all age groups, older adults have the greatest risk of severe COVID-19 and the associated complications (CDC 2020; Grabowski and Mor 2020).

Globally, there are many reports of the rapid spread of COVID-19 amongst residents of skilled nursing facilities following identification of an index case, with high associated rates of morbidity and mortality (Arons et al. 2020; Grabowski and Mor 2020; Graham et al. 2020). In the USA, at least 153,000 residents and employees of nursing homes have contracted COVID-19, accounting for 35% of the country's deaths (Werner et al. 2020). With over 1.3 million residents in nursing home care in the USA (CDC 2016), there is an urgent need for therapeutic strategies to prevent COVID-19 in these populations.

This study aims to evaluate the impact of LY3819253 alone and in combination with LY3832479 in preventing SARS-CoV-2 infection and COVID-19 in facility staff and residents in skilled nursing and assisted living facilities with a high risk of SARS-CoV-2 exposure.

Objectives and Endpoints
Part 1

To facilitate rapid prophylaxis and treatment of residents and facility staff, participants will be enrolled prior to assessment of baseline SARS-CoV-2 reverse transcription – polymerase chain reaction (RT-PCR) or serology results; thus, multiple analysis populations will exist. This includes separate prevention and treatment analysis populations (defined in the tables below) and baseline serology positive participants. Exploratory endpoints, including the treatment analysis population, are described in Section 3.

Safety, pharmacokinetics, and antidrug antibodies will be characterized in the overall intent to treat population and in the analysis populations.

Additional population subset analyses are detailed in Section 9 and/or in the statistical analysis plan.

Prevention Population Objectives and Endpoints Participants negative at baseline for SARS-CoV-2 RT-PCR and serology Comparison Groups: Placebo vs LY3819253 4200 mg	
Objectives	Endpoints
Primary	
• Compare the incidence of COVID-19	• Cumulative incidence of COVID-19 defined as the detection of SARS-CoV-2 by RT-PCR AND mild or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
Key Secondary	
• Compare the incidence of moderate or worse severity COVID-19	• Cumulative incidence of moderate or worse severity COVID-19; defined as the detection of SARS-CoV-2 by RT-PCR AND moderate or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
• Compare the incidence of SARS-CoV-2 infection	• Cumulative incidence of SARS-CoV-2; defined as the detection of SARS-CoV-2 by RT-PCR • Time frame for endpoint evaluation: 4 weeks from randomization

Other Secondary	
[time frame for endpoint evaluation: 8 weeks from randomization]	
• Compare the incidence of SARS-CoV-2 infection	• Cumulative incidence of SARS-CoV-2 infection defined as the detection of SARS-CoV-2 by RT-PCR
• Compare the frequency of hospitalization or death due to COVID-19	• Proportion of participants who are hospitalized or have died due to COVID-19
• Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events: o COVID-19 related hospitalization (defined as ≥24 hours of acute care), o COVID-19 related emergency room visit, or o death
• Compare the mortality due to COVID-19	• Proportion of participants who die due to COVID-19 (according to the investigator)

Abbreviations: COVID-19 = coronavirus disease – 2019; RT-PCR = reverse transcription – polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] As defined in Table 1.

Part 2 Prevention

Participants will be tested with point of care SARS-CoV-2 POC test to determine SARS-CoV-2 status. Participants with a negative POC test will randomize to the Prevention Cohort. Those with a positive test will enroll to the Treatment Cohort.

Safety, pharmacokinetics, and antidrug antibodies will be characterized in the overall intent to treat population and in the analysis populations.

Additional population subset analyses are detailed in Section 9 and/or in the statistical analysis plan.

Part 2 Prevention Population Objectives and Endpoints

Participant negative on screening Point of Care Test

&

negative at baseline for SARS-CoV-2 RT-PCR and serology

Comparison Groups:

- Placebo vs LY3819253 700 mg
- Placebo vs LY3819253 350 mg + LY3832479 700 mg

Objectives	Endpoints
Primary	
• Compare the incidence of COVID-19	• Cumulative incidence of COVID-19 defined as the detection of SARS-CoV-2 by RT-PCR AND mild or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
Key Secondary	
• Compare the incidence of moderate or worse severity COVID-19	• Cumulative incidence of moderate or worse severity COVID-19; defined as the detection of SARS-CoV-2 by RT-PCR AND moderate or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
• Compare the incidence of SARS-CoV-2 infection	• Cumulative incidence of SARS-CoV-2; defined as the detection of SARS-CoV-2 by RT-PCR, • Time frame for endpoint evaluation: 4 weeks from randomization

Other 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: COVID-19 = coronavirus disease – 2019; RT-PCR = reverse transcription – polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] As defined in Table 1.

Part 3 objectives are exploratory and therefore described in Section 3.

Overall Design

Study J2X-MC-PYAD is a randomized, double-blind, placebo-controlled, prophylaxis study to evaluate the efficacy and safety of intravenous LY3819253, alone and in combination with LY3832479, in preventing SARS-CoV-2 infection and COVID-19, compared to placebo. An independent Data Safety Monitory Board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to sample size.

Disclosure Statement: This is a three-part, 9-arm interventional study that is double-blinded.

Number of Participants:

For Part 1, a total of approximately 1700 participants (intent-to-treat [ITT] population) will be randomly assigned to study intervention such that approximately 1300 SARS-CoV-2 RT-PCR and serology negative participants are randomized in the study with the goal of achieving approximately 33 events (in each of the primary and key secondary endpoints) in the prevention population.

For Part 2, a total of approximately 2000 participants will be randomly assigned to study intervention based on rapid point of care (POC) testing such that approximately 1700 participants SARS-CoV-2 RT-PCR and serology negative participants are randomized in the Prevention Cohort with the goal of achieving approximately 56 events on each of the primary and key secondary endpoints.

Part 3 will enroll at least 30 participants and up to approximately 500 participants randomized to study intervention.

The maximum sample size for this study is approximately 5000 participants in the ITT population.

Intervention Groups and Duration:

Participants will receive one intravenous infusion of study intervention.

The maximum total duration of study participation for each participant of the prevention groups is 24 weeks.

The maximum total duration of study participation for each participant of the treatment group is 12 weeks.

<u>Part 1:</u>

Eligible participants will be randomized to one of two arms: placebo or LY3819253 4200 mg.

Participants will continue to enroll to Part 1 until the needed events for the primary and key secondary endpoints are achieved and the minimum number of residents enroll.

The evaluation period for Part 1 is 8 weeks, with follow-up to 24 weeks.

<u>Part 2:</u>

The Sponsor will decide when to trigger activation of Part 2. Activation of Part 2 will be communicated to sites.

All participants will be screened for SARS CoV-2 with a point of care (POC) test. Participants who are negative will be assigned to the "Prevention Cohort", while those who test positive will be assigned to the "Treatment Cohort".

- Prevention Cohort: Participants who are SARS-CoV-2 negative during screening on the POC test will be randomized to one of three arms: placebo, LY3819253 700 mg, or LY3819253-350 mg + LY3832479-700 mg.
  If enrolling to a placebo-controlled trial is challenged by an effective medication becoming available for prevention of COVID-19 and SARS-CoV-2, then the placebo arm may be dropped.
  Note: It is possible that some participants have SARS-CoV-2 negative result on the screening point of care test, but could be positive on the baseline SARS-CoV-2 PCR test. The results from the baseline test will not be available until after the participant is randomized. Once positive results are known from the baseline test, these participants will be unblinded and have the option to continue to be followed for safety according to the Prevention Cohort SoA. Unblinded participants will not be included as part of the defined prevention population.

  The evaluation period for the Prevention Cohort is 8 weeks, with follow-up to Day 169.

- Treatment Cohort: Participants who test SARS-CoV-2 positive during screening with the POC test will be randomized to one of two arms: LY3819253 700 mg, or LY3819253 700 mg + LY3832479 1400 mg.

  The evaluation period for the Treatment Cohort is 4 weeks, with follow-up to Day 85.

<u>Part 3</u>

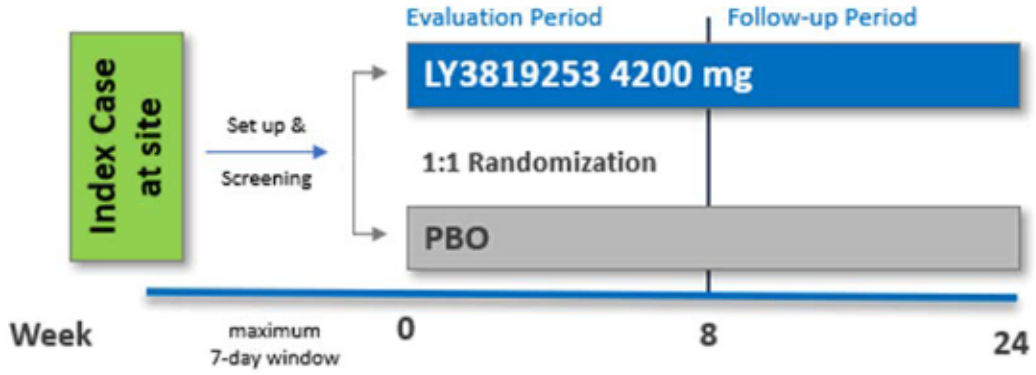
The Sponsor will decide when to trigger activation of Part 3. Activation of Part 3 will be communicated to sites. Part 3 may be activated prior to Part 2.

Eligible participants will be randomized to one of two arms: LY3819253 700 mg or LY3819253 700 mg + LY3832479 1400 mg. The evaluation period for Part 3 is 4 weeks, with follow-up to Day 85.

Data Monitoring Committee: Yes. Equivalent to Data Safety Monitoring Board for this study.

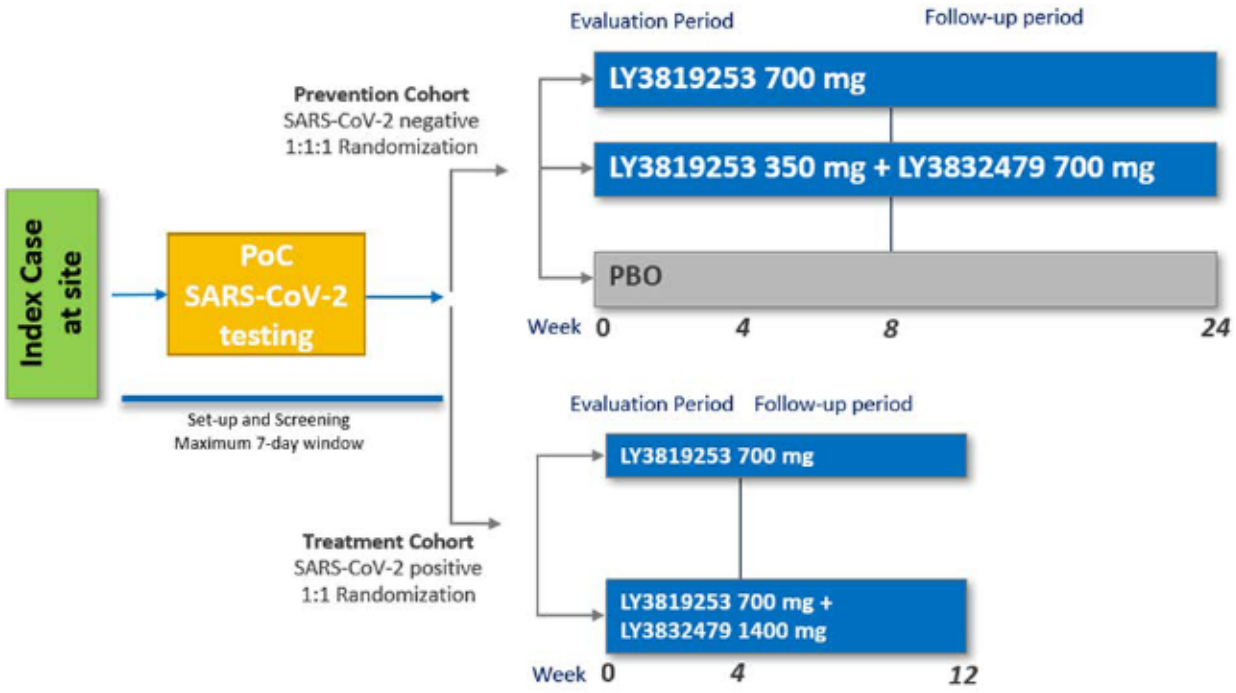
1.2. Schema

Part 1:



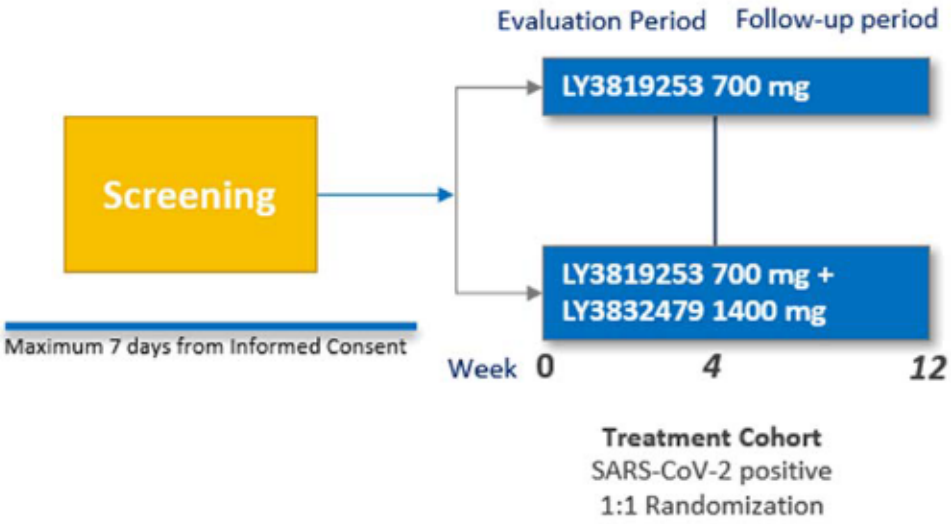
Abbreviations: PBO = placebo.

Part 2:



Abbreviations: PBO = placebo.

PART 3:



Treatment Cohort
SARS-CoV-2 positive
1:1 Randomization

1.3. Schedule of Activities (SoA)

Screening procedures may be conducted over more than 1 day, as long as all activities are completed within the allowed interval tolerance. Screening and Day 1 procedures may occur on the same day.

Participants who test positive for SARS-CoV-2 during the Evaluation Period may have their scheduled visit(s) conducted as a remote health assessment. Refer to the study day and visit type table in Section 4.1.2 for additional clarification.

Early Termination Visits are conducted when the participant is withdrawn from the study prior to the post-evaluation follow-up.

1.3.1. Part 1 and Prevention Cohort of Part 2

Procedures	**Screening**	**Evaluation Period**										**ETV**	**Post-Evaluation Follow-Up**			**Comments**
Study Day	Max 7-day window	1	2-7	8	15	22	29	36	43	50	57		85	141	169	
Visit window (± number of days)	--	--	--	2	2	2	2	2	2	2	2		7	7	7	
Randomization		X														
Administer study intervention (IV infusion)		X														
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. For participants with symptoms suggestive of COVID-19, obtain timing of onset of symptoms

Procedures	Screening	Evaluation Period										ETV	Post-Evaluation Follow-Up			Comments
Study Day	Max 7-day window	1	2-7	8	15	22	29	36	43	50	57		85	141	169	
Visit window (± number of days)	--	--	--	2	2	2	2	2	2	2	2		7	7	7	
Prior treatments of special interest	X															Within the last 2 weeks: NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators, or other investigational treatments. At any time: SARS-CoV-2 vaccine
Tobacco use		X														Never/ former/ current use
Concomitant medications		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, Appendix 3.
Physical examination	X															
Symptom-directed physical exam		X										X	X	X		As indicated based on participant status and standard of care.
Height		X														
Weight		X														
Vital signs	X	Daily										X	X	X		Documentation of hospital-based exam is acceptable. Includes: body temperature, pulse rate, BP, SpO2, respiratory rate, FiO2 if known, and method of delivery, if applicable. Record while participant is at rest.

Procedures	Screening	Evaluation Period										ETV	Post-Evaluation Follow-Up			Comments
Study Day	Max 7-day window	1	2-7	8	15	22	29	36	43	50	57		85	141	169	
Visit window (± number of days)	--	--	--	2	2	2	2	2	2	2	2		7	7	7	
Hospitalization events		Daily										X	X	X		Record if the following events occur: • Emergency room visits • hospitalized • ICU admittance, • Extended care facility admittance, • and discharge for any of the above
Clinical status and concomitant procedures of special interest in hospitalized participants		Daily										X	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 a high flow oxygen device • mechanical ventilation • extracorporeal membrane oxygenation, or • additional organ support (e.g. pressors, renal replacement)
Clinical symptoms and interventions of interest		Daily										X	X			See Table 1 for clinical symptoms and interventions of interest.

Procedures	Screening	Evaluation Period										ETV	Post-Evaluation Follow-Up			Comments
Study Day	Max 7-day window	1	2-7	8	15	22	29	36	43	50	57		85	141	169	
Visit window (± number of days)	--	--	--	2	2	2	2	2	2	2	2		7	7	7	
Symptoms Questionnaire	X	Daily										X	X			See Section 8.1.2.
SARS-CoV-2 POC Test (Nasal Swab)	X															Applies to participants in Part 2 only. Result must be determined prior to collecting swabs for PCR test.
SARS-CoV-2 Serology		X					X				X	X	X	X	X	Day 1: pre-dose. assessed at a central laboratory
SARS-CoV-2 nasopharyngeal swab (for PCR test) taken from both nostrils		X														Day 1: pre-dose. assessed at a central laboratory
SARS-CoV-2 nasal swab (for PCR test) taken from both nostrils		X		X	X	X	X	X	X	X	X	X	X	X		Day 1: pre-dose. assessed at a central laboratory No samples needed if participant is hospitalized.*

Procedures	Screening	Evaluation Period										ETV	Post-Evaluation Follow-Up			Comments
Study Day	Max 7-day window	1	2-7	8	15	22	29	36	43	50	57		85	141	169	
Visit window (± number of days)	--	--	--	2	2	2	2	2	2	2	2		7	7	7	
Urine pregnancy	X	X										X		X		Only for WOCBP (Section 10.4, Appendix 4) Local laboratory. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. No samples needed if participant is hospitalized.*
Hematology		X					X				X	X	X	X		Day 1: pre-dose. Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
Clinical Chemistry		X					X				X	X	X	X		Day 1: pre-dose. Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
LDH		X									X	X				Day 1: pre-dose. Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*

Procedures	**Screening**	**Evaluation Period**										**ETV**	**Post-Evaluation Follow-Up**			**Comments**
Study Day	Max 7-day window	1	2-7	8	15	22	29	36	43	50	57		85	141	169	
Visit window (± number of days)	--	--	--	2	2	2	2	2	2	2	2		7	7	7	
• C-reactive protein; high-sensitivity • Ferritin • D-dimer • Procalcitonin • Troponin		X									X	X				Day 1: pre-dose. Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
PK sample		X					X				X	X	X	X	X	Day 1: pre-dose. For participants in Part 2, Day 1 collection is post-dose only (approx. 30 minutes after end of infusion). Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
Immunogenicity (ADA) sample		X					X				X	X	X	X	X	Day 1: pre-dose. Remaining days: Collect with time-matched PK sample. No samples needed if participant is hospitalized.*
Exploratory biomarker samples		X					X				X	X	X	X		Day 1: pre-dose Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
Pharmacogenetics sample		X														Assayed by Lilly-designated laboratory

Abbreviations: ACVPU = alert, confusion, voice, pain, unresponsive; ADA = antidrug antibody; AE = adverse event; BP = blood pressure; COVID-19 = coronavirus disease – 2019; FiO2 = fraction of inspired oxygen in the air; ETV = early termination visit; FiO2 = fraction of inspired oxygen; ICU = intensive care unit; IV = intravenous; LDH = lactate dehydrogenase; NSAID = nonsteroidal anti-inflammatory drug; PCR = polymerase chain reaction; PK = pharmacokinetic; POC = point of care; SpO2 = saturation of peripheral oxygen; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of child-bearing potential

* Participants will continue to follow the Schedule of Activities upon discharge from hospital. No local lab result data will be collected in the eCRF while hospitalized.

1.3.2. Part 2 Treatment Cohort and Part 3

Screening for Part 2 is described in the table above (Section 1.3.1). Screening is provided below for reference.

Procedures	Screening	Evaluation Period			ETV	Post-treatment follow-up	Comments
Study Day	Max 7 day window	1	8	29		85	
Visit window (± number of days)	--	--	1	2		7	
Randomization		X					
Administer study intervention (IV infusion)		X					
Informed Consent	X						
Inclusion and exclusion criteria review	X						Note that eligibility criteria for Part 2 and Part 3 are different.
Demographics	X						Including age, gender, race, ethnicity
Preexisting conditions and medical history	X						Obtained from interview or available information. For participants with symptoms suggestive of COVID-19, obtain timing of onset of symptoms
Prior treatments of special interest	X						Within the last 2 weeks: NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators, or other investigational treatments. At any time: SARS-CoV-2 vaccine
Tobacco use		X					Never/ former/ current use
Concomitant medications		X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3, Appendix 3.
Physical examination	X						
Symptom-directed physical exam		X			X	X	As indicated based on participant status and standard of care.

Procedures	**Screening**	**Evaluation Period**			**ETV**	**Post-treatment follow-up**	**Comments**
Study Day	Max 7 day window	1	8	29		85	
Visit window (± number of days)	--	--	1	2		7	
Height		X					
Weight		X					
Vital signs	X	X	X	X	X	X	Documentation of hospital-based exam is acceptable. Includes: body temperature, pulse rate, BP, SpO2, respiratory rate, FiO2 if known, and method of delivery, if applicable. Record while participant is at rest.
Hospitalization events		X	X	X	X	X	Record if the following events occur: • Emergency room visits • hospitalized • ICU admittance, • Extended care facility admittance, • and discharge for any of the above
Clinical status and concomitant procedures of special interest in hospitalized participants		Daily			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 a high flow oxygen device • mechanical ventilation • extracorporeal membrane oxygenation, or • additional organ support (e.g. pressors, renal replacement)
SARS-CoV-2 Serology		X		X	X	X	Day 1: pre-dose. assessed at a central laboratory
Documentation of positive SARS-CoV-2 viral infection	X						Applies to participants in Part 3 only. Sample for first positive test must be collected within 10 days prior to start of infusion. Local laboratory and/or Point-of-Care testing.

Procedures	Screening	Evaluation Period			ETV	Post-treatment follow-up	Comments
Study Day	Max 7 day window	1	8	29		85	
Visit window (± number of days)	--	--	1	2		7	
SARS-CoV-2 nasopharyngeal swab taken from both nostrils		X	X	X	X	X	Day 1: pre-dose. assessed at a central laboratory No samples needed if participant is hospitalized.*
Urine pregnancy	X	X			X	X	Only for WOCBP (Section 10.4, Appendix 4) Local laboratory. Test performed in the 24 hours prior to study entry will be accepted for determination of eligibility. No samples needed if participant is hospitalized.*
Hematology		X		X	X	X	Day 1: pre-dose. Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
Clinical Chemistry		X		X	X	X	Day 1: pre-dose. Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
• C-reactive protein; high-sensitivity • Ferritin • D-dimer • Procalcitonin • Troponin		X		X	X		Day 1: pre-dose. Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
PK sample		X		X	X	X	Day 1: post-dose only (approx. 30 minutes after end of infusion) Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
Immunogenicity (ADA) sample		X		X	X	X	Day 1: pre-dose. Remaining days: Collect with time-matched PK sample. No samples needed if participant is hospitalized.*

Procedures	**Screening**	**Evaluation Period**			**ETV**	**Post-treatment follow-up**	**Comments**
Study Day	Max 7 day window	1	8	29		85	
Visit window (± number of days)	--	--	1	2		7	
Exploratory biomarker samples		X		X	X	X	Day 1: pre-dose Assayed by Lilly-designated laboratory No samples needed if participant is hospitalized.*
Pharmacogenetics sample		X					Assayed by Lilly-designated laboratory

Abbreviations: ACVPU = alert, confusion, voice, pain, unresponsive; ADA = antidrug antibody; AE = adverse event; BP = blood pressure; COVID-19 = coronavirus disease – 2019; FiO2 = fraction of inspired oxygen in the air; ETV = early termination visit; FiO2 = fraction of inspired oxygen; ICU = intensive care unit; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PK = pharmacokinetic; SpO2 = saturation of peripheral oxygen; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of child-bearing potential.

* Participants will continue to follow the Schedule of Activities upon discharge from hospital. No local lab result data will be collected in the eCRF while hospitalized.

2. Introduction

2.1. Study Rationale

The efficient community spread of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has resulted in the current pandemic of Coronavirus Disease – 2019 (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. Of all age groups, older adults have the greatest risk of severe COVID-19 and the associated complications (CDC 2020; Grabowski and Mor 2020).

Globally, there are many reports of the rapid spread of COVID-19 amongst residents of skilled nursing facilities following identification of an index case, with high associated rates of morbidity and mortality (Arons et al. 2020; Grabowski and Mor 2020; Graham et al. 2020). In the USA, at least 153,000 residents and employees of nursing homes have contracted COVID-19, accounting for 35% of the country's deaths (Werner et al. 2020). With over 1.3 million residents in nursing home care in the USA (CDC 2016), there is an urgent need for therapeutic strategies to prevent COVID-19 in these populations.

This study aims to evaluate the impact of LY3819253 and LY3819253 in combination with LY3832479 in preventing SARS-CoV-2 infection and COVID-19 in facility staff and residents in skilled nursing and assisted living facilities with a high risk of SARS-CoV-2 exposure.

2.2. Background

The SARS-CoV-2 gains entry to cells through binding of the spike (S) protein to ACE2 receptors on cells (Hoffmann 2020). LY3819253 and LY3832479 are neutralizing immunoglobulin G1 (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. The blocking of viral entry into respiratory cells and viral replication is expected to prevent and/or mitigate the severity of disease in people whom ongoing viral spread and replication is the primary driver of COVID-19 pathophysiology. For those that become infected, the decrease in viral replication may also shorten a patient's extent and duration of viral shedding and transmission, positively impacting public health.

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

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

In addition, the impact of LY3819253, alone or in combination with LY3832479, on viral load and clinical outcomes in participants with early mild to moderate COVID-19 illness is being

investigated in Study J2W-MC-PYAB (PYAB), a Phase 2, randomized, double-blind study. Interim analysis from this study suggests treatment with LY3819253 may decrease the risk of hospitalization in patients with mild to moderate COVID-19 (Chen et al. 2020)

Additional information about these studies can be found in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

Anticipated risk is considered low and is based on the known mechanism of action for human derived neutralizing antibodies in acute viral disease states. LY3819253 and LY3832479 consist of a highly specific mAbs directed at foreign (non-human) epitope(s) and will be given to participants at a high risk of SARS-CoV-2 exposure in a controlled setting. The complementarity determining regions of the mAbs were derived from B lymphocytes of 2 individually convalescent naturally SARS-CoV-2-infected patients 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. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for coronavirus infections, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome, and has not been reported to date with SARS-CoV-2. Additionally, limited experience with the use of convalescent serum as a treatment for patients with severe COVID-19 disease has not indicated safety concerns (Shen 2020; Duan 2020).

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.

To date, there is no evidence of productive enhancement of ADE with SARS-CoV-2.

Additional manageable risks associated with most therapeutic monoclonal antibodies are the potential for infusion-related hypersensitivity and cytokine release reactions. The single infusion in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made and/or the infusion stopped, if indicated. Additional information regarding infusion reaction management options is located in Section 6.1.1.2. As of 31 December 2020, approximately 4012 participants received blinded treatment of LY3819253 700 mg, 2800 mg, or 7000 mg, or placebo, of which approximately 3189 participants received LY3819253. 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 from post-authorization treatment within 24 hours of infusion. Signs and symptoms may include fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, sinus tachycardia, and bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known 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).

Data from Study PYAB interim analysis indicate treatment with LY3819253 or the combination of LY3819253 and LY3832479 may decrease the risk of hospitalization in patients with mild to moderate COVID-19 (Chen et al. 2020; Gottlieb et al. 2020) thus providing benefit to patients with COVID-19.

Given the totality of data on LY3819253 and LY3832479, the well-established safety profile of other therapeutic mAbs, and the lack of disease directed therapeutic options for patients with COVID-19 illness or to prevent the SARS-CoV-2 infection, the overall benefit/risk assessment of this study is considered favorable.

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

3. Objectives and Endpoints

Part 1

To facilitate rapid prophylaxis and treatment of residents and facility staff, participants will be enrolled prior to assessment of baseline SARS-CoV-2 reverse transcription – polymerase chain reaction (RT-PCR) or serology results; thus, multiple analysis populations will exist. This includes separate prevention and treatment analysis populations (defined in the tables below) and baseline serology positive participants.

Safety, pharmacokinetics, and antidrug antibodies will be characterized in the overall intent to treat population and in the analysis populations.

Additional population subset analyses are detailed in Section 9 and/or in the statistical analysis plan.

Prevention Population Objectives and Endpoints Participants negative at baseline for SARS-CoV-2 RT-PCR and serology Comparison Groups: Placebo vs LY3819253 4200 mg	
Objectives	Endpoints
Primary	
• Compare the incidence of COVID-19	• Cumulative incidence of COVID-19 defined as the detection of SARS-CoV-2 by RT-PCR AND mild or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
Key Secondary	
• Compare the incidence of moderate or worse severity COVID-19	• Cumulative incidence of moderate or worse severity COVID-19; defined as the detection of SARS-CoV-2 by RT-PCR AND moderate or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
• Compare the incidence of SARS-CoV-2 infection	• Cumulative incidence of SARS-CoV-2; defined as the detection of SARS-CoV-2 by RT-PCR • Time frame for endpoint evaluation: 4 weeks from randomization
Other Secondary	
[time frame for endpoint evaluation: 8 weeks from randomization]	

• Compare the incidence of SARS-CoV-2 infection	• Cumulative incidence of SARS-CoV-2 infection defined as the detection of SARS-CoV-2 by RT-PCR
• Compare the frequency of hospitalization or death due to COVID-19	• Proportion of participants who are hospitalized or have died due to COVID-19
• Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events: o COVID-19 related hospitalization (defined as ≥24 hours of acute care), o COVID-19 related emergency room visit, or o death
• Compare the mortality due to COVID-19	• Proportion of participants who die due to COVID-19 (according to the investigator)
Exploratory	
[time frame for endpoint evaluation: 8 weeks from randomization]	
• Compare time to improvement to mild severity symptoms in participants who develop moderate or worse severity[a] COVID-19	• Time to improvement to mild severity[a]
• Characterize COVID-19 illness and severity according to NIAID ordinal scale(s)	• Worst score on NIAID ordinal scale(s)
• Characterize SARS-CoV-2 viral endpoints in those participants that become RT-PCR positive	• Proportion of participants that achieve SARS-CoV-2 clearance within 1, 2, or 3 weeks of positive RT-PCR • Time to SARS-CoV-2 clearance
• Characterize emergence of viral resistance to LY3819253	• Comparison from the first positive sample to at least the last positive sample
• Compare the duration of hospitalization due to COVID-19	• Cumulative days of hospitalization in those who are hospitalized due to COVID-19

Abbreviations: COVID-19 = coronavirus disease – 2019; NIAID = National Institute of Allergy and Infectious Diseases; RT-PCR = reverse transcription – polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] As defined in Table 1.

Treatment Population Exploratory Objectives and Endpoints Participants positive at baseline for SARS-CoV-2 RT-PCR and negative at baseline for serology Comparison Groups: Placebo vs LY3819253 4200 mg [time frame for endpoint evaluation: 8 weeks from randomization]	
Objectives	Endpoints
• Compare the frequency of hospitalization or death due to COVID-19	• Proportion of participants who are hospitalized or have died due to COVID-19
• Compare the incidence of moderate or worse severity COVID-19 in participants without moderate or worse severity[a] COVID-19 at baseline	• Cumulative incidence of moderate or worse severity COVID-19; defined as moderate or worse disease severity[a] within 21 days of baseline
• Compare the incidence of COVID-19 in participants who are asymptomatic[a] baseline	• Cumulative incidence of COVID-19; defined as mild or worse disease severity[a] within 21 days of baseline
• Compare time to improvement to mild severity symptoms[a] in participants who have at baseline, or develop, moderate or worse COVID-19	• Time to improvement to mild severity[a]
• Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events: o COVID-19 related hospitalization (defined as ≥24 hours of acute care), o COVID-19 related emergency room visit, or o death
• Characterize COVID-19 illness and severity according to NIAID ordinal scale(s)	• Worst score on a NIAID ordinal scale(s)
• Compare the mortality due to COVID-19	• Proportion of participants who die due to COVID-19
• Characterize SARS-CoV-2 viral endpoints	• Proportion of participants that achieve SARS-CoV-2 clearance within 1, 2, or 3 weeks of baseline • Time to SARS-CoV-2 clearance
• Characterize emergence of viral resistance to LY3819253	• Comparison from baseline to at least the last positive sample
• Compare the duration of hospitalization due to COVID-19	• Cumulative days of hospitalization in those who are hospitalized due to COVID-19

Abbreviations: COVID-19 = coronavirus disease – 2019; NIAID = National Institute of Allergy and Infectious Diseases; RT-PCR = reverse transcription – polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] As defined in Table 1.

Part 2 Prevention

Participants will be tested with point of care SARS-CoV-2 POC test to determine SARS-CoV-2 status. Participants with a negative POC test will randomize to the Prevention Cohort. Those with a positive test will enroll to the Treatment Cohort.

Safety, pharmacokinetics, and antidrug antibodies will be characterized in the overall intent to treat population and in the analysis populations.

Additional population subset analyses are detailed in Section 9 and/or in the statistical analysis plan.

Part 2 Prevention Population Objectives and Endpoints

Participant negative on screening Point of Care Test

&

negative at baseline for SARS-CoV-2 RT-PCR and serology

Comparison Groups:

- Placebo vs LY3819253 700 mg
- Placebo vs LY3819253 350 mg + LY3832479 700 mg

Objectives	Endpoints
Primary	
• Compare the incidence of COVID-19	• Cumulative incidence of COVID-19 defined as the detection of SARS-CoV-2 by RT-PCR AND mild or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
Key Secondary	
• Compare the incidence of moderate or worse severity COVID-19	• Cumulative incidence of moderate or worse severity COVID-19; defined as the detection of SARS-CoV-2 by RT-PCR AND moderate or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization
• Compare the incidence of SARS-CoV-2 infection	• Cumulative incidence of SARS-CoV-2; defined as the detection of SARS-CoV-2 by RT-PCR • Time frame for endpoint evaluation: 4 weeks from randomization

Other 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: COVID-19 = coronavirus disease – 2019; RT-PCR = reverse transcription – polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] As defined in Table 1.

Part 2 and Part 3 Treatment Exploratory

For Part 3, results from external, non-study SARS-CoV-2 tests will be used to determine eligibility.

Safety, pharmacokinetics, and antidrug antibodies will be characterized in the overall intent to treat population and in the analysis populations.

Treatment Population Exploratory Objectives and Endpoints Participants positive on screening Point of Care Test (Part 2) & positive at baseline for SARS-CoV-2 RT-PCR and negative at baseline for serology [time frame for endpoint evaluation: **4 weeks from randomization**]	
Objectives	Endpoints
• Evaluate the frequency of hospitalization or death due to COVID-19	• Proportion of participants who are hospitalized or have died due to COVID-19
• Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events: o COVID-19 related hospitalization (defined as ≥24 hours of acute care), o COVID-19 related emergency room visit, or o death
• Characterize COVID-19 illness and severity according to NIAID ordinal scale(s)	• Worst score on a NIAID ordinal scale(s)
• Evaluate the mortality due to COVID-19	• Proportion of participants who died due to COVID-19
• Characterize SARS-CoV-2 viral endpoints	• Proportion of participants that achieve SARS-CoV-2 clearance within 8 or 29 days of baseline • Time to SARS-CoV-2 clearance
• Characterize emergence of viral resistance to LY3819253 or LY3832479	• Comparison from baseline to at least the last positive sample
• Evaluate the duration of hospitalization due to COVID-19	• Cumulative days of hospitalization in those who are hospitalized due to COVID-19

Abbreviations: COVID-19 = coronavirus disease – 2019; NIAID = National Institute of Allergy and Infectious Diseases; RT-PCR = reverse transcription – polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] As defined in Table 1.

4. Study Design

4.1. Overall Design

Study J2X-MC-PYAD is a randomized, double-blind, placebo-controlled, prophylaxis study to evaluate the efficacy and safety of intravenous LY3819253, alone and in combination with LY3832479, in preventing SARS-CoV-2 and COVID-19, compared to placebo. Skilled nursing and assisted living facilities will serve as the setting to find participants with a high risk of SARS-CoV-2 exposure. The Principal Investigator and site staff may be unaffiliated with the facility.

Residents and facility staff may be included in this study because infected facility staff, who may be asymptomatic, may be important in the spread of SARS-CoV-2 within long term care facilities (Graham et al. 2020). Therefore, providing prophylactic treatment to both residents and facility staff may be highly beneficial in preventing or limiting COVID-19 outbreaks.

An independent Data Safety Monitoring Board Committee (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to sample size (see Section 10.1.5, Appendix 1, for more information).

4.1.1. Screening Period

Interested participants or their legal authorized representative will sign the appropriate informed consent document(s) prior to completion of any procedures.

The investigator or qualified designee 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 site staff will perform the invasive procedures to confirm eligibility.

Part 1:

The screening period for each site opens when a confirmed SARS-CoV-2 index case at the facility is reported to study staff. Screening, randomization and investigational product (IP) administration must be completed within 7 days from reporting of the index case.

Part 2:

Prior to randomization in Part 2, participants will receive a point of care (POC) test for SARS-CoV-2 infection. Participants will be allocated to either Prevention or Treatment Cohorts based on the result. Screening and Day 1 may occur on the same day.

Part 3

The screening period for each participant starts at the signing of the ICF. Screening, randomization, and IP administration must be completed within 7 days from signing the ICF.

4.1.2. Evaluation Period

The evaluation period begins when the participant completes screening and is enrolled in the study. Assessments and procedures will be conducted as described in the SoA (Section 1.3).

Participants in Part 1 will be randomized to placebo or LY3819253. The Sponsor will decide when to trigger activation of Part 2. Activation of Part 2 will be communicated to sites.

Participants in Part 2 will be assigned to a cohort as follows:

- Prevention Cohort: Participants who are SARS-CoV-2 negative during screening on the POC test will be randomized to one of three arms: placebo, LY3819253 700 mg, or LY3819253 350 mg + LY3832479 700 mg.
  If enrolling to a placebo-controlled trial is challenged by an effective medication becoming available for prevention of COVID-19 and SARS-CoV-2, then the placebo arm may be dropped.
  Note: It is possible that some participants have SARS-CoV-2 negative result on the screening point of care test, but could be positive on the baseline SARS-CoV-2 PCR test. The results from the baseline test will not be available until after the participant is randomized. Once positive results are known from the baseline test, these participants will be unblinded and have the option to continue to be followed for safety according to the Prevention Cohort SoA. Unblinded participants will not be included as part of the defined prevention population

  The evaluation period for the Prevention Cohort is 8 weeks, with follow-up to Day 169.

- Treatment Cohort: Participants who test SARS-CoV-2 positive during screening with the POC test will be randomized to one of two arms: LY3819253 700 mg, or LY3819253 700 mg + LY3832479 1400 mg.

  The evaluation period for the Treatment Cohort is 4 weeks, with follow-up to Day 85.

Participants in Part 3 will be randomized to LY3819253 700 mg or LY3819253 700 mg and LY3832479 1400 mg. The evaluation period for Part 3 is 4 weeks, with follow-up to Day 85. The Sponsor will decide when to trigger activation of Part 3. Activation of Part 3 will be communicated to sites. Part 3 may be activated prior to Part 2.

Part 2 and Part 3 could be activated concurrently. However, Part 3 will not enroll concurrently with Part 2 at the same facility.

Participants will receive one intravenous infusion of study intervention.

The maximum total duration of study participation for each participant of the prevention groups is 24 weeks. See the SOA for prevention groups in Section 1.3.1.

The maximum total duration of study participation for each participant of the treatment group is 12 weeks. See the SOA for the treatment group in Section 1.3.2.

This table describes the visit types for the prevention population for this study.

Study Day	Activity	Visit Type
0,1	Follow SoA	Onsite
8, 15, 22, 29, 36, 43, 50, 57	Follow SoA Vital signs*	Onsite or Home (Virtual [record collection] if hospitalized)

Daily 2 - 57	Vital signs and symptoms questionnaire daily* Vital signs, clinical status, and concomitant procedures for hospitalized participants.	Onsite or Home (Virtual [record collection] if hospitalized)
ETV and follow-up (85, 141, 169)	Follow SoA	Onsite or Home

*Collected via direct data capture for onsite or home visits only.

This table describes the visit types for the treatment population for this study.

Study Day	**Activity**	**Visit Type**
0, 1	Follow SoA	Onsite
8, 29	Follow SoA Vital signs*	Onsite or Home (Virtual [record collection] if hospitalized)
Daily 2-29	Vital signs, clinical status, and concomitant procedures for hospitalized participants.	Virtual (record collection) if hospitalized
ETV and follow-up (85)	Follow SoA	Onsite or Home

*Collected via direct data capture for onsite or home visits only.

Hospitalization

If a participant is hospitalized, efforts will be made to retrieve hospital records and report procedures and assessments according to the SoA, as feasible.

Definitions for COVID-19 Severity

This table gives the definitions for COVID-19 severity of illness for those participants who are SARS-CoV-2 positive as determined by standard RT-PCR assay or equivalent test.

Table 1 Definitions for COVID-19 Severity

Severity	**Description**
Mild	Mild symptoms that could include: • fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea **AND** No clinical signs indicative of Moderate, Severe, or Critical Severity
Moderate	Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion **AND** Clinical signs suggestive of moderate illness with COVID-19, such as: • respiratory rate ≥ 20 breaths per minute,

	• heart rate ≥ 90 beats per minute • O2 utilization increase of ≥ 1L/min (for participants receiving O2 at baseline)* • IV fluid initiation* **AND** no clinical signs indicative of Severe or Critical Illness Severity
Severe	Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress **AND** Clinical signs indicative of severe systemic illness with COVID-19, such as • respiratory rate ≥ 30 breaths per minute, • heart rate ≥ 125 beats per minute, • SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 **AND** No clinical signs indicative of Critical Illness Severity

Critical	Evidence of critical illness, defined by at least one of the following:
	• Respiratory failure defined based on resource utilization requiring at least one of the following:
	  • endotracheal intubation and mechanical ventilation,
	  • oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥0.5),
	  • noninvasive positive pressure ventilation,
	  • extracorporeal membrane oxygenation (ECMO), or
	  • clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
	• Shock
	• Multi-organ dysfunction/failure

Death	

Abbreviations: COVID-19 = coronavirus disease – 2019; FiO2 = fraction of inspired oxygen in the air; IV = intravenous; PaO2 = partial pressure of oxygen; SpO2 = saturation of peripheral oxygen.

Adapted from FDA 2020.

*Addition to FDA Guidance applies only to residents at skilled nursing and assisted living facilities.

4.1.3. Follow-up Period

Part 1 and Prevention Cohort of Part 2

Post-evaluation follow-up assessments will be conducted at Days 85, 141, and 169 according to the SoA. Strategies to manage infection risks and reduce the burden of return visits may be used by sites, such as remote visits.

Part 2 Treatment Cohort and Part 3

A post-evaluation follow-up assessment will be conducted at Day 85 according to the SoA. Strategies to manage infection risks and reduce the burden of return visits may be used by sites, such as remote visits.

4.2. Scientific Rationale for Study Design

This study is designed to evaluate the efficacy of a single dose of LY3819253, alone and in combination with LY3832479, compared to placebo in preventing and treating SARS-CoV-2 infection and COVID-19 in residents and facility staff at skilled nursing and assisted living facilities.

The randomized, double-blind, placebo-controlled design will allow an objective assessment of the efficacy and safety of LY3819253, alone and in combination with LY3832479, in preventing SARS-CoV-2 infection and COVID-19. A placebo-controlled design is appropriate because there are currently no therapeutic agents with proven benefit for prevention. The incidence of COVID-19 represents a clinically meaningful endpoint for a prevention study.

Residents and facility staff are included in this study as infected facility staff members may be important in the spread of SARS-CoV-2 within long term care facilities (Graham et al. 2020). Therefore, providing prophylactic treatment to both residents and facility staff may be highly beneficial in preventing or limiting COVID-19 outbreaks.

Studies have shown that following the identification of an index case, infection can spread rapidly among residents and facility staff in skilled nursing facilities (Arons et al. 2020; Graham et al. 2020). Therefore, randomization and treatment of participants within 7 days of identification of the first confirmed positive case of SARS-CoV-2 at a given facility is a requirement for study participation at that facility.

In Part 1, to facilitate rapid prophylaxis and treatment of residents and facility staff, participants will be enrolled prior to assessment of baseline SARS-CoV-2 RT-PCR or serology results, thus multiple analysis populations will exist. This includes separate prevention and treatment analysis populations and baseline serology positive participants. However, the primary analysis population for evaluation of efficacy in preventing SARS-CoV-2 and COVID-19 will be restricted to participants who are SARS-CoV-2 negative by RT-PCR and serology negative at baseline. Exploratory analyses will be conducted to evaluate efficacy of LY3819253 for treatment in participants who are SARS-CoV-2 positive by RT-PCR and serology negative at baseline.

Monoclonal antibodies may provide benefit for the treatment of mild to moderate COVID-19 (FDA EUA fact sheet 2020). Therefore, prior to randomization in Part 2, participants will receive a POC test for SARS-CoV-2 infection. Participants will be assigned to either Prevention or Treatment Cohorts based on the result of this POC test. Despite using a SARS-CoV-2 POC test during screening to assign participants to either the Prevention or Treatment cohorts, baseline SARS-CoV-2 RT-PCR and serology test results will be used to determine the study analysis populations. Refer to Section 9.3, Populations for Analyses, for further information on study analysis populations and treatment arms.

Part 3 of the study is a two-arm, outpatient, open-label, exploratory cohort evaluating the efficacy and safety of LY3819253 and LY3819253 in combination with LY3832479 in participants positive for SARS-CoV-2 with or without symptoms in staff and residents who are at higher risk for more severe disease and hospitalization in skilled nursing and assisted living facilities. For Part 3 only, participants who were in independent living situations at the facilities could be enrolled to the study.

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

4.3. Justification for Dose

Part 1

The 4200 mg single dose LY3819253 is selected for this study based on preliminary safety, tolerability, PK data from the first-in-human Study PYAA, and preclinical PK/PD modeling. Based on an estimated human half-life of approximately 19 days, a single dose of 4200 mg may be necessary to have a sustained lung concentration above the in vitro IC_{90} of viral cell-entry neutralization in 100% of participants for 4 weeks and in 90% of participants for a minimum of 8 weeks.

Part 2 and Part 3

LY3819253

LY3819253 700 mg was estimated as the maximum therapeutic dose based on PK/PD viral dynamics modeling and observed data from Study PYAB and has a sustained concentration above the in vitro IC_{90} of viral cell-entry neutralization in the lung tissue (95th percentile of the estimates used) for at least 28 days in 90% of the participant population. The lower dose of 350 mg was selected to evaluate the lower limit of the confidence interval for clinical IC_{90}, based on emerging data from ongoing study. At dose levels greater than 700 mg, LY3819253 provides exposure coverage in at least 90% of participant population for approximately 8 weeks.

LY3832479

The LY3832479 1400 mg dose was selected as the maximum therapeutic dose based on PK/PD viral dynamics modeling, relative IC_{90} potency to LY3819253, and has a sustained concentration above the *in vitro* IC_{90} of viral cell-entry neutralization in the lung tissue for at least 28 days in 90% of the participant population. The LY3832479 700 mg dose was selected to evaluate the lower limit of the confidence interval for clinical IC_{90}. On average, the 3 dose levels are expected to provide exposure coverage (as described in Part 1) for approximately 8 weeks. At dose levels greater than 700 mg, LY3832479 provides exposure coverage in at least 90% of participant population for at least 8 weeks.

LY3819253 + LY3832479 Combination

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 individual dose rationale for a single mAb intervention described above.

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 assessment shown in the SoA.

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

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, their legal authorized representative, or family member, may be the source for pre-existing conditions 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:

1. Are ≥18 years of age at the time of randomization
2. For Part 1 and Part 2 participants: Resident or staff in a skilled nursing or assisted living facility with at least one confirmed case of SARS-CoV-2 detection ≤7 days prior to randomization.
3. Reproductive and Contraceptive agreements and guidance are provided in Section 10.4, Appendix 4. Contraceptive use by men or women should be consistent with local regulations for those participating in clinical studies.
4. Agree to the collection of nasal, mid-turbinate, oropharyngeal, and nasopharyngeal swabs, and venous blood as specified in the schedule of activities.
5. Have venous access sufficient to allow intravenous infusions and blood sampling as per the protocol.
6. The participant or legally authorized representative gives signed informed consent as described in Section 10.1.3, Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Part 3 participants only:

19. Resident or staff in a skilled nursing or assisted living facility who satisfies at least one of the following at the time of screening
    - 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.

20. Positive SARS-CoV-2 test and infusion within 10 days of symptom onset, OR positive SARS-CoV-2 test and infusion within 10 days of testing if asymptomatic

5.2. Exclusion Criteria

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

7. For Parts 1 and 2, recovered from COVID-19 disease or asymptomatic infection
8. For Parts 1 and 2, a prior history of a positive SARS-CoV-2 serology test
9. For Parts 1 and 2, a history of Convalescent COVID-19 plasma treatment
10. Are an inpatient in hospital
11. For Parts 1 and 2, participation in a previous SARS-CoV-2 vaccine trial or received an approved SARS-CoV-2 vaccine
12. For Parts 1 and 2, previous receipt of SAR-CoV-2-specific monoclonal antibodies
13. Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed. This criterion does not apply to products described in Criteria 9, 11, and 12.
14. Are pregnant or breast feeding
15. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
16. Have known allergies to related compounds of LY3819253, LY3832479 or any components of the formulation
17. Suspected or proven serious, active bacterial, fungal, viral, or other infection that in the opinion of the investigator could constitute a risk when taking investigational product
18. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.

5.3. Lifestyle Considerations

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

Participants should refrain from donating blood or blood products from the time of their screening visit until 90 days following the last dose of study intervention.

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 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. Re-evaluation of venous access does not constitute rescreening and is allowable within the screening window.

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 a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

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

Study Part	1 & 2	1	2 & 3	2 (Prevention Only)	2 & 3 (Treatment only)
Intervention Name	Placebo	LY3819253	LY3819253	LY3819253 + LY3832479	LY3819253 + LY3832479
Dose Formulation	0.9% sodium chloride solution	Solution			
Dosage Level(s)	Not applicable	4200 mg	700 mg	350 mg + 700 mg	700 mg + 1400 mg
Use	Placebo	Experimental			
IMP and NIMP	IMP	IMP			
Sourcing	Commercially available 0.9% sodium chloride solution	From Lilly			
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study Intervention will be provided in glass vials and will be labeled appropriately			

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product.

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 signs and symptoms of infusion reaction

- every 30 minutes during the infusion or at least once if infusion time is <30 minutes, and
- for at least 1 hour after completion of the infusion.

The site must have resuscitation equipment, emergency drugs, and appropriately trained site staff available during the infusion and for at least 1 hour after the completion of the infusion.

Infusion information may be found in the Dosing Solution Preparation Instructions.

6.1.1. Special Treatment Considerations

6.1.1.1. Premedication for Infusions

Premedication for infusions is not planned. However, if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) or qualified designee 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 AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected 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	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

		Prophylactic medications indicated for ≤24 hours		

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

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

Site Needs

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

Management of Infusion Reactions

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

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

6.2. Preparation/Handling/Storage/Accountability

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

To protect blinding, the interventions must be prepared by an unblinded site staff 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 site staff may supply or administer study intervention.

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

The investigator, institution, contracted pharmacist, or another appropriate individual who is under the supervision of the investigator 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

Participants who meet all criteria for enrollment will be randomized on Day 1 as follows:

- In Part 1, 1:1 to double-blind treatment
- In Part 2, will allocated as follows:
    - Prevention Cohort: 1:1:1 to double blinded treatment
    - Treatment Cohort: 1:1, as described in Part 2 Treatment Cohort below
- In Part 3, 1:1 to open label treatment

To achieve between-group comparability, block randomization within each facility will be used. Randomized participants within the facility will be stratified by role within the facility (resident versus facility staff), by sex, and whether or not the participant received a SARS-CoV-2 vaccine prior to screening (in Part 3 only).

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.

Blinding

Part 1 and Part 2 Prevention Cohort

Part 1 and Part 2 are blinded. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final database locks at the conclusion of the study, except as described in the following note.

Note: It is possible that some participants will have the SARS-CoV-2 negative result on the screening point of care test, but could be positive on the baseline SARS-CoV-2 PCR test. The results from the baseline PCR test will not be available until after the participant is randomized. Once positive results are known from the baseline PCR test, these participants will be unblinded and have the option to continue to be followed for safety according to the Prevention Cohort SoA. 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. • Participants who test negative at screening POC testing, then test positive at baseline PCR testing, will be unblinded. Unblinding is recorded and reported by the IWRS.

Abbreviations: IWRS = interactive web-response system.

If an investigator, site staff 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 as described in Section 7.1.

Part 2 Treatment Cohort

The Part 2 Treatment Cohort is blinded. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final database locks at the conclusion of the study.

If the participant is assigned to the Part 2 treatment cohort based on a positive POC test, the participant will be randomized to one of two arms. The participant will be informed that they are receiving active study intervention (that is, not placebo).

Part 3

Part 3 is open label.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or qualified designee, under medical supervision. The date and time of dosing will be recorded in the source documents and recorded in the case report form (CRF).

6.5. Concomitant Therapy

Concomitant Therapy

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

Remdesivir may be initiated as standard of care for participants requiring hospitalization.

If the local standard of care per written policies or guidelines (that is, not just an individual clinician decision) includes investigational agents to treat COVID-19, then starting these during the study is permitted, but may require additional safety monitoring.

Convalescent COVID-19 plasma treatment is not allowed, except in hospitalized participants.

Vaccines for SARS-CoV-2 should not be used prior to Week 8 of the evaluation period for the prevention cohort of Part 2.

Any medication, investigational agent, or vaccine, including over the counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest (such as convalescent COVID-19 plasma treatment) 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. 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

These sections describe reasons for a participant's

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

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 study intervention is definitively discontinued, the participant will remain in the study for follow-up and any further evaluations 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, legal authorized representative)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

Discontinuation is expected to be uncommon.

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

If the participant, or the participant's legal authorized representative, withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she or the participant's legal authorized representative, 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/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

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 who received investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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

8.1.1. SARS-CoV-2 Viral Swab and Serology

For details concerning viral swab, see Pharmacodynamics (Section 8.6). In Part 1, any positive result from a baseline SARS-CoV-2 test (NP or nasal swab) will result in the participant being declared SARS-CoV-2 positive in the analysis populations. In Part 2, the result from the screening POC test and baseline SARS-CoV-2 test are planned to be used to define SARS-CoV-2 status for the analysis populations.

Nasal swabs are planned during the evaluation and post-evaluation period at times described in the SoA. However, in the event nasal swabs cannot be supplied, the Sponsor may substitute with oropharyngeal, mid-turbinate or nasopharyngeal swabs. For instructions related to performing the nasopharyngeal, mid-turbinate, nasal, or oropharyngeal, swab, see guidance provided by Sponsor.

For Part 3, any positive result from a baseline SARS-CoV-2 test (NP) will result in the participant being declared SARS-CoV-2 positive in the analysis populations. NP swabs are planned during the evaluation and post-evaluation period at times described in the SoA.

For details concerning viral serology, see Pharmacodynamics (Section 8.6).

8.1.2. Participant Symptoms Questionnaire

Participants will be asked about the presence or absence of symptoms and signs associated with COVID-19 experienced during the past 24 hours, at the timepoints described in the SoA.

Signs and symptoms associated with COVID-19 should not be captured as AEs, unless more severe than expected. See Section 10.3.1. for additional information AE definitions used in this study.

Symptoms include

- shortness of breath with movement
- shortness of breath at rest
- cough
- chest pain or discomfort with breathing
- feeling feverish
- chills
- sore throat
- muscle or body aches and pain
- fatigue or loss of energy
- headache
- nausea
- diarrhea
- vomiting
- loss of appetite
- loss of taste, and
- loss of smell.

Participants requiring a legally authorized representative to provide signed informed consent will not be asked to report the presence or absence of symptoms. Only symptoms that may be observed by site staff other than the participant will be recorded, including

- shortness of breath with movement
- shortness of breath at rest
- cough
- diarrhea, and
- vomiting.

8.2. Safety Assessments

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

8.2.1. Physical Examinations, Clinical Signs and Symptoms

A complete physical examination and medical history (including preexisting clinical signs and symptoms) 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 at rest as specified in the SoA. 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.

If available during the study, optional remote vital status monitoring may be used to obtain vital data.

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

8.2.3. Clinical Safety 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 results, document this review, and record any clinically relevant changes occurring during the study in the CRF.

The laboratory reports must be filed with the source documents.

If laboratory values from non-protocol specified laboratory assessments performed at a local laboratory that require a change in participant management or are considered clinically significant by the investigator (i.e., SAE or AE), then the AE or SAE will be recorded by the investigator in 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
- intensive care unit admittance

- extended care facility admittance, and
- discharge for any of the above.

8.2.5. Procedures of Special Interest

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

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

8.3. Adverse Events and Serious Adverse Events

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet 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 (see Section 7).

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

All AEs and SAEs will be collected from the time of signing of the ICF until participation in 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 within the required timeframe begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving study intervention, it needs to be reported within the required timeframe ONLY 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 10.3.4, 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, Appendix 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, Appendix 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

Although normal pregnancy is not an adverse event, details of all pregnancies in female participants will be collected for 90 days after dosing.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.3, 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

Biologic agents carry the risk of systemic hypersensitivity reactions.

If such a reaction occurs, additional details describing each symptom should be provided to the sponsor in the infusion-related reaction/hypersensitivity CRF.

If symptoms and/or signs occur during or within 6 hours after infusion of LY3819253 and are believed to be hypersensitivity or due to cytokine release, then investigators are encouraged to

report the event as infusion-related immediate hypersensitivity reaction or cytokine release-associated infusion reaction, respectively.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

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

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

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

8.3.7. Infusion-related Reactions

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

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

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

Abbreviation: DAIDS = Division of AIDS.

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 (DAIDS 2017).

8.3.8. Product Complaints

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

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

Participants or participant's legal authorized representative 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 Section 10.3, Appendix 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 alone or 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 staff 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 Section 10.1.12, Appendix 1. Remaining samples used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate.

8.6. Pharmacodynamics

The SARS-CoV-2 viral RNA level and viral clearance will be evaluated by nasopharyngeal and/or mid-turbinate, nasal, or oropharyngeal swabs. See Section 10.2, Appendix 2; and Section 1.3, the SoA, for sample collection information.

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

8.7. Genetics

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

See Section 10.2, Appendix 2, and Section 1.3, the SoA, for sample collection information.

See Section 10.5, Appendix 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 alone and in combination with 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, Appendix 1.

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 and/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 antidrug antibodies (ADAs) in the presence of LY3819253 and/or LY3832479 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3819253 and/or LY3832479.

Sample retention

Sample retention is described in Section 10.1.12, Appendix 1.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

This study will compare LY3819253, alone and in combination with LY3832479, versus placebo in residents and facility staff of skilled nursing and assisted living facilities with a high risk of SARS-CoV-2 exposure. The primary study objective is to demonstrate superior efficacy of LY3819253 alone or in combination with LY3832479 over placebo in the prevention of COVID-19. Efficacy comparisons will be made without regard to changes to any background therapies. A graphical testing sequence strategy will be used to adjust for multiplicity in the primary and key secondary endpoints within Part 1 and Part 2 of the study. All analyses on Part 3 are considered exploratory.

9.2. Sample Size Determination

For Part 1, an estimated 33 events are needed to show superiority of LY3819253 4200 mg over placebo in each of the primary and key secondary endpoints, using the formula by Schoenfeld (1983). An average sample size of approximately 1300 participants who are SARS-CoV-2 PCR negative and serology negative at baseline is expected to obtain the needed number of events for each endpoint.

For Part 2, an estimated 56 events in the Prevention Cohort are needed to show superiority over placebo for either LY3819253 700 mg or LY3819253 350 mg+LY3832479 700 mg in each of the primary and key secondary endpoints. Approximately 2000 participants on average will be randomly assigned to study intervention such that approximately 1700 participants are randomized in the Prevention Cohort with the goal of achieving approximately 56 events on each of the primary and key secondary endpoints.

Due to the dynamic nature of the pandemic, Part 3 will enroll at least 30 participants and up to approximately 500 participants randomized to either LY3819253 700 mg or LY3819253 700 mg + LY3832479 1400 mg. Part 3 of the study is considered exploratory and is not powered for inference between the two treatment arms.

The maximum sample size for this study is approximately 5000 participants in the intent-to-treat (ITT) population.

Participants will be residents and staff of skilled nursing and assisted living facilities. Globally, there are many reports of the rapid spread of COVID-19 amongst residents of skilled nursing facilities following identification of an index case, with high associated rates of morbidity and mortality (Arons et al. 2020; Grabowski). Given that residents at these facilities are at higher risk for having a more severe disease course of COVID-19, this will be an important population to participate in the study. Therefore, a minimum of 300 residents will be enrolled. Operationally, this will be accomplished, when possible, by identifying facilities where approximately half of the participants interested in the study are residents.

For sample size determination for Part 1, the following assumptions were used:

1) two-sided significance level of 0.05;
2) 90% power for the primary and key secondary endpoints;
3) an 8-week placebo group event rate of 4.0% for moderate or worse severity COVID-19;

4) a risk ratio of 0.33 between LY3819253 and placebo in terms of the primary and key secondary endpoints.

For sample size determination for Part 2, the following assumptions were used:

1) two-sided significance level of 0.025;
2) 90% power for the primary and key secondary endpoints;
3) an 8-week placebo group event rate of 5.3% for moderate or worse severity COVID-19;
4) a risk ratio of 0.33 between active drug and placebo in terms of the primary and key secondary endpoints.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who provide informed consent.
Enrolled/ITT	All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.
Facility Staff	All participants in the Enrolled/ITT population who are staff/employees of the facility.
Residents	All participants in the Enrolled/ITT population who are residents of the facility.
Part 1 Safety	All participants randomly assigned to study intervention in Part 1 and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Part 2 Safety	All participants randomly assigned to study intervention in Part 2 and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Part 3 Safety	All participants randomly assigned to study intervention in Part 3 and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Fully Dosed	All participants in the Safety population who receive a complete infusion of study intervention.
Part 1 Prevention	All participants in the Enrolled/Intent-to-Treat population in Part 1 who are SARS-CoV-2 RT-PCR negative and serology negative at baseline.

Population	Description
Part 1 Treatment	All participants in the Enrolled/ITT population in Part 1 who are SARS-CoV-2 RT-PCR positive at baseline and serology negative.
Part 2 Prevention	All participants in the Enrolled/Intent-to-Treat population in the Prevention Cohort in Part 2 who are SARS-CoV-2 POC and RT-PCR negative and serology negative at baseline.
Part 2 Treatment	All participants in the Enrolled/ITT population in the Treatment Cohort in Part 2 who are SARS-CoV-2 POC and RT-PCR positive and serology negative at baseline.
Part 3 Treatment	All participants in the Enrolled/ITT population in Part 3 who are SARS-CoV-2 RT-PCR positive and serology negative at baseline.
Serology-Positive	All participants in the Enrolled/ITT population who are SARS-CoV-2 serology positive at baseline.
POC-Positive/RT-PCR Negative	All participants in the Enrolled/ITT population in Part 2 who are SARS-CoV-2 POC positive and RT-PCR negative at baseline.
POC-Negative/RT-PCR Positive	All participants in the Enrolled/ITT population in Part 2 who are SARS-CoV-2 POC negative and RT-PCR positive at baseline.
PK Analysis	All randomized participants who received study intervention and have evaluable PK sample. Participants will be analyzed according to the intervention they received.

Abbreviations: ITT = intent to treat; PK = pharmacokinetics; RT-PCR = reverse transcription – polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Throughout the document, the term “the Prevention populations” will be used to describe both the Part 1 Prevention and Part 2 Prevention populations. Analyses on the Prevention populations will be conducted on each Prevention population separately. The terms “the Treatment populations” and “the Safety populations” are defined similarly.

The following study arms are defined for the purposes of comparison:

Study Arm	Study Part	Dose	Intervention
1	Part 1	4200 mg	LY3819253
2	Part 1	---	Placebo
3	Part 2 (Prevention Cohort)	700 mg	LY3819253
4	Part 2 (Prevention Cohort)	350 mg + 700 mg	LY3819253 + LY3832479
5	Part 2 (Prevention Cohort)	---	Placebo

Study Arm	Study Part	Dose	Intervention
6	Part 2 (Treatment Cohort)	700 mg	LY3819253
7	Part 2 (Treatment Cohort)	700 mg + 1400 mg	LY3819253 + LY3832479
8	Part 3	700 mg	LY3819253
9	Part 3	700 mg + 1400 mg	LY3819253 + LY3832479

9.4. Statistical Analyses

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all confidence intervals will be given at a 2-sided 95% level.

For subgroup analyses, all tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

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 statistical analysis plan (SAP) and the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

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

For analyses on the Part 2 Prevention population, LY3819253 700 mg and LY3819253 350 mg + LY3832479 700 mg will be assessed against placebo separately.

For analyses on the Part 3 Treatment population, results will be summarized separately for LY3819253 700 mg and LY3819253 700 mg + LY3832479 1400 mg. Part 3 is not powered for inference between the two treatment arms.

If enrolling to a placebo-controlled trial is challenged by an effective medication becoming available for prevention of COVID-19 and SARS-CoV-2, then the placebo arm may be dropped.

9.4.1. General Considerations

Baseline values for all measurements will be the last measurement taking prior to receiving study intervention, unless otherwise specified.

The primary analyses of the primary endpoints and key secondary endpoints will be based on events that occurred after randomization.

The analysis model for time-to-event analyses will be a Cox proportional hazards regression model for the time to the first occurrence of the relevant event, with treatment as a fixed effect. For continuous measures, analysis of covariance (ANCOVA) and/or mixed-effects model for repeated measures (MMRM) will be used to analyze changes from baseline with the baseline

value as the covariate. The MMRM model will include fixed effects for treatment, visit, treatment-by-visit interaction, the baseline as a covariate and the participant as a random effect. Summary statistics will include sample size, mean, standard deviation, median, 10th and 90th percentiles for both the actual and the change from baseline measurements. Least-squares mean (LS mean) and standard error derived from the model will also be displayed for the change from baseline measurement. Treatment comparisons will be displayed showing the treatment difference LS Mean and the 95% confidence limits along with the p-value.

For continuous lab measurements, an analysis of variance (ANOVA) on ranks will be used and p-values for the difference between each study intervention and placebo will be reported.

For categorical measures, summary statistics will include sample size, frequency, and percentage. For primary and secondary analyses, a logistic regression model will be used. The model will include fixed effects for treatment and stratification factors such as facility. For other analyses, frequencies will be analyzed using Chi-square tests if the expected count is at least 5, in at least 80% of the cells, otherwise a Fisher's exact Test will be used.

All analyses will be implemented using SAS® Version 9.4 or higher, or R version 3.6.3 or higher.

9.4.2. Participant Disposition

A listing of participant discontinuation will be presented for all randomized participants. Summary analyses will be conducted for the Prevention, Treatment, and Safety populations.

Frequency counts and percentages will be presented for each treatment group and compared across treatment groups using Chi-square tests or Fisher's exact tests.

9.4.3. Participant Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the Prevention, Treatment, and Safety populations. For continuous measures, summary statistics will include sample size, mean, median, 10th and 90th percentiles and standard deviations. Means will be analyzed using ANOVA. For categorical measures, summary statistics will include sample size, frequency, and percentages.

9.4.4. Concomitant Therapy

Concomitant medications will be summarized by classes of medications and by treatment group using the ITT population. Frequencies will be analyzed using Chi-square tests or Fisher's exact tests.

9.4.5. Primary Endpoint

The endpoint for the primary analysis in the prevention populations is defined as cumulative incidence of COVID-19, defined as the detection of SARS-CoV-2 by RT-PCR AND mild or worse disease severity within 21 days of detection, up to 8 weeks after randomization.

The primary analysis model will be a logistic regression model which will include occurrence of a primary endpoint event as the response variable, and treatment and stratification factors such as facility as explanatory variables.

9.4.6. Secondary Endpoints

As key secondary analyses, the proportion of participants who experience each of the following will be assessed on the Prevention population:

- Cumulative incidence of moderate or worse severity COVID-19 (within 8 weeks from randomization)
- Cumulative incidence of SARS-CoV-2 infection (within 4 weeks from randomization)

The analysis model for the key secondary analyses will be similar to the primary analysis model. To control for multiplicity, a fixed-sequence approach will be used to test the primary and key secondary endpoints. A separate testing sequence will be used for each part of the study. The final testing sequences will be specified in the SAP.

Additionally, the following secondary analyses will be conducted on the Prevention population:

- The proportion of participants who experience each of the following will be compared across treatments:
    - Cumulative incidence of SARS-CoV-2 infection, up to 8 weeks from randomization
    - Hospitalization or death due to COVID-19, up to 8 weeks from randomization
    - Hospitalization due to COVID-19, COVID-19 related emergency visit, or death
    - Death due to COVID-19, up to 8 weeks from randomization

9.4.6.1. Safety Analyses

Unless otherwise noted, all safety analyses will be conducted on the Safety population.

All AEs will be listed by participant and may include information on treatment group, visit, preferred term, severity, seriousness, and relationship to the study medication, procedure, or device.

Treatment-emergent adverse events (TEAEs) will be defined as events that first occur or worsen (increase in severity) after the first injection of study drug following randomization. The count and proportion of participant with TEAEs will be summarized for each treatment group. Overall treatment group differences will be compared using Chi-square tests or Fisher's exact tests.

Serious adverse events will also be summarized. The counts and proportion of participants experiencing the event of interest will be reported for each treatment arm. Treatment groups will be compared by Chi-square tests or Fisher's exact tests.

Permanent discontinuations of study drug due to AEs will be listed. The count and proportion of discontinuations of study drug due to AEs will be reported. Time to discontinuation (due to AEs) will be compared between treatment groups using a Cox proportional hazard regression model with treatment as a fixed effect. Kaplan-Meier curves for both treatment groups will be reported.

9.4.6.2. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on data from all participants who receive intervention and have evaluable PK. Pharmacokinetic estimates for LY3819253 and LY3832479

may be summarized by sample time, such as, on Day 29. A population approach using a nonlinear mixed-effects modeling (NONMEM) program may also be performed.

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

9.4.7. Exploratory Endpoints

As exploratory analyses, the primary and secondary analyses may be repeated on the Treatment populations and on all participants who are in either the Prevention or Treatment populations in Part 1 and 2.

Additional exploratory analyses for Part 1 and Part 2 may include

- time to improvement of COVID-19 disease to mild severity, in the subset of the participants who have at baseline, or develop, moderate or worse COVID-19
- worst score according to NIAID ordinal scale(s)
- examination of virology for participants who become SARS-CoV-2 positive,
- examination of viral resistance to each study intervention,
- duration of hospitalization in participants who are hospitalized due to COVID-19, and
- subgroup analyses of primary and key secondary endpoints within residents versus staff.

For Part 3, exploratory analyses are listed in Section 3.

Additional exploratory analyses on Part 3 may be conducted.

Details on these analyses will be described in the SAP.

9.4.8. Other Safety Analyses

Other safety analyses will include vital signs and laboratory analytes. Categorical safety measures will be summarized with counts and proportions of participants, and compared by treatment using either a Chi-square test or a Fisher's exact test. Continuous safety measures will be summarized as mean change by visit and will be analyzed using an MMRM model with treatment included as an explanatory variable. Exposure to study intervention will be calculated for each participant and summarized by treatment group.

9.4.9. Immunogenicity Analyses

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

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer 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 each study intervention 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 each study intervention may also be assessed. Additional details may be provided in the SAP.

9.5. Interim Analyses

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by an external DSMB. The DSMB will make recommendations concerning the conduct of the studies, including changes to the informed consent form.

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

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

The SAP and DSMB charter will describe the planned interim analyses, including timing of any interim analyses, in greater detail.

9.6. Data Monitoring Committee (DMC)

The sponsor will form a DSMB 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 DSMB 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, Appendix 1. Details of the DSMB will be provided in the DSMB 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 International Ethical Guidelines
- Applicable International Council for Harmonisation Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, 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
- 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. Facility sites are compensated for the use of the grounds and building as outlined in the approved agreement.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

Due to strict respiratory isolation policies, limited access to COVID-19 participants 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. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

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 participant record must document how consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent and, if applicable, the individual designated to witness a verbal consent, must use the appropriate measure (that is, electronic, written) to provide signature and date.

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

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

10.1.4. Data Protection

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

The participant must be informed that his/her 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 his/her 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 DSMB will consist of members external to Lilly. DSMB membership will include, at a minimum, a statistician and two physicians with expertise in the appropriate specialties. Details about the DSMB membership, purpose, responsibilities, and operation will be described in a DSMB charter.

10.1.6. Dissemination of Clinical Study Data

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

10.1.7. Data Quality Assurance

Investigator Responsibilities

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

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

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

Data Monitoring and Management

The Monitoring Plan includes

- monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring
- methods
- responsibilities and requirements
- handling of noncompliance issues and
- monitoring techniques.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

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

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

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

Records Retention and Audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period.

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

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

Data Capture System

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

An 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, except for vital signs and symptom assessment. Vital signs and symptom assessments will be direct data captured in the EDC system, and will serve as the source documentation. The investigator does not maintain a separate written or electronic record of these data. If there are clinical or business continuity needs that do not enable these data to be direct data captured, these data will be captured as source via paper and transcribed into EDC. 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 results 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 by 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.

Definition of what constitutes source data can be found in 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 sufficient notice is given in advance of the intended termination.

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

- 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
- 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 participant and assures 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.

10.1.11. Investigator Information

Licensed physicians with a specialty in internal medicine, gerontology, infectious disease, critical care, or pulmonary disease or other specialty deemed to be appropriate by the sponsor 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 Patient 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 sample	Sponsor or designee	up to 2 years

Abbreviation: ADA = antidrug antibody.

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 SoA and 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 laboratory safety results.

Refer to Section 10.6, Appendix 6, for recommended laboratory testing for hypersensitivity events.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (Red Blood Cells - RBCs)	
Mean cell volume	
Mean cell hemoglobin	
Leukocytes (White Blood Cells - WBCs)	
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)	

Clinical Laboratory Tests	Comments
Calculations	
eGFR	calculated by CKD-EPI equation. Calculated by Lilly-designated laboratory. Results will not be provided to the investigative sites.
SARS-Cov-2 Panel	
C-Reactive Protein	
Ferritin	
D-dimer	
Procalcitonin	
Troponin	
Hormones (female)	
Urine Pregnancy	Local laboratory
Pharmacokinetic Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Pharmacodynamic sample	Assayed by Lilly-designated laboratory.
SARS-Cov-2 swab (nasopharyngeal, mid-turbinate, nasal, or oropharyngeal)	Negative results will not be provided to the investigative sites.
SARS-Cov-2 Serology	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Pharmacogenetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Exploratory Biomarker Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
RNA (PAXGene)	
Whole Blood (EDTA) Epigenetics	
Immunogenicity (ADA) 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., electrocardiogram, 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 immediately life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for 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 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 non-infusion-related 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 DAIDS ***Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected 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.

Infusion-related AE/SAE intensity/severity should be assessed and graded according to protocol Section 6.1.1.2.

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 AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always 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

10.4.1. Women

Woman of Childbearing Potential

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

Women in the following categories are not considered WOCBP

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

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

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

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

Participation in the Study

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

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

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

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

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

Acceptable Methods of Contraception

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

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

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

Not Acceptable Methods of Contraception

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

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

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

10.4.2. Men

Men, regardless of their fertility status, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 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.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

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

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

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

Female Participants who become pregnant

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

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

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

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

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

10.5. Appendix 5: Genetics

Sample collection information is found in Section 10.1.12, Appendix 1.

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 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 antidrug 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 = antidrug 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 <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥2 × baseline (except for participants with Gilbert's syndrome)

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

The laboratory tests listed in Section 10.2, Appendix 2, including alanine aminotransferase (ALT), AST, ALP, total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated when monitoring labs are performed.

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 between 3 times weekly and every other week, 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 <1.5× ULN	ALT or AST ≥3× ULN with hepatic signs/symptoms*, or ALT or AST ≥5× ULN
ALP <1.5× ULN	ALP ≥3× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline with hepatic signs/symptoms*, or ALT or AST ≥3× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥1.5× 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%.**

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

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 CRFs 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
ADA	antidrug antibody
ADE	antibody-dependent enhancement
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
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 subjects are aware of the treatment received.
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
COVID-19	Coronavirus disease - 2019
CRF	Case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRS	Clinical research scientist
CSR	clinical study report
CTA	Clinical trial agreement
DAIDS	Division of AIDS
DMC	Data monitoring committee; functionally equivalent to DSMB for this study
DSMB	Data safety monitoring board
Device Deficiencies	Equivalent to product complaint

EDC	Electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
Facility	The physical location for the conduct of study procedures. This will be the skilled nursing and assisted living facilities associated with the nursing home network. See also "Skilled nursing and Assisted Living facility".
Facility staff	Participants who are staff of the facility. For "facility", see "Facility" and "Skilled nursing and Assisted Living facility". Contrast to "Site staff"
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
IgG1	immunoglobulin G1
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.
IP	investigational product
IRB/IEC	Institutional review board / independent ethics committee
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
LS mean	least-squares mean
mAb	monoclonal antibody
MMRM	mixed-effects model for repeated measures

NIAID	National Institute of Allergy and Infectious Diseases
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
POC	Point of care test. In this study, the POC test is a rapid POC test that returns results in minutes.
Prevention Cohort	Participants in Part 2 who test negative during screening on the POC test. Contrast with "Treatment Cohort".
RT-PCR	reverse transcription – polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
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.
Site	The physical location of the primary investigator and associated study staff who will conduct study procedures at the facilities.
Site staff	Site personnel who perform study tasks. Contrast to "Facility staff"
Skilled nursing and Assisted Living facility	This terminology is intended to be broad and is inclusive of skilled nursing, assisted living, long-term care, or nursing home facilities. Memory care units in any of the above can be included. Also, this terminology includes residents who may need only short-term care.
SoA	Schedule of Activities
TBL	total bilirubin
TE-ADA	treatment-emergent antidrug antibody
TE-ADA+	treatment-emergent antidrug antibody positive
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
Treatment Cohort	Participants in Part 2 who test positive during screening on the POC test. Contrast with "Prevention Cohort".
WOCBP	women of childbearing potential

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 c

Overall Rationale for the Amendment:

The sponsor is adding Part 3 of Study PYAD.

Part 3 of the study is a two arm, outpatient, open label, exploratory cohort evaluating the efficacy and safety of LY3819253 and LY3819253 in combination with LY3832479 in participants positive for SARS-CoV-2 with or without symptoms in staff and residents who are at higher risk for more severe disease and hospitalization in skilled nursing and assisted living facilities.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated text to match the body of the protocol for Objectives and Endpoints, Overall Design, Number of Participants, and Intervention Groups and Duration.	Updates were made to the associated sections. See rationale for these sections below.
1.2 Schema	Part 3 schema added.	Activation of Part 3.
1.2 Schema 4.1.2 Evaluation Period 6.1 Study Intervention(s) Administered 9.3 Populations for Analyses	Modified dose for Part 2 Treatment	To align to the current dosing strategy being evaluated in the treatment studies evaluating monotherapy and combination therapy.
1.3.2 Part 2 Treatment Cohort and Part 3	Modified subsection title to reflect addition of Part 3. Added note for inclusion and exclusion criteria review, "Note that eligibility criteria for Part 2 and Part 3 are different." Added row for documentation of positive SARS-CoV-2 infection.	Activation of Part 3. Clarification. Activation of Part 3.
3 Objectives and Endpoints	Added Part 3 exploratory treatment objectives Added, "Safety, pharmacokinetics, and antidrug antibodies will be characterized in the overall intent to treat population and in the analysis populations" to Part 2 and Part 3 exploratory objectives and endpoints table. Updated Part 2 heading.	Activation of Part 3. Clarification.
4.1.1 Screening Period	Added screening description for Part 3.	Activation of Part 3.

Section # and Name	Description of Change	Brief Rationale
4.1.2 Evaluation Period	Modified description of Part 2 activation. Added evaluation period description for Part 3.	Clarification on activation of Part 2. Activation of Part 3.
4.1.3 Follow-up Period	Added Part 3 to subheader: Part 2 Treatment Cohort and Part 3.	Activation of Part 3.
4.2 Scientific Rationale for Study Design	Added rationale for study design of Part 3.	Activation of Part 3.
4.3 Justification for Dose	Added justification for doses chosen for Parts 2 and 3.	Activation of Part 3.
5.1 Inclusion Criteria	Added criteria 19 and 20 for participants of Part 3. Clarified criterion 2.	Part 3 population will consist of participants who are at higher risk for more severe disease and hospitalization. Clarification: only applies to Parts 1 and 2.
6.1 Study Intervention(s) Administered	Updated dose level for study intervention and Part 3. Updated monitoring for infusion times less than 30 minutes.	Activation of Part 3.
6.3 Measures to Minimize Bias: Randomization and Blinding	Added statement that Part 3 is open label.	Activation of Part 3.
8.1.1 SARS-CoV-2 Viral Swab and Serology	Added description of viral swab for Part 3.	Activation of Part 3.
9.1 Statistical Hypotheses	Added description of Part 3 analyses. Clarified Part 1 and Part 2 information.	Activation of Part 3. Clarification.
9.2 Sample Size Determination	Added sample size for Part 3.	Activation of Part 3.
9.3 Populations for Analyses	Added Part 3 populations and treatment groups.	Activation of Part 3.
9.4 Statistical Analyses	Added description of Part 3 analyses.	Activation of Part 3.
9.4.7 Exploratory Endpoints	Added description of Part 3 analyses. Clarified Part 1 and Part 2 information.	Activation of Part 3. Clarification.
11 References	Added FDA EUA fact sheet	Addition of reference.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described.

Amendment b (6 November 2020)

Overall Rationale for the Amendment:

This amendment addresses changes to the follow-up period for the treatment cohort in Part 2 per FDA feedback. The FDA recommended a follow-up period of at least 5 half-lives of the intervention. The follow-up period is changed from Day 57 to Day 85 and the maximum total duration of study for each participant in the treatment cohort is changed from 8 weeks to 12 weeks.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Post-treatment follow-up changed from study day 57 to 85	FDA feedback
1.1 Synopsis	Maximum total duration of study for each participant in the treatment cohort is changed from 8 weeks to 12 weeks	Change in follow-up period duration
1.2 Schema	Part 2 schema updated with change in follow-up period from 8 weeks to 12 weeks	Change in follow-up period duration
1.3.2 Part 2 Treatment Cohort Schedule of Activities (SoA)	Post-treatment follow-up changed from study day 57 to 85	FDA feedback
4.1.2 Evaluation Period	Follow-up changed from study day 57 to 85	FDA feedback
4.1.2 Evaluation Period	Maximum total duration of study for each participant in the treatment cohort is changed	Change in follow-up period duration
4.1.2 Evaluation Period	Treatment cohort visit type table updated from study day 57 to 85	FDA feedback
4.1.3 Follow-up Period	Part 2 Treatment Cohort changed post-evaluation follow-up assessment from study day 57 to 85	FDA feedback
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described.

Amendment a (27 October 2020)

Overall Rationale for the Amendment:

The sponsor is adding Part 2 of Study PYAD in order to further investigate the efficacy and safety of a lower dose level of LY3819253 and the combination intervention of LY3819253 and LY3832479 in preventing SARS-CoV-2 infection and COVID-19 in skilled nursing and assisted living facility residents and staff.

The primary endpoint for Part 1 and Part 2 has been changed to cumulative incidence of COVID-19 defined as the detection of SARS-CoV-2 by RT-PCR AND mild or worse disease severity within 21 days of detection [time frame for endpoint evaluation: 8 weeks from randomization]. The cumulative incidence of SARS-CoV-2 infection defined as the detection of SARS-CoV-2 by RT-PCR within 4 weeks from randomization is now a key secondary endpoint.

The changes in the primary endpoint aligns closely to the Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention,

> III.C.: "In prevention trials, the primary endpoint should be the occurrence of laboratory-confirmed SARS-CoV-2 infection (with or without symptoms) or SARS-CoV-2 infection with symptoms (i.e., COVID-19) through a prespecified time point" (FDA 2020)

Section # and Name	Description of Change	Brief Rationale
Title Page, Synopsis	Title and short title changed to include "alone and in combination with LY3832479."	Activation of Part 2 includes evaluation of combination therapy with LY3819253 and LY3832479.
1.1 Synopsis	Updated text to match the body of the protocol for Rationale, Objectives and Endpoints, Overall Design, Number of Participants, and Intervention Groups and Duration.	Updates were made to the associated sections. See rationale for these sections below.
	In Number of Participants, modified description, "…a total of approximately 1700 participants… ~~on average~~ will be randomly assigned…".	Clarity.
1.2 Schema	Added schema for Part 2.	Activation of Part 2.
1.3.1 Part 1 and Prevention Cohort of Part 2	Added SARS-CoV-2 POC Test (nasal swab) at Screening for participants in Part 2.	Cohort allocation is dependent on the POC test result.
	Added "(for PCR test)" to the SARS-CoV-2 nasopharyngeal and nasal swab test descriptions.	Clarity.
	Added comment to PK sample: "For participants in Part 2, Day 1	Collect C_{max} data post-infusion in Part 2.

Section # and Name	Description of Change	Brief Rationale
	collection is post-dose only (approx. 30 minutes after end of infusion)."	
1.3.2 Part 2 Treatment Cohort (SOA)	Added separate SOA table for the Part 2 Treatment Cohort.	Participants who test positive on the screening POC test for SARS-CoV-2 will be followed for a shorter duration (See Section 1.3.2), as they are not observed for the prevention endpoint and are an exploratory treatment group.
2.1 Study Rationale	Added LY3819253 in combination with LY3832479 to description of study aim.	Combination therapy has been added as a study intervention group.
2.2 Background	Added LY3832479 background.	Combination therapy has been added as a study intervention group.
2.3 Benefit/Risk Assessment	Added "No clinically relevant off-target binding has been observed in tissue cross reactivity studies of membrane targets in human tissues."	Added information on a potential risk.
	Removed "LY3819253 will be administered to participants at sufficiently high dose levels to neutralize SARS-CoV-2."	Rationale for dose described in Section 4.3.
	Added details on risk of clinical ADE and reasons for considering said risk as low.	Added information on a potential risk.
	Added references and benefit/risk information for LY3832479.	Combination therapy has been added as a study intervention group.
3 Objectives and Endpoints	Changed the primary endpoint for the Part 1 Prevention Population to: • Cumulative incidence of ~~SARS-CoV-2~~ COVID-19 defined as the detection of SARS-CoV-2 by RT-PCR AND mild or worse disease severity[a] within 21 days of detection • Time frame for endpoint evaluation: 8 weeks from randomization	Endpoint aligns with FDA *Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatments or Prevention,* III.C, and with the primary endpoints for ongoing SARS-CoV-2 vaccine trials.
	Changed the key secondary endpoint for Part 1 Prevention Population to:	Updated the secondary endpoint to evaluate prior primary endpoint.

Section # and Name	Description of Change	Brief Rationale
	• Cumulative incidence of ~~COVID-19~~SARS-CoV-2; defined as the detection of SARS-CoV-2 by RT-PCR, ~~AND mild or worse disease severity[a] within 21 days of detection~~ • Time frame for endpoint evaluation: 4 weeks from randomization	
	Modified other secondary and exploratory endpoints, "Compare the frequency of hospitalization or death due to COVID-19."	Added "death" to capture serious disease not captured by hospitalization.
	Added the objectives and endpoints for Part 2 of Study PYAD	Added objectives and endpoints for Part 2 to align with the design of Part 2.
4.1 Overall Design	Added "prophylaxis" to overall study description.	Alignment with synopsis.
	Added "…alone and in combination with LY3832479…" to study description.	Combination therapy with LY3832479 has been added as a study intervention group.
4.1.1 Screening Period	Added, "Prior to randomization in Part 2, participants will receive a point of care (POC) test for SARS-CoV-2 infection. Participants will be allocated to either Prevention or Treatment Cohorts based on the result."	The POC test is used to determine allocation to the Prevention or Treatment Cohort in Part 2.
4.1.2 Evaluation Period	Added, "Participants in Part 1 will be randomized to placebo or LY3819253. When the needed events for the primary and key secondary endpoints are achieved, and the minimum number of residents enroll, the sponsor will trigger activation of Part 2."	Ensures that Part 2 occurs after the primary endpoint for Part 1 can be evaluated.
	Added description of the Prevention and Treatment Cohorts.	Activation of Part 2.
	Added a visit type information table.	Clarification of visit types.

Section # and Name	Description of Change	Brief Rationale
	Updated Table 1 Definitions for COVID-19 Severity: removed definition of Shock.	The definition did not define participants in shock. Clinical judgement will be relied on.
4.1.3 Follow-up Period	Provided information on the follow-up period for Part 2.	Activation of Part 2.
4.2 Scientific Rationale for Study Design	Added "alone or in combination with LY3832479".	Combination therapy with LY3832479 has been added as a study intervention group.
	Added study design descriptions for POC and RT-PCR tests.	Activation of Part 2.
4.3 Justification for Dose	Updated to include justification for doses used in Part 2.	Activation of Part 2.
5.2 Exclusion Criteria	Added to criterion 7, "Recovered from ~~confirmed~~ COVID-19 disease or asymptomatic infection".	Included recovered from asymptomatic infection in exclusion as it is possible immunity could be established in people with symptomatic or asymptomatic disease. Removed "confirmed" because there is no specific definition.
	Added to criterion 11, "Participation in a previous SARS-CoV-2 vaccine trial or received an approved SARS-CoV-2 vaccine."	Anticipation of an EUA or approved vaccine during the study.
	Added LY3832479 to criterion 16.	Addition of LY3832479 to study.
6.1 Study Intervention(s) Administered	Added information that describes Part 2 treatment groups.	Activation of Part 2.
	Changed monitoring from 2 hours after completion of the infusion to 1 hour	Based on available safety data.
6.1.1.1 Premedication for Infusions	Modified text, "Premedication for infusions is not planned. However, ~~if an infusion reaction occurs during administration or~~ if the participant…".	Clarity: participants receive a single infusion in this study, so the text is not applicable.
6.3 Measures to Minimize Bias: Randomization and Blinding	Added information that describes blinding for Part 2.	Activation of Part 2.
	Updated table for general procedures for unblinding: "The date and reason that the	Clarification.

Section # and Name	Description of Change	Brief Rationale
	blind was broken must be recorded in the source documentation ~~and case report form~~."	
	Added to the general procedures for unblinding table, "Participants who test negative at screening POC testing, then test positive at baseline PCR testing, will be unblinded. Unblinding is recorded and reported by the IWRS."	Clarification.
6.5 Concomitant Therapy	Updated language on remdesivir, "~~Therefore,~~ remdesivir may be initiated as standard of care for participants requiring hospitalization~~ed with severe disease (if available through the FDA Emergency Use Authorizations) outside of local standard of care per written policies or guidelines~~."	Remdesivir is now approved for treatment of hospitalized COVID-19 patients.
	Added, "Vaccines for SARS-CoV-2 should not be used prior to Week 8 of the evaluation period for the prevention cohort of Part 2."	SARS-CoV-2 vaccines are prohibited during the evaluation period of the prevention cohort to maintain interpretability of study endpoints.
8.1.1 SARS-CoV-2 Viral Swab and Serology	Added information on the POC test. Edited language to clarify test usage in study.	Activation of Part 2.
	Added "However, for Part 1, a positive result from any baseline swab will be sufficient for positive baseline RT-PCR status."	Clarification.
8.4 Treatment of Overdose	Added "alone or in combination with LY3832479.	Activation of Part 2.
8.5 Pharmacokinetics	Added LY3832479.	Activation of Part 2.
8.5.1 Bioanalytical	Added LY3832479.	Activation of Part 2.
8.6 Pharmacodynamics	Added LY3832479.	Activation of Part 2.
8.8 Biomarkers	Added LY3832479.	Activation of Part 2.
8.9 Immunogenicity	Added LY3832479.	Activation of Part 2.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Hypotheses	Added reference to LY3832479.	Activation of Part 2.
	Updated primary endpoint description.	Endpoint aligns with FDA *Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatments or Prevention, III.C,* and with the primary endpoints for ongoing SARS-CoV-2 vaccine trials.
9.2 Sample Size Determination	Added sample size information for Part 2.	Activation of Part 2.
	Added dose strength (4200 mg) to describe primary endpoint.	Clarification.
9.3 Populations for Analyses	Updated table to include relevant Part 2 populations.	Activation of Part 2.
	Added table to define study arms for purposes of comparison.	Clarity.
	Added description for use of specified terms.	Clarity.
9.4 Statistical Analyses	Added analysis information for Part 2.	Activation of Part 2.
9.4.1. General Considerations	Modified language, "…for the difference between ~~LY3819253~~ each study intervention and placebo will be reported."	Addition of LY3832479.
9.4.5 Primary Endpoint	Updated primary endpoint.	Endpoint aligns with FDA *Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatments or Prevention, III.C,* and with the primary endpoints for ongoing SARS-CoV-2 vaccine trials.
9.4.6 Secondary Endpoints	Updated secondary endpoints.	As described in Section 3.
9.4.6.1 Safety Analyses	Removed study drug overdose language	Overdose is described in Section 8.4. AE definitions are detailed in Section 10.3.
9.4.6.2 Pharmacokinetic Analyses	Added subsection to describe PK analyses.	Clarity.

Section # and Name	Description of Change	Brief Rationale
9.4.7 Exploratory Endpoints	Modified language to be inclusive of all study interventions.	Addition of LY3832479.
9.4.8 Other Safety Analyses	Updated: "safety measures will be summarized with ~~incidence rates~~ counts and proportions of participants"	Correction.
9.4.9 Immunogenicity Analysis	Modified language to be inclusive of all study interventions.	Addition of LY3832479.
10.1.7 Data Quality Assurance	Added information on the data capture system: "If there are clinical or business continuity needs that do not enable these data to be direct data captured, these data will be captured as source via paper and transcribed into EDC."	Flexibility.
10.2 Clinical Laboratory Tests	Added "Anti-LY3832479 antibodies" to immunogenicity samples collected	Addition of LY3832479.
10.5 Genetics	Added LY3832479.	Activation of Part 2.
10.6 Recommended Laboratory Testing for Hypersensitivity Events	Added LY3832479.	Activation of Part 2.
10.8 Abbreviations	Added definitions for Prevention Cohort and Treatment Cohort.	Clarity.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described.

11. References

Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *NEJM*. 2020;382(22):2081-90. https://doi.org/10.1056/NEJMoa2008457

[CDC] Centers for Disease Control and Prevention. Nursing home care. Updated 11 March 2016. https://www.cdc.gov/nchs/fastats/nursing-home-care.htm. Accessed 1 June 2020.

[CDC] Centers for Disease Control and Prevention. Older adults. Updated 30 April 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html. Accessed 1 June 2020.

Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *NEJM*. Published 28 October 2020. https://doi.org/10.1056/NEJMoa2029849

[DAIDS] Division of AIDS, National Institutes of Health. Division of AIDS, US Department of Health and Human Services. Table for Grading the Severity of Adult and Pediatric Adverse Events. National Institute of Allergy and Infectious Diseases. Corrected version 2.1. July 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed: 14 April 2020.

FDA EUA fact sheet. Fact sheet for health care providers, Emergency Use Authorization (EUA) of bamlanivimab. Available at: https://www.fda.gov/media/143603/download. Accessed: 16 November 2020.

[FDA] Food and Drug Administration. COVID-19: developing drugs and biological products for treatment or prevention. May 2020. Available at https://www.fda.gov/media/137926/download. Accessed 1 June 2020.

Gottlieb RL, Nirula A, Chen P, et al. Effect of neutralizing monoclonal antibody bamlanivimab as monotherapy or in combination with etesevimab on viral load among patients with mild-to-moderate COVID-19: A randomized clinical trial. [published online 21 Jan 2021]. *JAMA* https://doi.org/10.1001/jama.2021.0202

Grabowski DC and Mor V. Nursing home care in crisis in the wake of COVID-19. [published online 22 May 2020]. *JAMA*. https://doi.org/10.1001/jama.2020.8524

Graham NSN, Junghans C, Downes R, et al. SARS-CoV-2 infection, clinical features and outcome of COVID-19 in United Kingdom nursing homes [published online ahead of print, 2020 Jun 3]. *J Infect.* 2020;S0163-4453(20)30348-0. https://doi.org/10.1016/j.jinf.2020.05.073

Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics.* 1983; 39(2):499-503.

Werner RM, Hoffman AK, Coe MB. Long-term care policy after Covid-19 — solving the nursing home crisis. [Published online 27 May 2020]. *NEJM.* https://doi.org/10.1056/NEJMp2014811

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