This Supplement contains the following items:

Title Page

Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of LY3819253 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

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

Amendment Number: This is the original protocol

Compound: LY3819253

Study Phase: 3

Short Title: A Study to Evaluate LY3819253 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)

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

Medical Monitor Name and Contact Information will be provided separately.

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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 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 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 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

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 – polymerous 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	
Objectives	Endpoints
Primary	
[time frame for endpoint evaluation: **4 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
Key Secondary	
[time frame for endpoint evaluation: **8 weeks** from randomization]	
• 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
• 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
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 due to COVID-19	• Proportion of participants who are hospitalized due to COVID-19
• Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events: ○ COVID-19 related hospitalization (defined as ≥24 hours of acute care), ○ COVID-19 related emergency room visit, or ○ 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.

Overall Design

Study J2X-MC-PYAD is a randomized, double-blind, placebo-controlled, prophylaxis study to evaluate the efficacy and safety of intravenous LY3819253 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 2-arm interventional study that is double-blinded.

Number of Participants:

Approximately 1700 participants (intent-to-treat [ITT] population) on average 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.

The maximum sample size for this study is approximately 2400 participants in the ITT population.

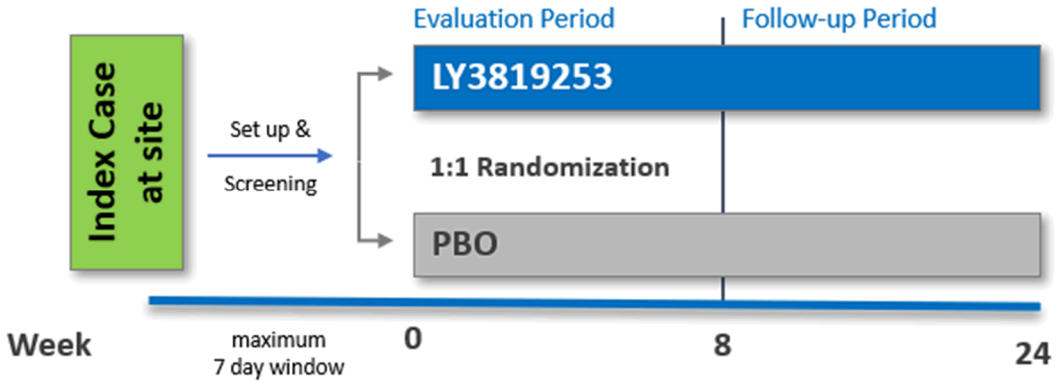
Intervention Groups and Duration:

Eligible participants will be randomized to one of two arms: placebo or LY3819253. Participants will receive one intravenous infusion of study intervention.

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

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

1.2. Schema



Abbreviations: PBO = placebo.

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 (maximum of 7 days from reporting of the index case). 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.

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

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
Prior treatments of special interest within the last 2 weeks	X															NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or other investigational treatments

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	
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)

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	
Clinical symptoms and interventions of interest		Daily										X	X			See Table 1 for clinical symptoms and interventions of interest.
Symptoms Questionnaire	X	Daily										X	X			See Section 8.1.2.
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 taken from both nostrils		X														Day 1: pre-dose. assessed at a central laboratory
SARS-CoV-2 nasal swab 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.*
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.*

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	
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.*
• 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. 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.*

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	
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; 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 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 is a neutralizing immunoglobulin G1 (IgG1) monoclonal antibody (mAb) to the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, and to neutralize the virus. 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. In addition, the impact of LY3819253 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. 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 consists of a highly

specific monoclonal antibody 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 monoclonal antibody were derived from B lymphocytes of a convalescent SARS-CoV-2-infected patient and, thus, have undergone natural positive and negative selection pressures in vivo, unlike humanized antibodies generated in mice. Therefore, off-target binding and tissue cross-reactivity are considered unlikely.

A theoretical risk is that LY3819253 may cause antibody-dependent enhancement (ADE) of viral replication. This is based on responses observed to some monoclonal antibody therapies used in other unrelated viral diseases. Unlike ADE associated with Dengue and Zika virus infections, this phenomenon has not been clearly established for 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). LY3819253 will be administered to participants at sufficiently high dose levels to neutralize 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.

Given the totality of data on LY3819253 and the well-established safety profile of other therapeutic monoclonal antibodies, 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 may be found in the IB.

3. Objectives and Endpoints

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 – polymerous 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	
Objectives	Endpoints
Primary	
[time frame for endpoint evaluation: **4 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
Key Secondary	
[time frame for endpoint evaluation: **8 weeks** from randomization]	
• 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
• 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
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 due to COVID-19	• Proportion of participants who are hospitalized due to COVID-19
• Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events: • COVID-19 related hospitalization (defined as ≥24 hours of acute care), • COVID-19 related emergency room visit, or • 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 [time frame for endpoint evaluation: **8 weeks** from randomization]	
Objectives	Endpoints
• 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]
• Compare the frequency of hospitalization due to COVID-19	• Proportion of participants who are hospitalized due to COVID-19
• Characterize clinical status for participants.	• Proportion (percentage) of participants who experience these events: ○ COVID-19 related hospitalization (defined as ≥24 hours of acute care), ○ COVID-19 related emergency room visit, or ○ 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.

4. Study Design

4.1. Overall Design

Study J2X-MC-PYAD is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intravenous LY3819253 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

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.

Screening and Day 1 may occur on the same day.

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.

4.1.2. Evaluation Period

The evaluation period begins when the participant completes screening and is enrolled in the study. Participants will be randomized to placebo or LY3819253. Assessments and procedures will be conducted as described in the SoA (Section 1.3).

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 (defined by systolic blood pressure <90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
	• 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

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.

4.2. Scientific Rationale for Study Design

This study is designed to evaluate the efficacy of a single dose of LY3819253 compared to placebo in preventing 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 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 SARS-CoV-2 infection 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.

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 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.

4.3. Justification for Dose

The 4200-mg single dose LY3819253 is selected for this study based on preliminary safety, tolerability, PK and PD data from the first-in-human Study PYAA, and 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.

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. Resident or staff in a skilled nursing or assisted living facility with at least one confirmed case of direct 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.

5.2. Exclusion Criteria

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

7. Recovered from confirmed COVID-19 disease
8. A prior history of a positive SARS-CoV-2 serology test
9. A history of Convalescent COVID-19 plasma treatment
10. Are an inpatient in hospital
11. Participation in a previous SARS-CoV-2 vaccine trial
12. 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
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 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 or LY3819253.

Intervention Name	Placebo	LY3819253
Dose Formulation	0.9% sodium chloride solution	Solution
Dosage Level(s)	Not applicable	4200 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, and
- for at least 2 hours 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 2 hours 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 an infusion reaction occurs during administration or 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 Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

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

Source: 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 1:1 to double-blind treatment on Day 1. 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), and by sex.

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

This is a blinded study. 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.

This table describes general procedures for unblinding.

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

Abbreviations: IWRS = interactive web-response system.

If an investigator, site 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.

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. Therefore, remdesivir may be initiated as standard of care for participants hospitalized with severe disease (if available through the FDA Emergency Use Authorizations) outside of local standard of care per written policies or guidelines.

If the local standard of care per written policies or guidelines (that is, not just an individual clinician decision) includes remdesivir, or other investigational agents, 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.

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). The result from the baseline nasopharyngeal swab is planned to be used to define SARS-CoV-2 RT-PCR status for the analysis populations. However, the result from the baseline mid-turbinate, nasal, or oropharyngeal swab may be used to determine baseline RT-PCR status when the nasopharyngeal swab result cannot be ascertained.

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 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
- 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
- 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 LY3819253 overdose.

In the event of an overdose, the investigator should

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

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

8.5. Pharmacokinetics

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

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.

Instructions for the collection and handling of biological samples will be provided by Lilly.

Site 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 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 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 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. 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 at a laboratory approved by the sponsor. Antibodies may be further characterized for their ability to neutralize the activity of LY3819253.

Sample retention

Sample retention is described in Section 10.1.12, 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 with 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 over placebo in the prevention of SARS-CoV-2 infection. Efficacy comparisons will be made without regard to changes to any background therapies. A fixed-sequence strategy will be used to adjust for multiplicity in the primary and key secondary endpoints.

9.2. Sample Size Determination

An estimated 33 events are needed to show superiority of LY3819253 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.

The maximum sample size for this study is approximately 2400 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 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.

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

Population	Description
	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.
Safety	All participants randomly assigned to study intervention 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.
Prevention	All participants in the Enrolled/Intent-to-Treat population who are SARS-CoV-2 RT-PCR negative and serology negative at baseline.
Treatment	All participants in the Enrolled/ITT population who are SARS-CoV-2 RT-PCR positive at baseline and serology negative.
Serology-Positive	All participants in the Enrolled/ITT population who are SARS-CoV-2 serology 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.

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.

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, 10^{th} and 90^{th} 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 LY3819253 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, 10^{th} and 90^{th} 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 population is defined as cumulative incidence of SARS-CoV-2 infection defined as the detection of SARS-CoV-2 by RT-PCR, up to 4 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 within 8 weeks from randomization will be assessed on the Prevention population:

- Cumulative incidence of COVID-19
- Cumulative incidence of moderate or worse severity COVID-19

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.

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 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. Study drug overdose will also be reported as a TEAE. Study drug overdose is defined as documented evidence of study drug injection more than once in a 3-day period. 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.

9.4.7. Exploratory Endpoints

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

Additional exploratory analyses may include the following:

- 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 LY3819253,
- 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.

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 incidence rates 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 LY3819253 will be tabulated.

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

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

9.5. 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 Harmonization 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. 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	

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

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

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

Abbreviations: ADA = 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
RT-PCR	reverse transcription – polymerous 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.
WOCBP	women of childbearing potential

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Title Page

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

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

Amendment Number: b

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 Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	27 October 2020
Original Protocol	28 Jun 2020

Amendment b

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.

Table of Contents

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

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 350mg + 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.

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 two-part, 7-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.

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

Intervention Groups and Duration:

Part 1:

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

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. Once those events have occurred, then the Sponsor will decide when to trigger activation of Part 2 (e.g., based on operational considerations).

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

Part 2:

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 700mg, 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 2800 mg + LY3832479 2800 mg.

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

Participants will receive one intravenous infusion of study intervention.

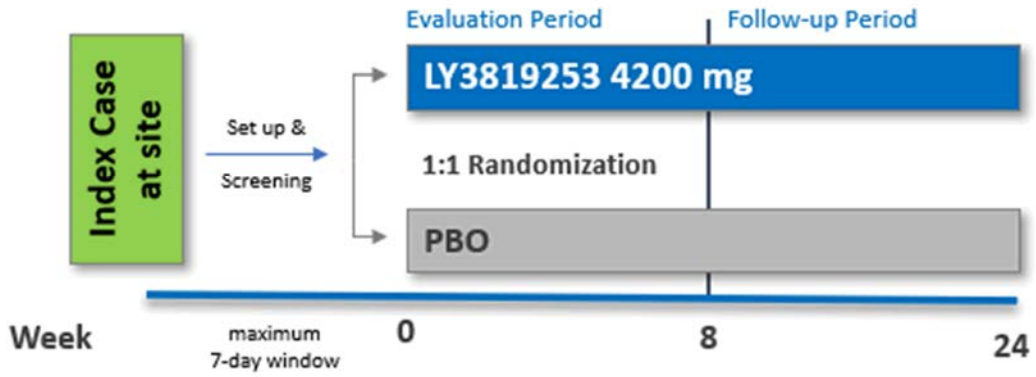
The maximum total duration of study participation for each participant of the prevention groups is 24 weeks.

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

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

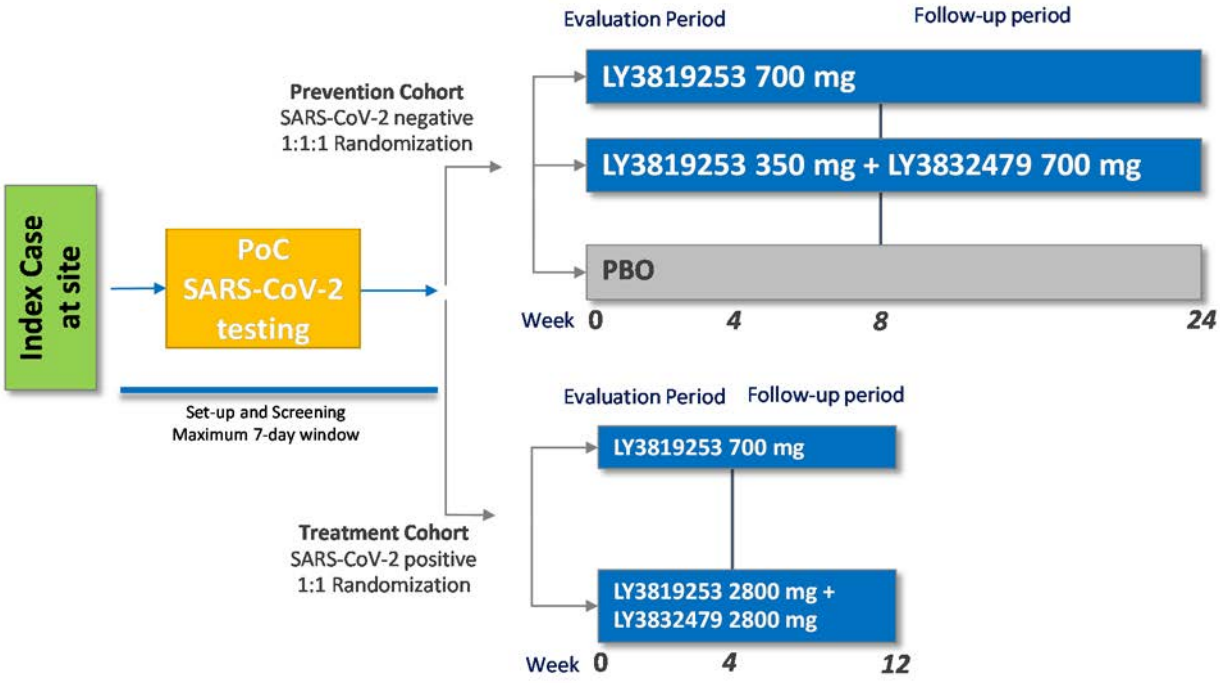
1.2. Schema

Part 1



Abbreviations: PBO = placebo.

Part 2



Abbreviations: PBO = placebo.

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 (maximum of 7 days from reporting of the index case). 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 within the last 2 weeks	X															NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or other investigational treatments
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 (Only use if positive on SARS-CoV-2 POC test in 1.3.1. SOA)

Screening 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						
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 within the last 2 weeks	X						NSAIDs, antivirals, antibiotics, anti-malarials, corticosteroids, immunomodulators or other investigational treatments
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						

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	
Symptom-directed physical exam		X			X	X	As indicated based on participant status and standard of care.
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

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 nasal 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.

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.

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: ○ COVID-19 related hospitalization (defined as ≥24 hours of acute care), ○ COVID-19 related emergency room visit, or ○ 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

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 350mg + 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.

Treatment Population Exploratory Objectives and Endpoints Participants positive on screening Point of Care Test & 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: ○ COVID-19 related hospitalization (defined as ≥24 hours of acute care), ○ COVID-19 related emergency room visit, or ○ 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 die 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

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.

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.

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.

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. When the needed events for the primary and key secondary endpoints are achieved, and the minimum number of residents enroll, the Sponsor will decide when to trigger activation of Part 2 (e.g., based on operational considerations).

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 2800 mg + LY3832479 2800 mg.

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

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

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. 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.

4.3. Justification for Dose

Part 1

The 4200 mg single dose LY3819253 is selected for this study based on preliminary safety, tolerability, PK and PD data from the first-in-human Study PYAA, and 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

LY3819253

LY3819253-700 mg was estimated as the maximum therapeutic dose based on PK/PD viral dynamics modeling of 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. The maximum dose of 2800 mg was selected to explore a wide exposure-response range to mitigate uncertainty and variability in the PK and PD and to establish the safety and tolerability limit of LY3819253. 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, LY3819253 provides exposure coverage in at least 90% of participant population for at least 8 weeks.

LY3832479

The LY3832479-700 mg dose was selected to evaluate the lower limit of the confidence interval for the maximum therapeutic dose based on PK/PD viral dynamics modeling 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 maximum 2800 mg dose of LY3832479 was selected to explore a wide exposure-response range to mitigate uncertainty and variability in the PK and PD and to establish safety and tolerability limit of LY3832479. On average, the 2 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.

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. 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.

5.2. Exclusion Criteria

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

7. Recovered from COVID-19 disease or asymptomatic infection
8. A prior history of a positive SARS-CoV-2 serology test
9. A history of Convalescent COVID-19 plasma treatment
10. Are an inpatient in hospital
11. Participation in a previous SARS-CoV-2 vaccine trial or received an approved SARS-CoV-2 vaccine
12. 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
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	2 (Prevention Only)	2 (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	2800 mg + 2800 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, 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 Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

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

Source: 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

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), and by sex.

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).

General procedures for unblinding follow the table above.

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 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 each part of the study.

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.

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.
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.
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.

Population	Description
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	4200mg	LY3819253
2	Part 1	---	Placebo
3	Part 2 (Prevention Cohort)	700mg	LY3819253
4	Part 2 (Prevention Cohort)	350mg + 700mg	LY3819253+LY3832479
5	Part 2 (Prevention Cohort)	---	Placebo
6	Part 2 (Treatment Cohort)	700mg	LY3819253
7	Part 2 (Treatment Cohort)	2800mg + 2800mg	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 700mg and LY3819253 350mg + LY3832479 700mg will be assessed against placebo separately.

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, 10^{th} and 90^{th} 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, 10^{th} and 90^{th} 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.

Additional exploratory analyses 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.

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 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.

Section # and Name	Description of Change	Brief Rationale
	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 collection is post-dose only (approx. 30 minutes after end of infusion)."	Collect C_{max} data post-infusion in Part 2.
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	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.

Section # and Name	Description of Change	Brief Rationale
	• Time frame for endpoint evaluation: 8 weeks from randomization	
	Changed the key secondary endpoint for Part 1 Prevention Population to: • 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	Updated the secondary endpoint to evaluate prior primary endpoint.
	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.

Section # and Name	Description of Change	Brief Rationale
	Added description of the Prevention and Treatment Cohorts.	Activation of Part 2.
	Added a visit type information table.	Clarification of visit types.
	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.

Section # and Name	Description of Change	Brief Rationale
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 blind was broken must be recorded in the source documentation ~~and case report form~~."	Clarification.
	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.

Section # and Name	Description of Change	Brief Rationale
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.
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.

Section # and Name	Description of Change	Brief Rationale
		AE definitions are detailed in Section 10.3.
9.4.6.2 Pharmacokinetic Analyses	Added subsection to describe PK analyses.	Clarity.
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.

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1. Statistical Analysis Plan: J2X-MC-PYAD: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of LY3819253 in Preventing SARS-CoV-2 infection in Skilled Nursing and Assisted Living Facility Residents and Staff; a NIAID and Lilly Collaborative Study

LY3819253 - Prevention of SARS-CoV-2 Infection

This is a Phase 3, randomized, double-blind, placebo-controlled, single-dose study in skilled nursing and assisted living facility residents and staff to evaluate the efficacy and safety of LY3819253 in preventing SARS-CoV-2 infection.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol J2X-MC-PYAD
Phase 3

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

Approval Date: 20-Jul-2020 GMT

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3. Revision History

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

4. Study Objectives

4.1. Primary Objective

The primary study objective is to demonstrate superior efficacy of LY3819253 over placebo in the prevention of SARS-CoV-2 infection among residents and facility staff of skilled nursing and assisted living facilities with a high risk of SARS-CoV-2 exposure. The primary endpoint is the proportion of participants who experience a SARS-CoV-2 infection, defined as the detection of SARS-CoV-2 by polymerase chain reaction (RT-PCR), within 4 weeks of randomization, in participants who are negative at baseline for SARS-CoV-2 RT-PCR and serology. Statistical hypothesis testing for the primary endpoint will be conducted using a logistic regression method at the 2-sided 0.05 level.

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. The primary endpoint will be assessed on participants who are negative at baseline for SARS-CoV-2 RT-PCR and serology.

4.2. Secondary Objectives

All secondary analyses will compare LY3819253 versus placebo at 8 weeks from randomization in participants who are negative at baseline for SARS-CoV-2 RT-PCR and serology.

Table PYAD.4.1. Secondary Objectives of Study J2X-MC-PYAD

Objectives	Endpoints
Key Secondary	
• 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.
• 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 polymerase chain reaction (RT-PCR) AND moderate or worse disease severity[a] within 21 days of detection.
Other Secondary	
• 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 due to COVID-19	• Proportion of participants who are hospitalized (defined as ≥24 hours of acute care) due to COVID-19.

Objectives	Endpoints
• Characterize clinical status for participants.	Proportion (percentage) of participants who experience these events: • COVID-19 related hospitalization (defined as ≥24 hours of acute care), • COVID-19 related emergency room visit, or • death
• Compare the mortality due to COVID-19	• Proportion of participants who die due to COVID-19

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 of the protocol.

4.3. Exploratory Objectives

Table PYAD.4.2. Exploratory Objectives of Study J2X-MC-PYAD in Participants Negative at Baseline for SARS-CoV-2 RT-PCR and Serology

Objectives	Endpoints
Exploratory	
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 in a subset of participants.
Compare the duration of hospitalization due to COVID-19	• Cumulative days of hospitalization in those who are hospitalized due to COVID-19.
Compare all-cause mortality	• Proportion of participants who die due to any cause

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 of the protocol

Table PYAD.4.3. Exploratory Objectives of Study J2X-MC-PYAD in Participants Positive at Baseline for SARS-CoV-2 RT-PCR and Negative at Baseline for Serology

Objectives	Endpoints
Exploratory	
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 or develop moderate or worse COVID-19 at baseline. RT-PCR	• Time to improvement to mild severity[a]. RT-PCR
Compare the frequency of hospitalization due to COVID-19	• Proportion of participants who are hospitalized due to COVID-19
Characterize clinical status for participants.	Proportion (percentage) of participants who experience these events: • COVID-19 related hospitalization (defined as ≥24 hours of acute care), • COVID-19 related emergency room visit, or • 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 in those participants that become RT-PCR positive.	• 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 in a subset of participants.

Objectives	Endpoints
Compare the duration of hospitalization due to COVID-19	• Cumulative days of hospitalization in those who are hospitalized due to COVID-19.
Compare all-cause mortality	• Proportion of participants who die due to any cause

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 of the protocol

Additional exploratory objectives not previously defined in the protocol are described in Section 6.16.1.6.

5. Study Design

5.1. Summary of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, single-dose study in skilled nursing and assisted living facility residents and staff to evaluate the efficacy and safety of LY3819253 in preventing SARS-CoV-2 infection.

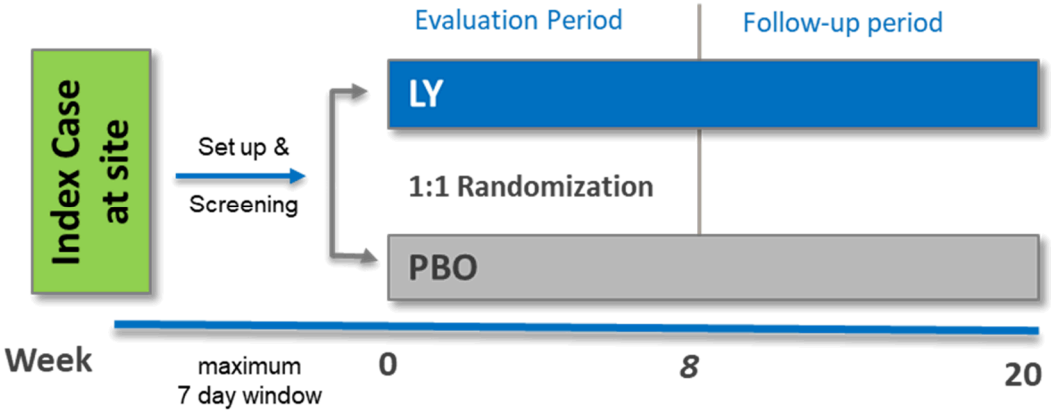

Figure PYAD.5.1. Overview of participant flow from time of Index Case at a facility to completion of follow-up

5.1.1. Screening Period

The screening period for each site opens when an SARS-CoV-2 index case at the facility is confirmed. A confirmed index case is the first direct SARS-CoV-2 detection result reported at a facility. Screening, randomization and IP administration must be completed within up to 7 days from the index case.

Screening and Day 1 may occur on the same day.

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

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

5.1.2. Evaluation Period

The evaluation period begins when the participant completes screening and is enrolled in the study. Participants will be randomized to placebo or LY3819253. Assessments and procedures will be conducted as described in the Schedule of Activities (SoA; Section 1.3 of the protocol).

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

5.1.3. Follow-up Period

Post-treatment follow-up assessments will be conducted at Days 85 and 141 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.

5.2. Determination of Sample Size

An estimated 33 events are needed to show superiority of LY3819253 over placebo in each of the primary and key secondary endpoints, using the formula by Schoenfeld (1983). An average sample size of approximately 1,300 participants who are SARS-CoV-2 RT-PCR negative & serology negative at baseline is expected to obtain the needed number of events for each endpoint.

The maximum sample size for this study is approximately 2,400 participants randomized.

Participants will be residents and staff of skilled nursing and assisted living facilities. 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 in the study. Therefore, a minimum of 300 residents will be enrolled.

For sample size determination the following assumptions were used: (1) two-sided significance level of 0.05; (2) At least 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) an evaluation period of 8 weeks; and (5) a risk ratio of 0.33 between LY3819253 and placebo in terms of the primary and key secondary endpoints.

5.3. Method of Assignment to Treatment

5.3.1. Randomization

All participants will be centrally randomized to study intervention using an interactive web-response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Block randomization within each site will be used to achieve between-group comparability, and participants will be stratified by role within the facility (resident versus facility staff), and by sex.

5.3.2. Blinding

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

Table PYAD.5.1 describes general procedures for unblinding.

Table PYAD.5.1. Unblinding Procedures for Study J2X-MC-PYAD

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

Abbreviation: IWRS = interactive web-response system.

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

6. A Priori Statistical Methods

6.1. General Considerations

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

All tables, figures, and listings will be created using the clinical trial database (unless otherwise noted), including data during study participation. While not reflected in a table, figure, or listing, any data collected after study participation (e.g., in the Lilly Safety System or collected through queries to the investigator) may be discussed in a clinical study report (CSR) or integrated summary document when deemed relevant.

Unless otherwise noted, displays will include columns for each treatment group, investigational product (IP) and another column for placebowill be displayed. A column that combines IP with placebo (i.e., a total column) will not be created.

Not all displays described in this statistical analysis plan (SAP) will necessarily be included in the CSR. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of, or in addition to, a static display. Any display described in this SAP and not provided would be available upon request.

All statistical analyses will be performed using SAS software Version 9.4 (or a higher version), FACTS 6.0 (or a higher version), and/or R 3.6 (or a higher version).

6.1.1. Analysis Populations

Patient populations are defined in Table PYAD.6.1 along with the analysis they will be used to conduct. The treatment groups and inferential comparisons described in Table PYAD.6.1 will be used unless otherwise specified. Also, unless otherwise specified, for all populations/analysis, patients will be analyzed according to the treatment to which they were assigned.

Table PYAD.6.1. Analysis Populations

Population	Description
Entered	**Definition:** All patients who signed informed consent. **Purpose:** Used for disposition analysis. **Treatment Groups:** None **Inferential Comparisons:** None
Enrolled/Intent-to-Treat (ITT)	**Definition:** All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Patients will be analyzed according to the treatment group to which they were assigned. **Purpose:** Used for disposition, demographic, and safety analyses. **Treatment Groups (Short Label): 4200** mg LY3819253 (4200 LY) and placebo (Pbo) **Inferential Comparisons:** LY versus placebo

Analysis Populations

Population	Description
Prevention	**Definition:** All participants in the Enrolled/Intent-to-Treat population who are SARS-CoV-2 RT-PCR negative and serology negative at baseline. **Purpose:** Used for efficacy and health outcomes analyses. **Treatment Groups (Short Label): 4200** mg LY3819253 (4200 LY) and placebo (Pbo) **Inferential Comparisons:** LY versus placebo
Treatment	**Definition:** All participants in the Enrolled/Intent-to-Treat population who are SARS-CoV-2 RT-PCR positive at baseline and serology negative at baseline. **Purpose:** Used for efficacy and health outcomes analyses. **Treatment Groups (Short Label): 4200** mg LY3819253 (4200 LY) and placebo (Pbo) **Inferential Comparisons:** LY versus placebo
Safety	**Definition:** All participants randomly assigned and who received any amount of study intervention. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses. **Treatment Groups (Short Label): 4200** mg LY3819253 (4200 LY) and placebo (Pbo) **Inferential Comparisons:** LY versus placebo
Fully Dosed	**Definition:** All participants in the Safety population who receive either placebo or a complete infusion of 4200 mg LY3819253. **Purpose:** Used for sensitivity assessments in the event that there are patients who do not receive a complete infusion of study drug. **Treatment Groups (Short Label): 4200** mg LY3819253 (4200 LY) and placebo (Pbo) **Inferential Comparisons:** LY versus placebo
Pharmacokinetic	**Definition:** All randomized participants who received study intervention and have at least 1 postdose PK sample. Participants will be analyzed according to the intervention they received. **Purpose:** Used for PK analyses. **Treatment Groups (Short Label): 4200** mg LY3819253 (4200 LY) and placebo (Pbo) **Inferential Comparisons:** LY versus placebo

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

6.1.2. Definition of Study Baseline

Unless otherwise specified, for all measurements, baseline is defined as the last nonmissing assessment recorded on, or prior to, the date of the study drug administration at study Day 1.

Baseline for safety analysis is described in the safety section.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline value or the value at the visit is missing for a particular variable, then the change from baseline is defined as missing.

6.1.3. Study Time Intervals

To calculate the length of any time interval or time period in this study, the following formula will be used:

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

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

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

Only for the purpose of calculating the length of study period time intervals, the words "prior to" in Table PYAD.6.2 should be understood to mean "the day before" while the words "after" should be understood to mean "the day after." For the purpose of determining whether a date/time lies within an interval, these words are intended to convey whether the start or end of the period is inclusive of the specified date.

For the purposes of the endpoints assessing the incidence of SARS-CoV-2 infection, the words "by Day 29" should be understood to mean "at any time prior to and including the Day 29 visit, provided the visit occurs within the specified visit window." The words "by Day 57" should be understood to have a similar meaning. For all other endpoints, similar definitions will apply, but results from visits outside of the specified visit window may be used.

Table PYAD.6.2. Definition of Study Period Time Intervals

Study Period	Interval Start Definition	Interval End Definition
Screening: All patients who sign informed consent are considered as entering the Screening Period.	Informed consent date	Prior to the start of Evaluation Period.
Evaluation Period: All patients who are randomized to the study are considered as entering the Evaluation Period.	At the start of study drug administration date/time following randomization. For patients who are randomized but not dosed, the Evaluation Period starts on the date of randomization.	The minimum of Evaluation Period discontinued date, study discontinuation date, or first Follow-Up visit date.
Follow-Up: All patients who had a follow up visit are considered as entering follow-up period.	After the Evaluation Period ends.	The maximum of the last study visit date or study disposition date.

6.1.4. Analysis Methods

Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. SARS-CoV-2 viral load data will be evaluated in log base 10 scale. The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, Mann-Whitney, or van Elteren tests, is deemed to be more appropriate.

All hypothesis tests will be 2-sided at an alpha level of 0.05. A fixed-sequence strategy will be used to adjust for multiplicity in the primary and key secondary endpoints.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Additional exploratory analyses of the data may be conducted as deemed appropriate.

Table PYAD.6.3. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Method	Analysis
Descriptive Statistics	Number of participants, mean, standard deviation, median, minimum, maximum, and 10^{th} and 90^{th} percentiles for continuous measures, and frequency counts and percentages for categorical measures
Kaplan-Meier curves and summary statistics, Cox proportional hazards	Treatment comparisons of time-to-event based endpoints
Logistic regression analysis	Treatment comparisons of binary variables with treatment, facility, and randomization stratification variables in the model
Nonparametric (e.g., Mann-Whitney or van Elteren tests)	Treatment comparison of ordinal, nominal, and non-normally distributed continuous variables
Mixed-effects model repeated measures (MMRM) analysis	Treatment comparisons of continuous efficacy and health outcome variables

Chi-square test or Fisher's exact test	Treatment comparison of binary endpoints

Treatment comparisons of continuous safety variables with multiple postbaseline measurements will be made using MMRM analysis. When MMRM is used, it includes: (a) treatment group, (b) facility, (c) role within the facility (resident vs staff), (d) sex , (e) baseline value in the model, (f) visit, and (g) the interactions of treatment-by-visit as fixed factors, and the patient as a random effect. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The first structure to yield convergence will be used for inference. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% confidence interval (CI) will also be reported. Unless otherwise specified, for MMRM, reported data from only planned visits will be used as the primary analysis.

Treatment comparisons of continuous efficacy and safety variables with a single postbaseline timepoint will be made using analysis of covariance (ANCOVA) with:- (a) treatment group, (b) facility, (c) role within the facility (resident vs staff), (d) sex and (be) baseline value in the model. Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value-, and 95% CI, unless otherwise specified, will also be reported. Missing data imputation method for the ANCOVA model is specified in Section 6.3.

Treatment comparisons for binary efficacy endpoints will be made using logistic regression. The model will include the treatment groups, facility, and the stratification factors (resident/staff and sex) as explanatory variables. For the primary and key secondary endpoints, results from a Lagrange multiplier test (or score test) will be reported (Silvey 1959). For all other endpoints, results from a Wald test will be reported. The odds ratio and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be reported.

For other binary endpoints, treatment comparisons will be made 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.

The Kaplan-Meier (KM) product limit method will be used for time-to-event analyses. The hazard ratio and log-rank test will be reported. Time for all analyses will be described in units of days.

6.1.5. Timing of Primary Analysis

To ensure that all primary and key secondary endpoints are well-powered, database lock for the primary and key secondary endpoints (the Primary Database Lock) will be triggered when at least 300 facility residents have been enrolled and when 33 participants in the Prevention population experience a moderate or worse severity case of COVID-19. All pre-specified analyses will be based on the Primary Database Lock. However, if the accumulation of moderate or worse severity cases of COVID-19 occurs slower than expected, the Primary Database Lock may be triggered when at least 36 participants in the Prevention population test positive for

SARS-CoV-2 within 4 weeks of randomization. If this is the case, only the primary endpoint will be evaluated at the Primary Database Lock.

To account for participants who have not finished the Evaluation Period at the time of the Primary Database Lock, a supplementary database lock (the End of Evaluation Database Lock) will occur once all participants have completed the Evaluation Period or discontinued from the study. The analyses conducted during the Primary Database Lock will be re-evaluated at the End of Evaluation Database Lock.

6.2. Adjustments for Covariates

Unless otherwise specified, efficacy analyses will adjust for the baseline value of the endpoint when modeling estimates and calculating p-values.

6.3. Handling of Dropouts or Missing Data

The SoA, outlined in the protocol, specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis but may be reported as a protocol deviation (see Section 6.14).

6.3.1. Missing SARS-CoV-2 Infection Status

For the primary endpoint, weights equal to the proportion of the Evaluation Period completed will be used in the logistic regression analysis. If a participant has a missing SARS-CoV-2 Infection Status due to death, study discontinuation, or the triggering of the Primary Database Lock, the participant will be treated as SARS-CoV-2 negative with a weight equal to the proportion of the Evaluation Period (up to Day 29) completed prior to the discontinuation event or the Database Lock.

6.3.2. Missing COVID-19 Status or Disease Severity

For the key secondary endpoints, the approach described in Section 6.3.1 will be used to handle missing COVID-19 status or disease severity due to death unrelated to COVID-19, study discontinuation, or the triggering of the Primary Database Lock. Participants with missing information will be treated as not experiencing the associated endpoint event and will be weighted based on the proportion of the Evaluation Period that was completed.

6.3.3. Non-Responder Imputation (NRI)

For analysis of other categorical efficacy, missing data will be imputed using a NRI method. Patients will be considered nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest.

In addition, patients who were not adequately assessed to determine if they meet the clinical requirements for response at the time point of interest are also considered to have failed treatment.

6.3.4. Last Observation Carried Forward (LOCF)

A last observation analysis is performed by carrying forward the last postbaseline assessment for continuous measures. For patients discontinuing the study, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation.

After LOCF imputation, data from patients with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. These LOCF analyses help ensure that the maximum number of randomized patients who were assessed postbaseline will be included in the analyses.

6.3.5. Mixed-effects Model Repeated Measures (MMRM)

For continuous variables with multiple postbaseline measurements, the primary analysis will be MMRM with the missing-at-random (MAR) assumption for handling missing data. This analysis considers both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis.

6.3.6. Highest Disease States Imputation (HDSI)

For the analyses related to National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale, the following imputation will be considered if applicable.

For patients whose data is missing during the hospitalization period (not yet recovered), a score of 2, which is the worst value for a hospitalization status, will be used for imputation.

For patients whose data is missing after recovery or discharged, a score of 7, the worst value for a recovery or nonhospitalized status, will be used for imputation.

6.4. Multicenter Studies

Differences between study centers will not be a feature of the statistical analyses for this study. Baseline variables and demographics may be described by site.

Individual center results may be presented, where appropriate, when the centers have sufficient numbers of patients to make such analysis potentially valuable. The possibility of qualitative or quantitative treatment-by-center interaction may be explored.

6.5. Multiple Comparisons/Multiplicity

To control for multiplicity, a fixed-sequence approach will be used to test the primary and key secondary endpoints. The endpoints will be tested at the two-sided 0.05 significance level in the following order, and only if there is success on all of the previous endpoints:

1) Incidence of SARS-CoV-2 infection by Week 4 (Primary Endpoint)
2) Incidence of moderate-or-worse severity COVID-19 (Secondary Endpoint)
3) Incidence of COVID-19 (Secondary Endpoint)

All other analyses will be conducted at the two-sided 0.05 significance level without adjustments for multiplicity.

6.6. Participant Disposition

The evaluation period disposition and study disposition will be summarized for the Prevention, Treatment, and Safety populations. Disposition summaries will be by treatment group. Summaries will also include reason for discontinuation from the study tabulated by treatment group.

All patients who are randomized and discontinued from the study will be listed, and the timing of discontinuing (from receiving study treatment) the study will be reported. If known, a reason for their discontinuation will be given.

In addition, a graphical summary (i.e., KM plot) of time from study treatment to early permanent discontinuation of study due to AEs may be generated if there are a substantial number of such events. This graphical summary would be by treatment group and include the log-rank test results.

Table PYAD.6.4. Tables and Figures Related to Disposition

Analysis	Details
Patient Disposition	Number and percentage of participants by reason for • study discontinuation and • study evaluation period discontinuation A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) p-value from Chi-square or Fisher's exact test
Listing of study disposition	--
Listing of participants discontinuing due to a decision-related reason (loss to follow-up, patient decision, or investigator decision)	Variables included the reason for study discontinuation, the text collected in the specify field associated with the reasons for discontinuation, and the dates of discontinuation The text in the specified field should provide information to support that the reason is unrelated to efficacy or safety
Time to early discontinuation of study due to AEs	Presented as a figure (if necessary)

Abbreviation: AE = adverse event.

6.7. Participant Characteristics

Patient demographic variables and baseline characteristics will be summarized by treatment and overall for the Prevention, Treatment, and Safety populations. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. Comparability of baseline covariates across treatment groups will be performed using an analysis of variance (ANOVA). By-patient listings of basic demographic characteristics (i.e., age, sex, race, racial subgroup, ethnicity, and body weight) for the Enrolled/ITT population will be provided.

Within each population, demographic variables and baseline characteristics will be summarized by treatment group and overall for each role within the facility (residents and staff). No comparisons across treatment groups will be made within these subgroups.

Table PYAD.6.5. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Analysis	Details
Baseline Demographic Characteristics	**Variables to be included:** • Age • Sex • Race (Amerian Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple), and • Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported) • Height • Weight **Statistics to be included:** Continuous: Mean, standard deviation, min, max, median, and 10^{th} and 90^{th} percentiles Categorical: n and percent (denominator for percentages will be the number of participants with nonmissing values) A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) No inferential statistics
Medical History and Preexisting conditions	Number and percentage of participants with medical history events and preexisting conditions using MedDRA PT nested within SOC • Ordered by decreasing frequency within SOC on the LY arm Preexisting conditions are defined as those conditions with a start date prior to the first dose of the study drug and stop dates that are at or after the informed consent date or have no stop date (i.e., are ongoing).
Listing demographics	--

Abbreviations: max = maximum; MedDRA = Medical Dictionary for Regulatory Activities; min = minimum; PT = preferred term; SOC = System Organ Class.

6.8. Treatment Compliance

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 CRF. Treatment compliance will not be reported.

6.9. Prior Medication and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the WHO drug dictionary. Medication start and stop dates will be compared to the date of the first dose of treatment to allow medications to be classified as concomitant.

Prior medications are those medications that start and stop prior to the date of the first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the

first day of study treatment and continue into the evaluation period. For all summary tables of concomitant medications, Preferred Terms of concomitant medication will be sorted by descending frequency in the LY arm.

Table PYAD.6.6. Summary Tables Related to Concomitant Medications

Analysis	Details
Prior medications	Number and percentage of participants using Preferred Terms of prior medication • Ordered by decreasing frequency p-value from Chi-square or Fisher's exact test.
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication • Ordered by decreasing frequency p-value from Chi-square or Fisher's exact test

6.10. Efficacy Analyses

6.10.1. Primary Outcome and Methodology

The endpoint for the primary analysis is defined as the first occurrence of SARS-CoV-2 infection, defined as the detection of SARS-CoV-2 by reverse transcription – polymerase chain reaction (RT-PCR) by Day 29 (4 weeks after randomization).

The percentage of patients in the Prevention population who are SARS-CoV-2 positive postbaseline by Day 29 will be summarized by treatment group. Results of SARS-CoV-2 tests during the study will be listed for each participant.

Statistical comparison between LY3819253 and placebo will be done using a weighted logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. Participants without an occurrence of SARS-CoV-2 infection will be weighted based on the proportion of the Evaluation Period completed (up to Day 29), as described in Section 6.3.1. The odds ratio and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be computed using the score test and reported.

6.10.2. Additional Analyses of the Primary Outcome

6.10.2.1. Random Effect for Facility

As a sensitivity assessment, the primary outcome will be assessed using a generalized linear mixed model (GLMM). The model will include treatment and the randomization stratification factors as fixed effects and facility as a random effect.

6.10.2.2. Risk Difference Assessment

The risk difference for SARS-CoV-2 infection between treatments will be estimated by the difference in the percentages of patients in the Prevention population who are SARS-CoV-2 positive postbaseline, unadjusted for other covariates. A 95% confidence interval for the risk difference will be computed using a Kaplan-Meier approach. Participants who have yet to

complete the Evaluation Period at the time of the analysis will be censored at the date of their last visit prior to the analysis.

6.10.2.3. Fully Dosed Population

As a sensitivity anaylsis, the primary and key secondary outcomes will be assessed using the Fully Dosed Population. Similar methodology, as described in Section 6.10.16.10.1 will be utilized for statistical hypothesis testing.

6.10.2.4. Death or SARS-CoV-2 infection

As a sensitivity anaylsis, the percentage of patients in the Prevention population who experience death or are SARS-CoV-2 positive postbaseline by Day 29 will be summarized by treatment group. Similar methodology, as described in Section 6.10.16.10.1 will be utilized for statistical hypothesis testing.

6.10.3. Secondary Efficacy Analyses

6.10.3.1. Incidence of Moderate-or-Worse Severity COVID-19 by Day 57

As a key secondary endpoint, the proportion of patients in the Prevention population who develop moderate-or-worse severity COVID-19 (defined as the detection of SARS-CoV-2 by polymerase chain reaction (RT-PCR) AND moderate or worse disease severity within 21 days of detection) by Day 57 will be summarized by treatment group. Similar methodology, as described in Section 6.10.16.10.1 will be utilized for statistical hypothesis testing, following the testing scheme described in Section 6.5.

As a sensitivity assessment, participants who develop COVID-19 within 21 days of becoming SARS-CoV-2 positive by RT-PCR, then continue on to develop moderate-or-worse disease severity by Day 57, will be included as moderate-or-worse severity COVID-19 events in the assessment.

As an exploratory analysis, the incidence of moderate-or-worse severity COVID-19 within 21 days of randomization will be compared across treatment groups in the subset of participants in the Treatment population who did not have moderate-or-worse severity COVID-19 at baseline. Statistical comparisons will use similar methodology as described in Section 6.10.1.

6.10.3.2. Incidence of COVID-19 by Day 57

As a key secondary endpoint, the proportion of patients in the Prevention population who develop COVID-19 (Table PYAD.4.1) by Day 57 will be summarized by treatment group. Similar methodology, as described in Section 6.10.1will be utilized for statistical hypothesis testing, following the testing scheme described in Section 6.5.

As an exploratory analysis, the incidence of COVID-19 within 21 days of randomization will be compared across treatment groups in the subset of participants in the Treatment population who are asymptomatic at baseline (as defined in Table 1 of the protocol). Statistical comparisons will use similar methodology as described in Section 6.10.1.

6.10.3.3. SARS-CoV-2 Infection by Day 57

The percentage of patients in the Prevention population who are SARS-CoV-2 positive postbaseline by Day 57 will be summarized by treatment group. Statistical comparison between LY3819253 and placebo will be done using the weighted logistic regression model described in Section 6.10.1, with the weights for participants with missing SARS-CoV-2 infection status equal to the proportion of the Evaluation Period completed (up to Day 57).

6.10.3.4. Hospitalization Due to COVID-19 by Day 57

The proportion of patients who experience hospitalization due to COVID-19 during the Evaluation Period will be summarized for participants in the Prevention population. In addition, the number of patients that experience hospitalization due to COVID-19 will be analyzed using logistic regression to compare LY3819253 versus placebo, if there are sufficient data available. Statistical comparisons between LY3819253 and placebo will be done using a logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. Missing data will be imputed using the NRI method as described in Section 6.3.3.

A listing of hospitalization status during the Evaluation Period will be created.

As an exploratory analysis, this analysis will be repeated on participants in the Treatment population. Additionally, at the End of Evaluation Database Lock, the number of patients who are hospitalized due to COVID-19 anytime after randomization will be analyzed to compare LY3819253 versus placebo in the Prevention and Treatment populations, if there are sufficient data available.

6.10.3.5. COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 57)

Proportion (percentage) of participants who experience deterioration by Day 57 will be analyzed and is defined as:

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

The proportion of patients that experience deterioration by Day 57 will be summarized by treatment group in frequency tables and listed for participants in the Prevention Population.

In addition, the number of patients that experience deterioration by Day 57 will be analyzed using logistic regression to compare LY3819253 versus placebo, if there are sufficient data available. Statistical comparisons between LY3819253 and placebo will be done using a logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. Missing data will be imputed using the NRI method as described in Section 6.3.3.

As an exploratory analysis, this analysis will be repeated on participants in the Treatment population.

6.10.3.6. COVID-19-Related Mortality by Day 57

The proportion of patients that experience death due to COVID-19 by Day 57 will be summarized by treatment in frequency tables and listed for participants in the Prevention Population.

In addition, the number of patients that experience death due to COVID-19 by Day 57 will be analyzed using logistic regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available. Statistical comparisons between LY3819253 and placebo will be done using a logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. Missing data will be imputed using the NRI method as described in Section 6.3.3.

As an exploratory analysis, this analysis will be repeated on participants in the Treatment population. Additionally, at the End of Evaluation Database Lock, the number of patients who experienced death due to COVID-19 anytime after randomization will be analyzed to compare LY3819253 versus placebo in the Prevention and Treatment populations, if there are sufficient data available.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK) analysis will be the responsibility of the Eli Lilly PK/Pharmacodynamics (PD) group prior to database lock.

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

The primary parameters for analysis will be geometric mean of concentration on Day 29. Other noncompartmental parameters, such as half-life (t1/2), AUC from time 0 to infinity (AUC[0-∞]), AUC(0-D29), maximum observed drug concentration (C_{max},) clearance, and volume of distribution may be reported.

Additional population PK model-based analyses may be performed.

Noncompartmental methods, applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the serum concentrations of LY3819253, will be used to determine the following PK parameters (Table PYAD.6.7) when possible.

Table PYAD.6.7. Pharmacokinetic Parameters

Parameter	Units[a]	Definition
AUC(0-D29)	µg.h/mL	Area under the concentration-time curve from time zero to time t, where t is Day 29
AUC(0-t_{last})	µg.h/mL	Area under the concentration-time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	µg.h/mL	Area under the concentration-time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
t_{last}		Time of the last observed drug concentration
C_{max}	µg/mL	Maximum observed drug concentration
C_{D29}	µg/mL	Observed drug concentration on Day 29
t_{max}	h	Time of maximum observed drug concentration
$t_{½}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL	L/h	Total body clearance of drug calculated
V_z	L	Volume of distribution during the terminal phase
V_{ss}	L	Volume of distribution at steady state

[a] Units of source LY3819253 serum concentration data will be ng/mL, to 1 decimal place.

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures, and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: Non-Compartmental Pharmacokinetic Style Guide. The version of the tool effective at the time of PK analysis will be followed.

6.11.1. General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for nonbolus predose sampling times, which will be set to zero.
- Maximum observed drug concentration and time of maximum observed drug concentration (t_{max}) will be reported from observed values. If C_{max} occurs at more than 1 time point, t_{max} will be assigned to the first occurrence of C_{max}.
- Area under the concentration-time curve parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive serum concentrations above the lower limit of quantification, with at least 1 of these concentrations following C_{max}.

- Area under the concentration-time curve from time 0 to infinity values, where the percentage of the total area extrapolated is more than 20%, will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.
- Half-life will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of <2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.
- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.
- The parameters, based on predicted last quantifiable drug concentration, will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters will be reported).

6.11.2. Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (BQL). Serum concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:
    - The compound is nonendogenous.
    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.
    - The time points occur before the first quantifiable concentration.
- All other BQL concentrations that do not meet the above criteria will be set to missing.
- Also, where 2 or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated, and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

6.11.3. Individual Concentration versus Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semilogarithmic plot.

6.11.4. Average Concentration versus Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.
- The predose average concentration for single-dose data from nonendogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ±10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if two-thirds of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ±10%. An average concentration estimated with less than two-thirds, but more than 3 data points, may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

6.11.5. Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

6.11.5.1. Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent postdose samples.
- For PK profiles during single dosing of nonendogenous compounds, the concentration in a predose sample is quantifiable.
- For any questionable data that do not satisfy the above criteria, the profiles will be evaluated and results reported with and without the suspected data.

6.11.5.2. Data Between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.

b. Find the most extreme value from the arithmetic mean of the log-transformed values and exclude that value from the dataset.

c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains other atypical data suspected to be an outlier and n≥6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only 1 suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

6.11.5.3. Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will imply approval of the exclusion.

6.11.6. Pharmacokinetic Statistical Methodology

All PK parameters will be summarized by treatment group using descriptive statistics.

6.12. Safety Analyses

Percentages will be calculated using the Safety population as the denominator. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex. In the event of differential dropout rates, additional summary tables comparing exposure-adjusted incidence rates will be generated instead of, or in addition to, percentages.

Generally, the following statistical methods will be used, unless otherwise noted:

- percentage-based analyses:
  - p-values based on Fisher's exact test, and
  - odds ratios with treatment as the numerator and placebo as the denominator
- continuous measurements (single postbaseline timepoint):
  - p-value based on ANCOVA:
    - model containing terms for treatment and the continuous covariate of baseline measurement, and
    - Type III sums of squares will be used.
- continuous measurements (multiple postbaseline timepoints):

- p-value based on MMRM:
  - model containing terms for treatment, visit, the continuous covariate of baseline measurement, and the interactions of treatment by visit, and
  - Type III sums of squares will be used.

6.12.1. Baseline and Postbaseline Definitions for Safety Groups

Table PYAD.6.8 provides conceptual definitions of baseline and postbaseline by analysis type. More specific detail for each submission is provided in an appendix, if necessary.

Table PYAD.6.8. Baseline and Postbaseline Definitions for Safety Groups Initial Controlled Periods of Individual Studies Controlled Integrated Analysis Sets

Analysis Type	Baseline	Postbaseline
TEAEs	Start of screening and ends prior to the study drug dose.	Starts after initiation of the study drug dose and ends on or prior to the day of study disposition
Treatment-Emergent Abnormal Laboratory Values and Vital Signs	Start of screening and ends prior to the study drug dose. All scheduled and unscheduled measurements will be included.	Starts after initiation of the study drug dose and ends on or prior to the day of study disposition. All scheduled and unscheduled measurements will be included.

Baseline and Postbaseline Definitions for Safety Groups
Initial Controlled Periods of Individual Studies
Controlled Integrated Analysis Sets

Analysis Type	Baseline	Postbaseline
Change from Last Baseline to Week *xx* and to Last Postbaseline for Laboratory Values and Vital Signs	Start of screening and ends prior to the study drug dose. The last scheduled nonmissing assessment recorded prior to the date of the first dose.	Starts after initiation of the study drug dose and ends on or prior to the day of study disposition. Only scheduled visits will be included. The early termination visits are considered scheduled visits.

Abbreviation: TEAE = treatment-emergent adverse event.

6.12.2. Extent of Exposure

Exposure to therapy will be represented as either a complete or incomplete infusion, and will be summarized using descriptive statistics.

6.12.3. Adverse Events

Summaries of AEs will include the number of patients with at least 1 AE for each treatment group. When reporting by System Organ Class (SOC) and PT, the reports will present the SOC

in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT will be counted only once in the frequency tables for that PT.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by SOC, PT, severity, and relationship to IP as assessed by the investigator. For each event classification term, the number of subjects experiencing a treatment-emergent AE (TEAE) with that classification term will be tabulated.

In an overview table, the number and percentage of patients who experienced a TEAE, serious adverse event (SAE), AE related to study drug, died due to an AE, discontinued from the study treatment, or discontinued from the study due to an AE will be summarized by treatment. Treatment-emergent AEs may be reported separately for the evaluation period and follow-up period.

Treatment-Emergent Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the baseline period, it will be treated as "mild" in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment emergence will be determined by comparing with baseline severity. Missing severity will be reported as missing, without imputation.

Additional types of AEs to be summarized are described in Table PYAD.6.9.

Table PYAD.6.9. Additional Types of Adverse Events to be Summarized

Event Type	Summary Method
SAEs	SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.
TEAEs Resulting in Death	If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of preferred term.
TEAEs Leading to Study Discontinuation	TEAEs for which the action taken is 'Study Discontinuation' will be identified as TEAEs that lead to study discontinuation. The TEAEs that lead to study discontinuation will be summarized for each treatment group by SOC and PT for the safety population. A by-patient listing of the TEAEs that lead to study discontinuation will also be provided.
Treatment-Related TEAEs	Every AE will be assessed by the investigator for its relationship to the randomly assigned study treatment.

TEAEs by Maximal Severity	Every AE will be graded by the investigator as mild, moderate, or severe, so for each patient the greatest severity observed can be obtained by comparing the severity of all a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.
TEAEs (Not Including Serious)	The most common nonserious TEAEs will be summarized. All PT that occur in at least 5% of the safety population patients in any treatment group, when not counting the serious TEAEs, will be tabulated by SOC and PT for each treatment group. These reports will also present the total number of TEAEs for each SOC and PT.

Abbreviations: AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

SOC mapping

Medical Dictionary for Regulatory Activities PTs are assigned to a SOC through primary mappings (defined by MedDRA). Thus MedDRA PTs will appear in only 1 SOC.

Events not summarized

Events considered related by the investigator will not be summarized. Medical representatives may use the relatedness assessment when reviewing individual cases.

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

The following are "notable" events, from start of study drug through end of study participation:

- Deaths
- SAEs, and
- Discontinuations of study treatment due to AEs.

Narratives (patient-level data and summary paragraph) will be provided for participants in the safety population with at least 1 notable event.

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

The following events (observed at any time point during the study evaluation period) will be summarized using descriptive statistics:

- Proportion of participants hospitalized
- Duration of hospitalization (DOH; in days),
- proportion (percentage) of participants admitted to Intensive Care Unit (ICU),
- proportion (percentage) of participants requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation")

All hospitalization events, procedures of special interest, and environmental risk factors will be listed.

In the event that a participant has an ongoing hospitalization event at the time of study disposition, the hospitalization end date will be imputed to the study disposition date.

6.12.6. Clinical Laboratory Evaluation

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol (See Protocol Appendix 2). However, unscheduled measurements of planned analytes will be included/excluded as specified in the relevant sections. Examples of unplanned measurements include those that the clinical investigator orders as a repeat test or "retest" of a laboratory test in case of an abnormal value, and those the investigator orders for a "follow-up visit" due to clinical concerns. Some planned analytes are intended for individual case reviews and will not be included in group-level summaries.

6.12.7. Vital Signs and Other Physical Findings

The planned summaries are provided in Table PYAD.6.10. The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, weight, and temperature.

The criteria for identifying subjects with treatment-emergent abnormalities are based on Table PYAD.6.11.

Some of the analyses of vital signs may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in Table PYAD.6.10 and not provided would be available upon request. For example, box plots for observed values, scatter plots, and shift tables could be provided as interactive displays for medical review.

Table PYAD.6.10. Tables and Figures Produced to Support Vital Signs and Physical Characteristics

Analysis Type	Analysis Details
Box plots for observed values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • No inferential statistics.
Box plots for change from baseline values by visit	• Includes participants who have both a baseline and a postbaseline planned measurement. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot along with a p-value using the ANCOVA model.

Analysis Type	Analysis Details
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	• Each study individually and studies combined will be displayed. • Includes participants who have both a baseline and postbaseline observation. • Unplanned measurements will be included. • Lines indicating the reference limits will be included. • **Max vs Max:** Maximum baseline versus maximum postbaseline. • **Min vs Min:** Minimum baseline versus minimum postbaseline.
Summary tables for shifts to high/low	• Limits provided by the central lab service will be used to define low and high. • **Normal/high to low:** Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low. o Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 postbaseline result. • **Normal/low to high:** Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high. o Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period. • Statistical comparisons will be included.

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

Table PYAD.6.11. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes in Adults

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥129 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Temperature	<96°F (<35.6°C) and decrease ≥2°F (≥1.1°C) from baseline	≥101°F (≥38.3°C) and increase ≥2°F (≥1.1°C) from baseline

Abbreviations: BP = blood pressure; bpm = beats per minute.

6.12.8. Immunogenicity

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

Treatment-emergent ADAs are defined as participants

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

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

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

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

6.13. Subgroup Analyses

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

Subgroup analyses will be conducted for the primary and key secondary endpoints. Subgroups may include

- role within the facility (resident, staff)
- age group by role within the facility (residents < median resident age, residents ≥ median resident age, staff < median staff age, staff ≥ median staff age)
- sex (male, female)
- race
- ethnicity
- concomitant medication of interest use (yes/no)

Additionally, AEs, SAEs, and TEAEs will be summarized by role within the facility (resident vs staff).

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. Treatment group differences will not be evaluated within each category of the subgroup if the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided, that is, no inferential testing.

The analysis of additional subgroups and/or subgroup analyses on additional endpoints will not require an amendment to the SAP.

Within each subgroup category the relevant summary measure by treatment, treatment differences (compared to placebo) and 95% CIs will be displayed. Also, p-values using appropriate statistical tests for treatment comparison will be provided. Forest plots may be generated to display the treatment difference and 95% CIs for selected efficacy subgroup analyses.

Concomitant therapies of interest include remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine, anticoagulants, or other investigational interventions. Details of the

medications included in this subgroup are provided below in Table PYAD.6.12. Other concomitant therapies of interest may be evaluated based on available external information.

Table PYAD.6.12. Concomitant Medications of Interest Subgroup

Drug name	ATC Code	ATC Preferred Term
Remdesivir	---	REMDESIVIR
Kaletra	J05AR	KALETRA
Lopinavir	J05AR	LOPINAVIR
Hydroxychloroquine	P01BA	HYDROCHLOROQUINE
Dexamethasone	R01AD	DEXAMETHASONE

Concomitant Medications of Interest Subgroup

Drug name	ATC Code	ATC Preferred Term
Chloroquine	P01BA	CHLOROQUINE
Baricitinib	L04AA	BARICITINIB
Heparin	B01AB	HEPARIN
Fondaparinux	B01AX	FONDIIPARINUX
Argatroban	B01AE	ARGATROBAN

Abbreviation: ATC = anatomical therapeutic chemical.

6.14. Protocol Violations

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) are defined as those deviations from the protocol that would potentially compromise patients' safety, data integrity, or study outcome.

A separate document known as the "PYAD Trial Issues Management Plan" describes the categories and subcategories of IPDs and how the IPDs would be identified.

The number and percentage of patients having IPDs will be summarized within category and subcategory of deviations by dosing regimen.

A by-patient listing of IPDs will be provided.

6.15. Interim Analyses and Data Monitoring

6.15.1. Interim Analyses

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

The DSMB will review summary unblinded data monthly from the first participant entering treatment. Safety will be evaluated at each of these interim analyses and benefit/risk of LY3819253 will be assessed if needed.

The DSMB will review the following types of data:

- Demographics
- Baseline characterisitcs
- AEs
- SAEs
- Laboratory data
- PK/PD data (if available)
- Vital signs
- Concomitant medications

- Historical/pre-existing conditions
- Discontinuations
- Product complaints

The PYAD study may be stopped early based on an unacceptable safety signal(s).

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

Further details regarding the interim analyses can be found in the DSMB Charter.

6.15.2. Data Monitoring Committee/Assessment Committee

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.

Details of the DSMB will be provided in the DSMB charter. Unblinding details are specified in a separate blindind and unblinding plan document.

6.16. Additional Exploratory Analyses

6.16.1. Protocol Defined Exploratory Endpoints

Protocol defined exploratory endpoints are described in Section 4.3 and analysis details are provided in the following sections.

6.16.1.1. Time to Improvement to Mild Severity Symptoms

Time to improvement to mild severity symptoms will be is defined (in days) as:

(Date when participant's symptoms first meet definition of mild severity – Date when participant's symptoms first meet definition of moderate or worse severity + 1)

Only patients who have at baseline or later develop moderate-or-worse severity COVID-19 will be included in the analysis. If a patient has not experienced improvement to mild symptoms by completion or early discontinuation of the Evaluable Period, the patient will be censored at the date of their last visit during the Evaulation Period.

Time to improvement to mild severity symptoms will be summarized by treatment group and listed for the Prevention and Treatment populations. In addition, a graphical presentation of the symptom improvement will be provided using a KM plot.

6.16.1.2. Worst NIAID Score

The lowest daily value from Day 1 through Day 57 for a patient on the NIAID ordinal scale will be analyzed using a nonparametric rank-sum test (such as Mann-Whitney or van Elteren test) adjusting for facility and for the randomization stratification factors. Missing data will be imputed using HDSI, as described in Section 6.3.6. Mean value by treatment group will be plotted over time. This comparison will be made on the Prevention and Treatment populations.

6.16.1.3. SARS-CoV-2 Clearance

For qualitative determination of viral clearance, the lab determination of "positive"/"negative" will be used. SARS-CoV-2 clearance (yes/no) is defined as a single negative RT-PCR test for the SARS-CoV-2 virus. The date of viral clearance is defined as the date of the first occurrence of a negative test.

The proportion of patients that achieve SARS-CoV-2 clearance within 1, 2, or 3 weeks of becoming SARS-CoV-2 positive will be summarized by treatment group in frequency tables and listed for the Prevention and Treatment populations.

In addition, the number of patients that achieve SARS-CoV-2 clearance within 1, 2, or 3 weeks of becoming SARS-CoV-2 positive will be analyzed using logistic regression to comparetreatment groups, if there are sufficient data available. Missing data will be imputed using the NRI method as described in Section 6.3.3. This comparison will be made on the Prevention and Treatment populations.

6.16.1.4. Time to SARS-CoV-2 Clearance

See Section 6.16.1.3 for more details on the definition of viral clearance and date of viral clearance.

Time to SARS-CoV-2 clearance is defined (in days) as:

(Date of first negative SARS-CoV-2 RT-PCR test – Date of first positive SARS-CoV-2 RT-PCR test + 1)

Only patients who have at baseline or later develop SARS-CoV-2 infection will be included in the analysis. If a patient has not experienced SARS-CoV-2 clearance by completion or early discontinuation of the evaluation period, the patient will be censored at the date of their last visit during the evaluation period.

Time to SARS-CoV-2 clearance will be evaluated during the study evaluation period only and will be summarized by treatment group, and listed for the Prevention and Treatment populations. Cox proportional hazard methodology will be used.

Time to SARS-CoV-2 clearance will be presented graphically.

6.16.1.5. Viral Resistance

If appropriate, the evaluation of viral resistance will be conducted as described in a separate bioanalytical analysis plan for the Prevention and Treatment populations.

6.16.1.6. Duration of Hospitalization

Treatment comparisons of the mean DOH (in days) due to COVID-19 will be compared between LY3819253 and placebo using a nonparametric rank-sum test (such as Mann-Whitney or van Elteren test) adjusting for facility and for the randomization stratification factors. This comparison will be made on the Prevention and Treatment populations.

6.16.2. Additional Exploratory Analyses not Defined in the Protocol

In addition to the protocol defined endpoints, additional sensitivity analyses may be performed if deemed appropriate.

Additional analyses include:

6.16.2.1. SARS-CoV-2 Viral Load over Time

For quantitative viral load endpoints in the trial, the Ct values will be utilized with the following considerations:

- Two Ct values will be provided on 2 different genes: N1 and N2. N1 will be used as the primary measure; N2 will only be used when the Ct value for N1 is not available.
- Ct values range between 0 and 45.
- Negative SARS-CoV-2 tests will be associated with a Ct value of 45.
- The (log base 10) viral load will be calculated from the Ct value $(45\text{-Ct})/\log_2 10$, or (45-Ct)/3.321928.

For participants who are SARS-CoV-2 positive at baseline or at any time during the Evaluation Period, change from the date of confirmed infection to Day 57 of SARS-CoV-2 viral load data in the log base 10 scale will be statistically analyzed using a MMRM analysis method. The model will contain log base 10 transformed viral load at time of confirmed infection as a covariate, treatment, days since confirmed infection (day), treatment-by-day interaction, facility, and the randomization stratification factors as fixed effects.

6.16.2.2. Clinical Worsening based on the NIAID Scale

Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Day 57. Treatment group comparisons will be analyzed using logistic regression, if there are sufficient data available. Missing data will be imputed using the NRI method as described in Section 6.3.3.

6.16.2.3. NIAID Overall Improvement

Treatment group comparisons for overall improvement on the NIAID ordinal scale will be made using proportional odds model with facility, randomization stratification factors and treatment group in the model. Overall improvement will be evaluated at Day 57. Missing data will be imputed using HDSI, as described in Section 6.3.6.

6.16.2.4. Time to Hospitalization from first positive SARS-CoV-2 test

Time to Hospitalization is defined (in days) as:

(First study day when hospitalized status is changed to "Yes" – Date of first positive SARS-CoV-2 test +1)

Only patients who have at baseline or later develop SARS-CoV-2 infection will be included in the analysis. If a patient has not been admitted to the hospital or ICU by completion or early discontinuation of the evaluation period, the patient will be censored at the date of their last visit during the evaluation period.

Time to hospitalization will be evaluated during the study evaluation period only and will be summarized by treatment group, and listed for the Prevention and Treatment populations. Cox proportional hazard methodology will be used.

Time to hospitalization may be presented graphically.

6.16.2.5. Time to Admission to ICU from first positive SARS-CoV-2 test

Time to ICU is defined (in days) as:

(First study day when ICU status is changed to "Yes" – Date of first positive SARS-CoV-2 test +1)

Only patients who have at baseline or later develop SARS-CoV-2 infection will be included in the analysis. If a patient has been admitted to the hospital or ICU by completion or early discontinuation of the evaluation period, the patient will be censored at the date of their last visit during the evaluation period.

Time to ICU will be evaluated during the study evaluation period only and will be summarized by treatment, and listed for the Prevention and Treatment populations. Cox proportional hazard methodology will be used.

Time to ICU may be presented graphically.

6.16.2.6. Proportions of Patients Hospitalized, Admitted to the ICU, Requiring Mechanical Ventilation

The proportion of patients hospitalized, admitted to the ICU, requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation") will be evaluated separately using a logistic regression analysis with treatment, facility, and randomization stratification in the model. Missing data will be imputed using the NRI method as described in Section 6.3.3. These endpoints will be evaluated for the Prevention and Treatment populations at Day 57.

6.16.2.7. All Cause Mortality

The proportion of patients that experience death after randomization will be summarized by treatment in frequency tables and listed for participants in the Safety Population.

Additionally, at the End of Evaluation Database Lock, the number of patients who experienced death anytime after randomization will be analyzed to compare LY3819253 versus placebo in the Prevention and Treatment populations, if there are sufficient data available. In addition, the number of patients that experience death after randomization will be analyzed using logistic

regression to compare LY3819253 versus placebo at each dose level, if there are sufficient data available.

6.17. Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.18. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (e.g., the CSR, manuscripts, and so forth).

7. References

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

Silvey, S.D. The Lagrangian Multiplier Test. Ann. Math. Statistics. 1959;30(2):389-407. doi:10.1214/aoms/1177706259.

8. Appendices

Appendix 1. NIAID Scoring Scale

The National Institute of Allergy and Infectious Diseases (NIAID) scoring scale will be assessed daily and defined as the lowest score achieved for that day.

The scoring is based on the clinical status of the patient as described below.

NIAID Score	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3	Hospitalized, on noninvasive ventilation or high flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities

1. Statistical Analysis Plan: J2X-MC-PYAD(b): A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of LY3819253 in Preventing SARS-CoV-2 infection in Skilled Nursing and Assisted Living Facility Residents and Staff; a NIAID and Lilly Collaborative Study

LY3819253 - Prevention of SARS-CoV-2 Infection

This is a Phase 3, randomized, double-blind, placebo-controlled, single-dose study in skilled nursing and assisted living facility residents and staff to evaluate the efficacy and safety of LY3819253 in preventing SARS-CoV-2 infection.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol J2X-MC-PYAD(b)
Phase 3

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

Approval Date: 12-Nov-2020 GMT

2. Table of Contents

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3. Revision History

Statistical Analysis Plan (SAP) Version 3 was approved prior to unblinding.

DOCUMENT HISTORY	
Document	**Date**
Vesion 3	12-Nov-2020
Version 2	26-Oct-2020
Original SAP	20-Jul-2020

Overall Rationale for the revision on Version 2:

Details regarding the analysis methods for the efficacy endpoints were adjusted. All changes were specified prior to first unblinding.

Additionally, the sponsor received feedback from FDA requesting a change in the amount of follow-up for the participants in the Treatment Cohort in Part 2 of the study. The schema for Part 2 has been updated in amendment (b) of the protocol to reflect this.

Finally, additional updates were made for the SAP to be consistent with changes from amendment (a) of the protocol.

Section # and Name	**Description of Change**	**Brief Rationale**
Figure PYAD.5.1 and Section 5.1.3 – Follow-up Period	Changed Follow-Up time of Treatment Cohort in Part 2 from 8 weeks to 12 weeks.	Protocol update due to FDA feedback.
Footer	Added LY3832479 as one of the investigated interventions.	Protocol Update – amendment (a).
Section 6.1.4 – Analysis Methods	Lagrange Multiplier Test replaced with Rao Test.	Consistency with prior simulation work.
Section 6.3.1 – Missing SARS-CoV-2 Infection Status	Replaced wording referring to the analysis as the primary endpoint. Additional information on missing test results included. Weighting of missing status moved to a supplementary analysis.	Primary endpoint was changed in amendment (a) of the protocol. Sponsor decision.
Section 6.3.2 – Missing COVID-19 Status or Disease Severity	Replaced wording referring to the analyses as key secondary endpoints.	Secondary endpoints were changed in amendment (a) of the protocol. Sponsor decision.

Section # and Name	Description of Change	Brief Rationale
	Weighting of missing status moved to a supplementary analysis.	
6.10.1 – Primary Outcome and Methodology	Weighting removed from logistic regression model. Rao score test specified for p-value and Wald method specified for odds ratio and CIs.	Sponsor decision.
6.10.2.2. – Risk Difference/Time-to-Event Assessment	Method of computing confidence interval for the risk difference changed to Wald Added Cox proportional hazards assessment	Sponsor decision.
6.10.3.3 SARS-CoV-2 Infection by Day 57	Weighting removed from logisting regression model.	Sponsor decision.
6.12.5 Hospitalization, Clinical Events, and Clinical Status	References to and analyses on environmental risk factors removed	Environmental risk factors not collected in this study.
6.16.2.3 – NIAID Overall Improvement	Endpoint removed.	Vast majority of patients not hospitalized at baseline. Improvement on the NIAID scale will be minimal and not meaningful.
7 – References	Rao score test reference added. Lagrange multiplier test reference removed.	Score test method changed due to sponsor decision.

4. Study Objectives

4.1. Primary Objective

The primary study objective is to demonstrate superior efficacy of LY3819253 and LY3819253 in combination with LY3832479 over placebo in the prevention of COVID-19 among residents and facility staff of skilled nursing and assisted living facilities with a high risk of SARS-CoV-2 exposure.

The primary endpoint for each part of the study is the proportion of participants who experience a case of COVID-19, defined as the detection of SARS-CoV-2 by polymerase chain reaction (RT-PCR) with mild or worse disease severity in the 21 days after detection, within 8 weeks of randomization, in participants who are negative at baseline for SARS-CoV-2 RT-PCR and serology. In Part 2 of the study, participants must also test negative on a point-of-care (POC) test at baseline. Statistical hypothesis testing for the primary endpoint for each Part of the study will be conducted using a logistic regression method at the 2-sided 0.05 level.

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. The primary endpoint will be assessed on participants who are negative at baseline for SARS-CoV-2 RT-PCR and serology.

4.2. Secondary Objectives

For Part 1, all secondary analyses will compare LY3819253 versus placebo in participants who are negative at baseline for SARS-CoV-2 RT-PCR and serology.

Table PYAD.4.1. Secondary Objectives of Part 1 of Study J2X-MC-PYAD(b)

Objectives	Endpoints
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-19; defined as the detection of SARS-CoV-2 by RT-PCR, • Time frame for endpoint evaluation: 4 weeks from randomization

Objectives	Endpoints
Other Secondary	
• 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 • Time frame for endpoint evaluation: 8 weeks from randomization
• Compare the frequency of hospitalization due to COVID-19	• Proportion of participants who are hospitalized (defined as ≥24 hours of acute care) due to COVID-19. • Time frame for endpoint evaluation: 8 weeks from randomization
• Characterize clinical status for participants.	Proportion (percentage) of participants who experience these events: • COVID-19 related hospitalization (defined as ≥24 hours of acute care), • COVID-19 related emergency room visit, or • death Time frame for endpoint evaluation: 8 weeks from randomization
• Compare the mortality due to COVID-19	• Proportion of participants who die due to COVID-19 • Time frame for endpoint evaluation: 8 weeks from randomization

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 of the protocol.

For Part 2, 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.

All secondary analyses in Part 2 will compare LY3819253 and LY3819253 in combination with LY3832479 versus placebo in participants in the Prevention Cohort who are negative at baseline for SARS-CoV-2 RT-PCR and serology.

Table PYAD.4.2. Secondary Objectives of Part 2 of Study J2X-MC-PYAD(b)

Objectives	Endpoints
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-19; 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 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 of the protocol.

4.3. Exploratory Objectives

Table PYAD.4.3. Exploratory Objectives of Part 1 of Study J2X-MC-PYAD(b) in Participants Negative at Baseline for SARS-CoV-2 RT-PCR and Serology

Objectives	Endpoints
Exploratory	
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 in a subset of participants.
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 of the protocol

Table PYAD.4.4. Exploratory Objectives of Part 1 of Study J2X-MC-PYAD(b) in Participants Positive at Baseline for SARS-CoV-2 RT-PCR and Negative at Baseline for Serology

Objectives	Endpoints
Exploratory	
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].
Compare the frequency of hospitalization due to COVID-19	• Proportion of participants who are hospitalized due to COVID-19
Characterize clinical status for participants.	Proportion (percentage) of participants who experience these events: • COVID-19 related hospitalization (defined as ≥24 hours of acute care), • COVID-19 related emergency room visit, or • 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 in those participants that become RT-PCR positive.	• 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 in a subset of participants.

Objectives	Endpoints
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 of the protocol

Table PYAD.4.5. Exploratory Objectives of Part 2 of Study J2X-MC-PYAD(b) in Participants in the Treatment Cohort who are Positive at Baseline for SARS-CoV-2 RT-PCR and Negative at Baseline for Serology

Objectives	Endpoints
Exploratory	
Evaluate the frequency of hospitalization due to COVID-19	• Proportion of participants who are hospitalized due to COVID-19
Characterize clinical status for participants.	Proportion (percentage) of participants who experience these events: • COVID-19 related hospitalization (defined as ≥24 hours of acute care), • COVID-19 related emergency room visit, or • 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 die 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 in a subset of participants.
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 of the protocol

Additional exploratory objectives not previously defined in the protocol are described in Section 6.16.2.

5. Study Design

5.1. Summary of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, single-dose study in skilled nursing and assisted living facility residents and staff to evaluate the efficacy and safety of LY3819253, alone and in combination with LY3832479, in preventing SARS-CoV-2 infection and COVID-19.

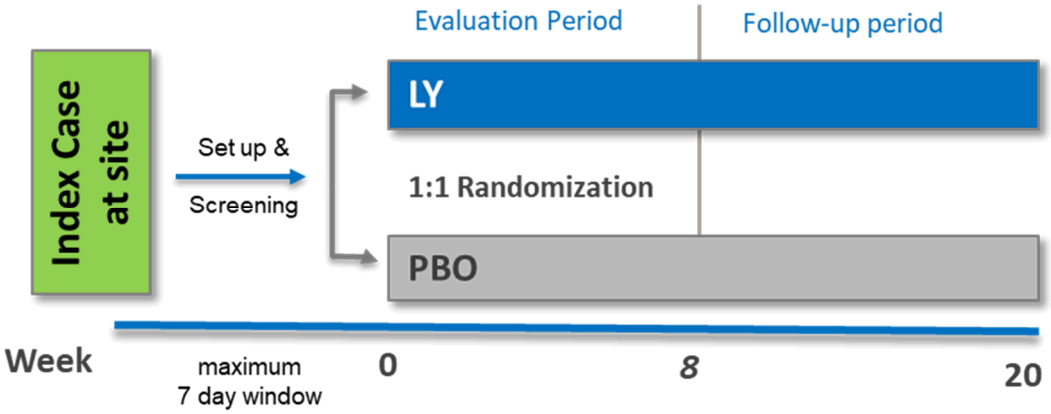

Figure PYAD.5.1. Overview of participant flow from time of Index Case at a facility to completion of follow-up for Part 1 of the study

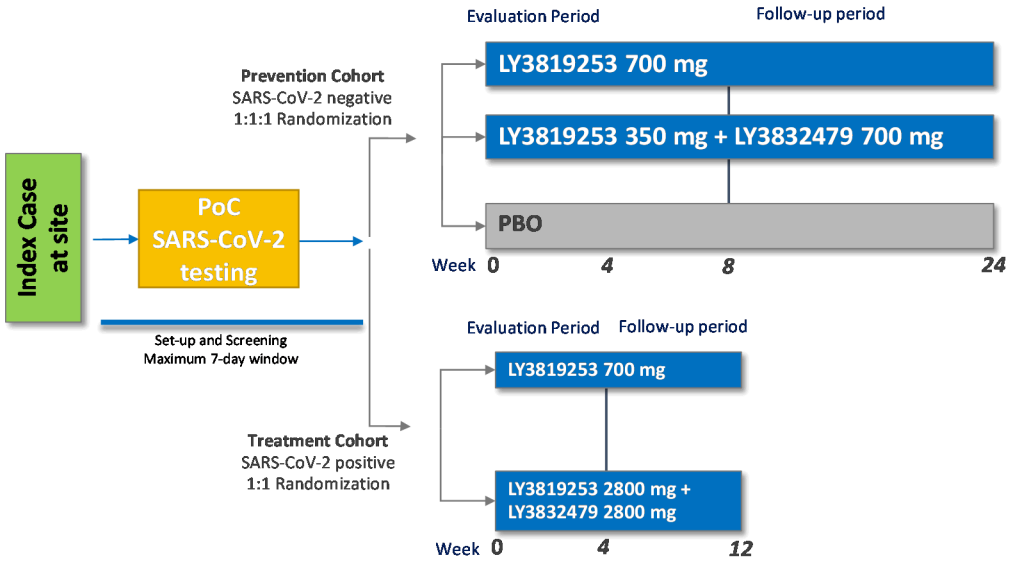

Figure PYAD.5.2. Overview of participant flow from time of Index Case at a facility to completion of follow-up for Part 2 of the study

5.1.1. Screening Period

The screening period for each site opens when an SARS-CoV-2 index case at the facility is confirmed. A confirmed index case is the first direct SARS-CoV-2 detection result reported at a facility. Screening, randomization and IP administration must be completed within up to 7 days from the index case.

Screening and Day 1 may occur on the same day.

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

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

5.1.2. Evaluation Period

The evaluation period begins when the participant completes screening and is enrolled in the study. Participants will be randomized to placebo or LY3819253 in Part 1; in Part 2, participants will be randomized to placebo, LY3819253, or LY3819253 in combination with LY3832479. Assessments and procedures will be conducted as described in the Schedule of Activities (SoA; Section 1.3 of the protocol).

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

5.1.3. Follow-up Period

For Part 1 and for the Prevention Cohort in Part 2, post-treatment follow-up assessments will be conducted at Days 85, 141, and 169 according to the SoA.

For the Treatment Cohort in Part 2, 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.

5.2. Determination of Sample Size

For Part 1, an estimated 33 events are needed to show superiority of LY3819253-4200mg 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 LY3819253-700mg or LY3819253-350mg+LY3832479-700mg 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.

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.

5.3. Method of Assignment to Treatment

5.3.1. Randomization

All participants will be centrally randomized to study intervention using an interactive web-response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Block randomization within each site will be used to achieve between-group comparability, and participants will be stratified by role within the facility (resident versus facility staff), and by sex.

5.3.2. Blinding

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

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 according to the Prevention Cohort SoA. Unblinded participants will not be included as part of the defined prevention population. Table PYAD.5.1 describes general procedures for unblinding.

Table PYAD.5.1. Unblinding Procedures for Study J2X-MC-PYAD(b)

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

Abbreviation: IWRS = interactive web-response system.

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

6. A Priori Statistical Methods

6.1. General Considerations

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

All tables, figures, and listings will be created using the clinical trial database (unless otherwise noted), including data during study participation. While not reflected in a table, figure, or listing, any data collected after study participation (e.g., in the Lilly Safety System or collected through queries to the investigator) may be discussed in a clinical study report (CSR) or integrated summary document when deemed relevant.

Unless otherwise noted, displays will include columns for each treatment group, investigational product (IP) and another column for placebowill be displayed. A column that combines IP with placebo (i.e., a total column) will not be created.

Not all displays described in this statistical analysis plan (SAP) will necessarily be included in the CSR. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of, or in addition to, a static display. Any display described in this SAP and not provided would be available upon request.

All statistical analyses will be performed using SAS software Version 9.4 (or a higher version), FACTS 6.0 (or a higher version), and/or R 3.6 (or a higher version).

6.1.1. Analysis Populations

Patient populations are defined in Table PYAD.6.1 along with the analysis they will be used to conduct. The treatment groups and inferential comparisons described in Table PYAD.6.1 will be used unless otherwise specified. Also, unless otherwise specified, for all populations/analysis, patients will be analyzed according to the treatment to which they were assigned.

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 in Part 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.

Table PYAD.6.1. Analysis Populations

Population	Description
Entered	**Definition:** All patients who signed informed consent. **Purpose:** Used for disposition analysis. **Treatment Groups:** None **Inferential Comparisons:** None
Enrolled/Intent-to-Treat (ITT)	**Definition:** All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Patients will be analyzed according to the treatment group to which they were assigned. **Purpose:** Used for disposition, demographic, and safety analyses. **Treatment Groups (Short Label):** **Part 1:** 4200 mg LY3819253 (4200 LY) and placebo (Pbo) **Part 2:** 700 mg LY3819253, 350 mg LY3819253 + 700mg LY3832479, and placebo **Inferential Comparisons:** LY versus placebo

Analysis Populations

Population	Description
Part 1 Prevention	**Definition:** 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. **Purpose:** Used for efficacy and health outcomes analyses. **Treatment Groups (Short Label):** 4200 mg LY3819253 (4200 LY) and placebo (Pbo)**Inferential Comparisons:** LY versus placebo
Part 2 Prevention	**Definition:** All participants in the Enrolled/Intent-to-Treat population in the Prevention Cohort in Part 2 who are SARS-CoV-2 RT-PCR negative and serology negative at baseline. **Purpose:** Used for efficacy and health outcomes analyses. **Treatment Groups (Short Label):** 700 mg LY3819253, 350 mg LY3819253 + 700mg LY3832479, and placebo **Inferential Comparisons:** LY3819253 versus placebo, LY3819253 + LY3832479 versus placebo
Part 1 Treatment	**Definition:** All participants in the Enrolled/Intent-to-Treat population in Part 1 who are SARS-CoV-2 RT-PCR positive at baseline and serology negative at baseline. **Purpose:** Used for efficacy and health outcomes analyses. **Treatment Groups (Short Label):** 4200 mg LY3819253 (4200 LY) and placebo (Pbo)**Inferential Comparisons:** LY versus placebo
Part 2 Treatment	**Definition:** All participants in the Enrolled/Intent-to-Treat population in the Treatmene Cohort in Part 2 who are POC positive, RP-PCR positive, and SARS-CoV-2 serology negative at baseline. **Purpose:** Used for efficacy and health outcomes analyses. **Treatment Groups (Short Label):** 700 mg LY3819253, 350 mg LY3819253 + 700mg LY3832479, and placebo **Inferential Comparisons:** LY3819253 versus placebo, LY3819253 + LY3832479 versus placebo

Part 1 Safety	**Definition:** All participants randomly assigned and who received any amount of study intervention in Part 1. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses. **Treatment Groups (Short Label):** 4200 mg LY3819253 (4200 LY) and placebo (Pbo) **Inferential Comparisons:** LY versus placebo
Part 2 Safety	**Definition:** All participants randomly assigned and who received any amount of study intervention in Part 2. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses. **Treatment Groups (Short Label):** 700 mg LY3819253, 350 mg LY3819253 + 700mg LY3832479, and placebo **Inferential Comparisons:** LY3819253 versus placebo, LY3819253 + LY3832479 versus placebo
Fully Dosed	**Definition:** All participants in the Safety population who receive either placebo or a complete infusion of study intervention. **Purpose:** Used for sensitivity assessments in the event that there are patients who do not receive a complete infusion of study drug. **Treatment Groups (Short Label): Part 1:** 4200 mg LY3819253 (4200 LY) and placebo (Pbo) **Part 2:** 700 mg LY3819253, 350 mg LY3819253 + 700mg LY3832479, and placebo **Inferential Comparisons:** LY versus placebo
Pharmacokinetic	**Definition:** All randomized participants who received study intervention and have at least 1 postdose PK sample. Participants will be analyzed according to the intervention they received. **Purpose:** Used for PK analyses. **Treatment Groups (Short Label):** **Part 1:** 4200 mg LY3819253 (4200 LY) and placebo (Pbo) **Part 2:** 700 mg LY3819253, 350 mg LY3819253 + 700mg LY3832479, and placebo**Inferential Comparisons:** LY versus placebo

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

6.1.2. Definition of Study Baseline

Unless otherwise specified, for all measurements, baseline is defined as the last nonmissing assessment recorded on, or prior to, the date of the study drug administration at study Day 1.

Baseline SARS-CoV-2 RT-PCR and serology status will be based on evaluable test results on, or prior to, the date of study drug administration at study Day 1. A participant will be considered RT-PCR positive at baseline if any RT-PCR result is determined to be positive.

Baseline for safety analysis is described in the safety section.

Change from baseline will be calculated as the visit value of interest minus the baseline value. If a baseline value or the value at the visit is missing for a particular variable, then the change from baseline is defined as missing.

6.1.3. Study Time Intervals

To calculate the length of any time interval or time period in this study, the following formula will be used:

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

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

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

Only for the purpose of calculating the length of study period time intervals, the words "prior to" in Table PYAD.6.2 should be understood to mean "the day before" while the words "after" should be understood to mean "the day after." For the purpose of determining whether a date/time lies within an interval, these words are intended to convey whether the start or end of the period is inclusive of the specified date.

For the purposes of the endpoints assessing the incidence of SARS-CoV-2 infection, the words "by Day 29" should be understood to mean "at any time prior to and including the Day 29 visit, provided the visit occurs within the specified visit window." The words "by Day 57" should be understood to have a similar meaning. For all other endpoints, similar definitions will apply, but results from visits outside of the specified visit window may be used.

Table PYAD.6.2. Definition of Study Period Time Intervals

Study Period	Interval Start Definition	Interval End Definition
Screening: All patients who sign informed consent are considered as entering the Screening Period.	Informed consent date	Prior to the start of Evaluation Period.
Evaluation Period: All patients who are randomized to the study are considered as entering the Evaluation Period.	At the start of study drug administration date/time following randomization. For patients who are randomized but not dosed, the Evaluation Period starts on the date of randomization.	The minimum of Evaluation Period discontinued date, study discontinuation date, or first Follow-Up visit date.
Follow-Up: All patients who had a follow up visit are considered as entering follow-up period.	After the Evaluation Period ends.	The maximum of the last study visit date or study disposition date.

6.1.4. Analysis Methods

Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. SARS-CoV-2 viral load data will be evaluated in log base 10 scale. The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, Mann-Whitney, or van Elteren tests, is deemed to be more appropriate.

Each part of the study will have an experiment-wise error rate of 0.05 for the primary and key secondary endpoints. A graphical testing sequence strategy will be used to adjust for multiplicity in the primary and key secondary endpoints within each part of the study. All other hypothesis tests will be conducted at a 2-sided alpha level of 0.05.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Additional exploratory analyses of the data may be conducted as deemed appropriate.

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

Table PYAD.6.3. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Method	Analysis
Descriptive Statistics	Number of participants, mean, standard deviation, median, minimum, maximum, and 10^{th} and 90^{th} percentiles for continuous measures, and frequency counts and percentages for categorical measures
Kaplan-Meier curves and summary statistics, Cox proportional hazards	Treatment comparisons of time-to-event based endpoints
Logistic regression analysis	Treatment comparisons of binary variables with treatment, facility, and randomization stratification variables in the model

Nonparametric (e.g., Mann-Whitney or van Elteren tests)	Treatment comparison of ordinal, nominal, and non-normally distributed continuous variables
Mixed-effects model repeated measures (MMRM) analysis	Treatment comparisons of continuous efficacy and health outcome variables
Chi-square test or Fisher's exact test	Treatment comparison of binary endpoints

Treatment comparisons of continuous safety variables with multiple postbaseline measurements will be made using MMRM analysis. When MMRM is used, it includes: (a) treatment group, (b) facility, (c) role within the facility (resident vs staff), (d) sex , (e) baseline value in the model, (f) visit, and (g) the interactions of treatment-by-visit as fixed factors, and the patient as a random effect. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The first structure to yield convergence will be used for inference. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% confidence interval (CI) will also be reported. Unless otherwise specified, for MMRM, reported data from only planned visits will be used as the primary analysis.

Treatment comparisons of continuous efficacy and safety variables with a single postbaseline timepoint will be made using analysis of covariance (ANCOVA) with:- (a) treatment group, (b) facility, (c) role within the facility (resident vs staff), (d) sex and (be) baseline value in the model. Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value-, and 95% CI, unless otherwise specified, will also be reported. Missing data imputation method for the ANCOVA model is specified in Section 6.3.

Treatment comparisons for binary efficacy endpoints will be made using logistic regression. The model will include the treatment groups, facility, and the stratification factors (resident/staff and sex) as explanatory variables. For the primary and key secondary endpoints, p-values from Rao's score test (or score test) will be reported (Rao 1948). For all other endpoints, results from a Wald test will be reported. The odds ratio and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be reported.

For other binary endpoints, treatment comparisons will be made 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.

The Kaplan-Meier (KM) product limit method will be used for time-to-event analyses. The hazard ratio and log-rank test will be reported. Time for all analyses will be described in units of days.

6.1.5. Timing of Primary Analysis

6.1.5.1. Part 1 Primary Analysis

To ensure that all primary and key secondary endpoints are well-powered, database lock for the primary and key secondary endpoints in Part 1 (the Part 1 Primary Database Lock) will be triggered when at least 300 facility residents have been enrolled and when 33 participants in the Part 1 Prevention population experience a moderate or worse severity case of COVID-19. All pre-specified analyses will be based on the Primary Database Lock. However, if the accumulation of moderate or worse severity cases of COVID-19 occurs slower than expected, the Primary Database Lock may be triggered when at least 36 participants in the Part 1 Prevention population test positive for SARS-CoV-2 within 4 weeks of randomization. If this is the case, only the primary endpoint will be evaluated at the Primary Database Lock. At the time of the primary analysis for Part 1, only data from patients enrolled in Part 1 will be unblinded to the sponsor.

To account for participants who have not finished the Evaluation Period at the time of the Primary Database Lock, a supplementary database lock (the Part 1 End of Evaluation Database Lock) will occur once all participants have completed the Evaluation Period or discontinued from the study. The analyses conducted during the Primary Database Lock will be re-evaluated at the End of Evaluation Database Lock.

6.1.5.2. Part 2 Primary Analysis

Database lock for the primary and key secondary endpoints in Part 2 (the Part 2 Primary Database Lock) will be triggered when 56 participants in the Part 2 Prevention population experience a moderate or worse severity case of COVID-19. All pre-specified analyses for participants in Part 2 will be based on the Part 2 Primary Database Lock.

To account for participants who have not finished the Evaluation Period at the time of the Primary Database Lock, a supplementary database lock (the Part 2 End of Evaluation Database Lock) will occur once all participants have completed the Evaluation Period or discontinued from the study. The analyses conducted during the Primary Database Lock will be re-evaluated at the End of Evaluation Database Lock.

6.2. Adjustments for Covariates

Unless otherwise specified, efficacy analyses will adjust for the baseline value of the endpoint when modeling estimates and calculating p-values.

6.3. Handling of Dropouts or Missing Data

The SoA, outlined in the protocol, specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis but may be reported as a protocol deviation (see Section 6.14).

6.3.1. Missing SARS-CoV-2 Infection Status

For the primary and key secondary endpoints, participants in the Prevention population with zero post-baseline RT-PCR test results will be excluded. If a participant has at least one post-baseline RT-PCR test result and has not yet tested positive or is missing additional test results during the time frame of the endpoint, the participant will be treated at SARS-CoV-2 negative at all visits before the last available RT-PCR test, and will be treated as not experiencing the event of interest in the primary and key secondary analyses.

As a supplementary analysis on the key secondary endpoint for incidence of SARS-CoV-2 infection, weights equal to the proportion of the Evaluation Period completed will be used in the logistic regression analysis. If a participant has a missing SARS-CoV-2 Infection Status due to death, study discontinuation, or the triggering of the Primary Database Lock, the participant will be treated as SARS-CoV-2 negative with a weight equal to the proportion of the Evaluation Period (up to Day 29) completed prior to the discontinuation event or the Database Lock.

6.3.2. Missing COVID-19 Status or Disease Severity

For the primary and key secondary enpoints, if a participant has at least one post-baseline RT-PCR test result and has not yet met the criterial for COVID-19 or is missing data used to determine COVID-19 status, the participant will be treated as not experiencing COVID-19. The same logic will be used for moderate-or-worse severity COVID-19.

As a supplementary analysis on these endpoints, the approach described in Section 6.3.1 will be used to handle missing COVID-19 status or disease severity due to death unrelated to COVID-19, study discontinuation, or the triggering of the Primary Database Lock. Participants with missing information will be treated as not experiencing the associated endpoint event and will be weighted based on the proportion of the Evaluation Period that was completed.

6.3.3. Non-Responder Imputation (NRI)

For analysis of other categorical efficacy, missing data will be imputed using a NRI method. Patients will be considered nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest.

In addition, patients who were not adequately assessed to determine if they meet the clinical requirements for response at the time point of interest are also considered to have failed treatment.

6.3.4. Last Observation Carried Forward (LOCF)

A last observation analysis is performed by carrying forward the last postbaseline assessment for continuous measures. For patients discontinuing the study, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation.

After LOCF imputation, data from patients with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. These LOCF analyses help ensure that the

maximum number of randomized patients who were assessed postbaseline will be included in the analyses.

6.3.5. Mixed-effects Model Repeated Measures (MMRM)

For continuous variables with multiple postbaseline measurements, the primary analysis will be MMRM with the missing-at-random (MAR) assumption for handling missing data. This analysis considers both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis.

6.3.6. Highest Disease States Imputation (HDSI)

For the analyses related to National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale, the following imputation will be considered if applicable.

For patients whose data is missing during the hospitalization period (not yet recovered), a score of 2, which is the worst value for a hospitalization status, will be used for imputation.

For patients whose data is missing after recovery or discharged, a score of 7, the worst value for a recovery or nonhospitalized status, will be used for imputation.

6.4. Multicenter Studies

Differences between study centers will not be a feature of the statistical analyses for this study. Baseline variables and demographics may be described by site.

Individual center results may be presented, where appropriate, when the centers have sufficient numbers of patients to make such analysis potentially valuable. The possibility of qualitative or quantitative treatment-by-center interaction may be explored.

6.5. Multiple Comparisons/Multiplicity

To control for multiplicity, a graphical testing sequence approach will be used to test the primary and key secondary endpoints within each part of the study.

For Part 1, the primary endpoint will be tested at the two-sided 0.05 significance level. If the primary endpoint is successful, then the secondary endpoint of incidence of SARS-CoV-2 infection will be tested at the two-sided 0.01 significance level. The secondary endpoint of incidence of moderate-or-worse severity COVID-19 will be tested simultaneously at the two-sided 0.04 significance level. If either secondary endpoint is successful, the other secondary endpoint will be tested at the two-sided 0.05 significance level. This testing scheme is displayed in Figure PYAD.6.1.

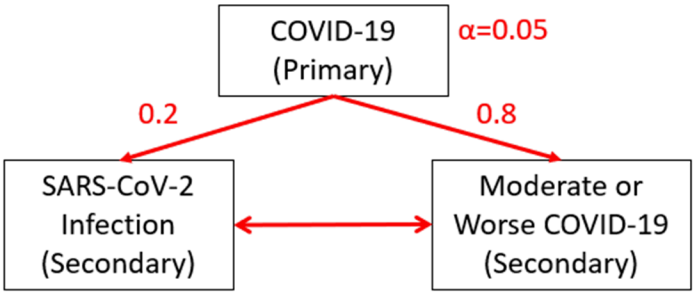

Figure PYAD.6.1. Graphical testing scheme for the primary and key secondary endpoints in Part 1

For Part 2, the graphical approach shown in Figure PYAD.6.1 will be repeated to compare LY3819253-350mg+LY3832479-700mg versus placebo. If all three endpoints are successful, the testing scheme will then be repeated to compare LY3819253-700mg versus placebo.

All other analyses will be conducted at the two-sided 0.05 significance level without adjustments for multiplicity.

6.6. Participant Disposition

The evaluation period disposition and study disposition will be summarized for the Prevention, Treatment, and Safety populations. Disposition summaries will be by treatment group. Summaries will also include reason for discontinuation from the study tabulated by treatment group.

All patients who are randomized and discontinued from the study will be listed, and the timing of discontinuing (from receiving study treatment) the study will be reported. If known, a reason for their discontinuation will be given.

In addition, a graphical summary (i.e., KM plot) of time from study treatment to early permanent discontinuation of study due to AEs may be generated if there are a substantial number of such events. This graphical summary would be by treatment group and include the log-rank test results.

Table PYAD.6.4. Tables and Figures Related to Disposition

Analysis	Details
Patient Disposition	Number and percentage of participants by reason for • study discontinuation and • study evaluation period discontinuation A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) p-value from Chi-square or Fisher's exact test
Listing of study disposition	--

Analysis	Details
Listing of participants discontinuing due to a decision-related reason (loss to follow-up, patient decision, or investigator decision)	Variables included the reason for study discontinuation, the text collected in the specify field associated with the reasons for discontinuation, and the dates of discontinuation The text in the specified field should provide information to support that the reason is unrelated to efficacy or safety
Time to early discontinuation of study due to AEs	Presented as a figure (if necessary)

Abbreviation: AE = adverse event.

6.7. Participant Characteristics

Patient demographic variables and baseline characteristics will be summarized by treatment and overall for the Prevention, Treatment, and Safety populations. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. Comparability of baseline covariates across treatment groups will be performed using an analysis of variance (ANOVA). By-patient listings of basic demographic characteristics (i.e., age, sex, race, racial subgroup, ethnicity, and body weight) for the Enrolled/ITT population will be provided.

Within each population, demographic variables and baseline characteristics will be summarized by treatment group and overall for each role within the facility (residents and staff). No comparisons across treatment groups will be made within these subgroups.

Table PYAD.6.5. Tables and Figures Related to Demographics and Other Characteristics of Study Population

Analysis	Details
Baseline Demographic Characteristics	**Variables to be included:** • Age • Sex • Race (Amerian Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple), and • Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported) • Height • Weight **Statistics to be included:** Continuous: Mean, standard deviation, min, max, median, and 10^{th} and 90^{th} percentiles Categorical: n and percent (denominator for percentages will be the number of participants with nonmissing values) A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) No inferential statistics
Medical History and Preexisting conditions	Number and percentage of participants with medical history events and preexisting conditions using MedDRA PT nested within SOC • Ordered by decreasing frequency within SOC on the LY arm

Analysis	Details
	Preexisting conditions are defined as those conditions with a start date prior to the first dose of the study drug and stop dates that are at or after the informed consent date or have no stop date (i.e., are ongoing).
Listing demographics	--

Abbreviations: max = maximum; MedDRA = Medical Dictionary for Regulatory Activities; min = minimum; PT = preferred term; SOC = System Organ Class.

6.8. Treatment Compliance

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 CRF. Treatment compliance will not be reported.

6.9. Prior Medication and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the WHO drug dictionary. Medication start and stop dates will be compared to the date of the first dose of treatment to allow medications to be classified as concomitant.

Prior medications are those medications that start and stop prior to the date of the first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment and continue into the evaluation period. For all summary tables of concomitant medications, Preferred Terms of concomitant medication will be sorted by descending frequency in the LY arm.

Table PYAD.6.6. Summary Tables Related to Concomitant Medications

Analysis	Details
Prior medications	Number and percentage of participants using Preferred Terms of prior medication • Ordered by decreasing frequency p-value from Chi-square or Fisher's exact test.
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication • Ordered by decreasing frequency p-value from Chi-square or Fisher's exact test

6.10. Efficacy Analyses

6.10.1. Primary Outcome and Methodology

The endpoint for the primary analysis is defined as the first occurrence of COVID-19, defined as the detection of SARS-CoV-2 by reverse transcription – polymerase chain reaction (RT-PCR) AND mild or worse disease severity within 21 days of detection, by Day 57 (8 weeks after randomization).

The percentage of patients in the Prevention population who experience COVID-19 by Day 57 will be summarized by treatment group.

Statistical comparison between each study intervention and placebo will be done using a logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. The odds ratio and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be computed using the Wald method and reported. A p-value from the Rao's score test will be reported.

As an exploratory analysis, the incidence of COVID-19 within 21 days of randomization will be compared across treatment groups in the subset of participants in the Treatment population who are asymptomatic at baseline (as defined in Table 1 of the protocol). Statistical comparisons will use similar methodology as described in Section 6.10.1.

6.10.2. Additional Analyses of the Primary Outcome

6.10.2.1. Random Effect for Facility

As a sensitivity assessment, the primary outcome will be assessed using a generalized linear mixed model (GLMM). The model will include treatment and the randomization stratification factors as fixed effects and facility as a random effect.

6.10.2.2. Risk Difference/Time-to-EventAssessment

The risk difference for COVID-19 between treatments will be estimated by the difference in the percentages of patients in the Prevention population who experience COVID-19 by Day 57, unadjusted for other covariates. A Wald 95% confidence interval for the risk difference will be computed.

The time from randomization to first incidence of COVID-19 will be summarized by treatment for participants within the Prevention population. A 95% confidence interval for the hazard ratio will be computed using a Cox proportional hazards model. Participants who have yet to complete the Evaluation Period at the time of the analysis will be censored at the date of their last visit prior to the analysis.

6.10.2.3. Fully Dosed Population

As a sensitivity anaylsis, the primary and key secondary outcomes will be assessed using the Fully Dosed Population. Similar methodology, as described in Section 6.10.1 will be utilized for statistical hypothesis testing.

6.10.3. Secondary Efficacy Analyses

6.10.3.1. Incidence of Moderate-or-Worse Severity COVID-19 by Day 57

As a key secondary endpoint, the proportion of patients in the Prevention populations who develop moderate-or-worse severity COVID-19 (defined as the detection of SARS-CoV-2 by polymerase chain reaction (RT-PCR) AND moderate or worse disease severity within 21 days of

detection) by Day 57 will be summarized by treatment group. Similar methodology, as described in Section 6.10.1 will be utilized for statistical hypothesis testing, following the testing scheme described in Section 6.5.

As a sensitivity assessment, participants who develop COVID-19 within 21 days of becoming SARS-CoV-2 positive by RT-PCR, then continue on to develop moderate-or-worse disease severity by Day 57, will be included as moderate-or-worse severity COVID-19 events in the assessment.

As an exploratory analysis, the incidence of moderate-or-worse severity COVID-19 within 21 days of randomization will be compared across treatment groups in the subset of participants in the Treatment populations who did not have moderate-or-worse severity COVID-19 at baseline. Statistical comparisons will use similar methodology as described in Section 6.10.1.

6.10.3.2. Incidence of SARS-CoV-2 Infection by Day 29

As a key secondary endpoint, the proportion of patients in the Prevention populations who are SARS-CoV-2 positive postbaseline (Table PYAD.4.1) by Day 29 will be summarized by treatment group. Similar methodology, as described in Section 6.10.1 will be utilized for statistical hypothesis testing, following the testing scheme described in Section 6.5.

Results of SARS-CoV-2 tests during the study will be listed for each participant.

As a sensitivity anaylsis, the percentage of patients in the Prevention population who experience death or are SARS-CoV-2 positive postbaseline by Day 29 will be summarized by treatment group. Similar methodology, as described in Section 6.10.1 will be utilized for statistical hypothesis testing.

6.10.3.3. SARS-CoV-2 Infection by Day 57

The percentage of patients in the Prevention population who are SARS-CoV-2 positive postbaseline by Day 57 will be summarized by treatment group. Statistical comparison between each study intervention and placebo will be done using the logistic regression model described in Section 6.10.1.

6.10.3.4. Hospitalization or Death Due to COVID-19 by Day 57

The proportion of patients who experience hospitalization or death due to COVID-19 during the Evaluation Period will be summarized for participants in the Prevention population. In addition, the number of patients that experience hospitalization or death due to COVID-19 will be analyzed using logistic regression to compare each study intervention versus placebo, if there are sufficient data available. Statistical comparisons will be done using a logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. Missing data will be imputed using the NRI method as described in Section 6.3.3.

A listing of hospitalization status during the Evaluation Period will be created.

As an exploratory analysis, this analysis will be repeated on participants in the Treatment population. Additionally, at each End of Evaluation Database Lock, the number of patients who are hospitalized or have died due to COVID-19 anytime after randomization will be analyzed to compare each study intervention versus placebo in the Prevention and Treatment populations, if there are sufficient data available.

6.10.3.5. COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 57)

Proportion (percentage) of participants who experience deterioration by Day 57 will be analyzed and is defined as:

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

The proportion of patients that experience deterioration by Day 57 will be summarized by treatment group in frequency tables and listed for participants in the Prevention Population.

In addition, the number of patients that experience deterioration by Day 57 will be analyzed using logistic regression to compare each study intervention versus placebo, if there are sufficient data available. Statistical comparisons between each study intervention and placebo will be done using a logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. Missing data will be imputed using the NRI method as described in Section 6.3.3.

As an exploratory analysis, this analysis will be repeated on participants in the Treatment populations for events up deterioration up to the end of their respective Evaluation Periods.

6.10.3.6. COVID-19-Related Mortality by Day 57

The proportion of patients that experience death due to COVID-19 by Day 57 will be summarized by treatment in frequency tables and listed for participants in the Prevention Populations.

In addition, the number of patients that experience death due to COVID-19 by Day 57 will be analyzed using logistic regression to compare each study intervention versus placebo, if there are sufficient data available. Statistical comparisons between each study intervention and placebo will be done using a logistic regression model. The model will include treatment, facility, role within the facility (resident vs staff) and sex as fixed effects. Missing data will be imputed using the NRI method as described in Section 6.3.3.

As an exploratory analysis, this analysis will be repeated on participants in the Treatment populations for deaths due to COVID-19 by the end of their respective Evaluation Periods. Additionally, at each End of Evaluation Database Lock, the number of patients who experienced death due to COVID-19 anytime after randomization will be analyzed to compare each study intervention versus placebo in the Prevention and Treatment populations, if there are sufficient data available.

6.11. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK), pharmacodynamic (PD) and PK/PD analyses are the responsibility of Eli Lilly and Company PK/PD group.

A summary of LY3819253 and LY3832479 concentration-time data will be reported in the clinical study report. Population PK model-based analyses, exploratory exposure-response analyses (a.k.a., population PK/PD modeling) of safety, pharmacology and efficacy, and any alternative approaches to efficacy analysis (including viral load definition in Section 6.16.2.1) may be performed.

6.12. Safety Analyses

Percentages will be calculated using the Safety populations as the denominator. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex. In the event of differential dropout rates, additional summary tables comparing exposure-adjusted incidence rates will be generated instead of, or in addition to, percentages.

Generally, the following statistical methods will be used, unless otherwise noted:

- percentage-based analyses:
  - p-values based on Fisher's exact test, and
  - odds ratios with treatment as the numerator and placebo as the denominator
- continuous measurements (single postbaseline timepoint):
  - p-value based on ANCOVA:
    - model containing terms for treatment and the continuous covariate of baseline measurement, and
    - Type III sums of squares will be used.
- continuous measurements (multiple postbaseline timepoints):
  - p-value based on MMRM:
    - model containing terms for treatment, visit, the continuous covariate of baseline measurement, and the interactions of treatment by visit, and
    - Type III sums of squares will be used.

6.12.1. Baseline and Postbaseline Definitions for Safety Groups

Table PYAD.6.7 provides conceptual definitions of baseline and postbaseline by analysis type. More specific detail for each submission is provided in an appendix, if necessary.

Table PYAD.6.7. Baseline and Postbaseline Definitions for Safety Groups Initial Controlled Periods of Individual Studies Controlled Integrated Analysis Sets

Analysis Type	Baseline	Postbaseline
TEAEs	Start of screening and ends prior to the study drug dose.	Starts after initiation of the study drug dose and ends on or prior to the day of study disposition
Treatment-Emergent Abnormal Laboratory Values and Vital Signs	Start of screening and ends prior to the study drug dose. All scheduled and unscheduled measurements will be included.	Starts after initiation of the study drug dose and ends on or prior to the day of study disposition. All scheduled and unscheduled measurements will be included.

Baseline and Postbaseline Definitions for Safety Groups
Initial Controlled Periods of Individual Studies
Controlled Integrated Analysis Sets

Analysis Type	Baseline	Postbaseline
Change from Last Baseline to Week *xx* and to Last Postbaseline for Laboratory Values and Vital Signs	Start of screening and ends prior to the study drug dose. The last scheduled nonmissing assessment recorded prior to the date of the first dose.	Starts after initiation of the study drug dose and ends on or prior to the day of study disposition. Only scheduled visits will be included. The early termination visits are considered scheduled visits.

Abbreviation: TEAE = treatment-emergent adverse event.

6.12.2. Extent of Exposure

Exposure to therapy will be represented as either a complete or incomplete infusion, and will be summarized using descriptive statistics.

6.12.3. Adverse Events

Summaries of AEs will include the number of patients with at least 1 AE for each treatment group. When reporting by System Organ Class (SOC) and PT, the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence overall. A patient with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT will be counted only once in the frequency tables for that PT.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by SOC, PT, severity, and relationship to IP as assessed by the investigator. For each event classification term, the number of subjects experiencing a treatment-emergent AE (TEAE) with that classification term will be tabulated.

In an overview table, the number and percentage of patients who experienced a TEAE, serious adverse event (SAE), AE related to study drug, died due to an AE, discontinued from the study treatment, or discontinued from the study due to an AE will be summarized by treatment. Treatment-emergent AEs may be reported separately for the evaluation period and follow-up period.

Treatment-Emergent Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the baseline period, it will be treated as “mild” in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as

"severe" and treatment emergence will be determined by comparing with baseline severity. Missing severity will be reported as missing, without imputation.

Additional types of AEs to be summarized are described in Table PYAD.6.8.

Table PYAD.6.8. Additional Types of Adverse Events to be Summarized

Event Type	Summary Method
SAEs	SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.
TEAEs Resulting in Death	If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of preferred term.
TEAEs Leading to Study Discontinuation	TEAEs for which the action taken is 'Study Discontinuation' will be identified as TEAEs that lead to study discontinuation. The TEAEs that lead to study discontinuation will be summarized for each treatment group by SOC and PT for the safety population. A by-patient listing of the TEAEs that lead to study discontinuation will also be provided.
Treatment-Related TEAEs	Every AE will be assessed by the investigator for its relationship to the randomly assigned study treatment.
TEAEs by Maximal Severity	Every AE will be graded by the investigator as mild, moderate, or severe, so for each patient the greatest severity observed can be obtained by comparing the severity of all a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.
TEAEs (Not Including Serious)	The most common nonserious TEAEs will be summarized. All PT that occur in at least 5% of the safety population patients in any treatment group, when not counting the serious TEAEs, will be tabulated by SOC and PT for each treatment group. These reports will also present the total number of TEAEs for each SOC and PT.

Abbreviations: AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

SOC mapping

Medical Dictionary for Regulatory Activities PTs are assigned to a SOC through primary mappings (defined by MedDRA). Thus MedDRA PTs will appear in only 1 SOC.

Events not summarized

Events considered related by the investigator will not be summarized. Medical representatives may use the relatedness assessment when reviewing individual cases.

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

The following are "notable" events, from start of study drug through end of study participation:

- Deaths
- SAEs, and
- Discontinuations of study treatment due to AEs.

Narratives (patient-level data and summary paragraph) will be provided for participants in the safety population with at least 1 notable event.

6.12.5. Hospitalization, Clinical Events, and Clinical Status

The following events (observed at any time point during the study evaluation period) will be summarized using descriptive statistics:

- Proportion of participants hospitalized
- Duration of hospitalization (DOH; in days),
- proportion (percentage) of participants admitted to Intensive Care Unit (ICU),
- proportion (percentage) of participants requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation")

All hospitalization events, and procedures of special interest will be listed.

In the event that a participant has an ongoing hospitalization event at the time of study disposition, the hospitalization end date will be imputed to the study disposition date.

6.12.6. Clinical Laboratory Evaluation

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol (See Protocol Appendix 2). However, unscheduled measurements of planned analytes will be included/excluded as specified in the relevant sections. Examples of unplanned measurements include those that the clinical investigator orders as a repeat test or "retest" of a laboratory test in case of an abnormal value, and those the investigator orders for a "follow-up visit" due to clinical concerns. Some planned analytes are intended for individual case reviews and will not be included in group-level summaries.

6.12.7. Vital Signs and Other Physical Findings

The planned summaries are provided in Table PYAD.6.9. The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, weight, and temperature.

The criteria for identifying subjects with treatment-emergent abnormalities are based on Table PYAD.6.10.

Some of the analyses of vital signs may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in Table PYAD.6.9 and not provided would be available upon request. For example, box plots for observed values, scatter plots, and shift tables could be provided as interactive displays for medical review.

Table PYAD.6.9. Tables and Figures Produced to Support Vital Signs and Physical Characteristics

Analysis Type	Analysis Details
Box plots for observed values by visit	• Includes participants who have both a baseline and a postbaseline measurement from a planned visit. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • No inferential statistics.
Box plots for change from baseline values by visit	• Includes participants who have both a baseline and a postbaseline planned measurement. • Unplanned measurements will be excluded. • Last baseline will be used. • Descriptive summary statistics will be included in a table below the box plot. • Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot along with a p-value using the ANCOVA model.
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	• Each study individually and studies combined will be displayed. • Includes participants who have both a baseline and postbaseline observation. • Unplanned measurements will be included. • Lines indicating the reference limits will be included. • **Max vs Max:** Maximum baseline versus maximum postbaseline. • **Min vs Min:** Minimum baseline versus minimum postbaseline.

Summary tables for shifts to high/low	• Limits provided by the central lab service will be used to define low and high.
	• **Normal/high to low:** Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low.
	  ○ Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 postbaseline result.
	• **Normal/low to high:** Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high.
	  ○ Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period.
	• Statistical comparisons will be included.

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

Table PYAD.6.10. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes in Adults

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥129 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Temperature	<96°F (<35.6°C) and decrease ≥2°F (≥1.1°C) from baseline	≥101°F (≥38.3°C) and increase ≥2°F (≥1.1°C) from baseline

Abbreviations: BP = blood pressure; bpm = beats per minute.

6.12.8. Immunogenicity

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

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer 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.

6.13. Subgroup Analyses

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

Subgroup analyses will be conducted for the primary and key secondary endpoints. Subgroups may include

- role within the facility (resident, staff)
- age group by role within the facility (residents < median resident age, residents ≥ median resident age, staff < median staff age, staff ≥ median staff age)
- sex (male, female)

- race
- ethnicity
- concomitant medication of interest use (yes/no)

Additionally, AEs, SAEs, and TEAEs will be summarized by role within the facility (resident vs staff).

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. Treatment group differences will not be evaluated within each category of the subgroup if the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided, that is, no inferential testing.

The analysis of additional subgroups and/or subgroup analyses on additional endpoints will not require an amendment to the SAP.

Within each subgroup category the relevant summary measure by treatment, treatment differences (compared to placebo) and 95% CIs will be displayed. Also, p-values using appropriate statistical tests for treatment comparison will be provided. Forest plots may be generated to display the treatment difference and 95% CIs for selected efficacy subgroup analyses.

Concomitant therapies of interest include remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine, anticoagulants, or other investigational interventions. Details of the medications included in this subgroup are provided below in Table PYAD.6.11. Other concomitant therapies of interest may be evaluated based on available external information.

Table PYAD.6.11. Concomitant Medications of Interest Subgroup

Drug name	ATC Code	ATC Preferred Term
Remdesivir	---	REMDESIVIR
Kaletra	J05AR	KALETRA
Lopinavir	J05AR	LOPINAVIR
Hydroxychloroquine	P01BA	HYDROCHLOROQUINE
Dexamethasone	R01AD	DEXAMETHASONE

Concomitant Medications of Interest Subgroup

Drug name	ATC Code	ATC Preferred Term
Chloroquine	P01BA	CHLOROQUINE
Baricitinib	L04AA	BARICITINIB
Heparin	B01AB	HEPARIN
Fondaparinux	B01AX	FONDIIPARINUX
Argatroban	B01AE	ARGATROBAN

Abbreviation: ATC = anatomical therapeutic chemical.

6.14. Protocol Violations

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) are defined as those deviations from the protocol that would potentially compromise patients' safety, data integrity, or study outcome.

A separate document known as the "PYAD Trial Issues Management Plan" describes the categories and subcategories of IPDs and how the IPDs would be identified.

The number and percentage of patients having IPDs will be summarized within category and subcategory of deviations by dosing regimen.

A by-patient listing of IPDs will be provided.

6.15. Interim Analyses and Data Monitoring

6.15.1. Interim Analyses

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

The DSMB will review summary unblinded data monthly from the first participant entering treatment. Safety will be evaluated at each of these interim analyses and benefit/risk of LY3819253 will be assessed if needed.

The DSMB will review the following types of data:

- Demographics
- Baseline characterisitcs
- AEs
- SAEs
- Laboratory data
- PK/PD data (if available)
- Vital signs
- Concomitant medications

- Historical/pre-existing conditions
- Discontinuations
- Product complaints

The PYAD(b) study may be stopped early based on an unacceptable safety signal(s).

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

Further details regarding the interim analyses can be found in the DSMB Charter.

6.15.2. Data Monitoring Committee/Assessment Committee

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.

Details of the DSMB will be provided in the DSMB charter. Unblinding details are specified in a separate blindind and unblinding plan document.

6.16. Additional Exploratory Analyses

6.16.1. Protocol Defined Exploratory Endpoints

Protocol defined exploratory endpoints are described in Section 4.3 and analysis details are provided in the following sections.

6.16.1.1. Time to Improvement to Mild Severity Symptoms

Time to improvement to mild severity symptoms will be is defined (in days) as:

(Date when participant's symptoms first meet definition of mild severity – Date when participant's symptoms first meet definition of moderate or worse severity + 1)

Only patients who have at baseline or later develop moderate-or-worse severity COVID-19 will be included in the analysis. If a patient has not experienced improvement to mild symptoms by completion or early discontinuation of the Evaluable Period, the patient will be censored at the date of their last visit during the Evaulation Period.

Time to improvement to mild severity symptoms will be summarized by treatment group and listed for the Prevention populations and the Part 1 Treatment population. In addition, a graphical presentation of the symptom improvement will be provided using a KM plot.

6.16.1.2. Worst NIAID Score

The lowest daily value from Day 1 through the end of the Evaluation Period for a patient on the NIAID ordinal scale will be analyzed using a nonparametric rank-sum test (such as Mann-Whitney or van Elteren test) adjusting for facility and for the randomization stratification factors. Missing data will be imputed using HDSI, as described in Section 6.3.6. Mean value by treatment group will be plotted over time. This comparison will be made on the Prevention and Treatment populations.

6.16.1.3. SARS-CoV-2 Clearance

For qualitative determination of viral clearance, the lab determination of "positive"/"negative" will be used. SARS-CoV-2 clearance (yes/no) is defined as a single negative RT-PCR test for the SARS-CoV-2 virus. The date of viral clearance is defined as the date of the first occurrence of a negative test.

The proportion of patients that achieve SARS-CoV-2 clearance within 1, 2, or 3 weeks of becoming SARS-CoV-2 positive will be summarized by treatment group in frequency tables and listed for the Prevention populations and the Part 1 Treatment population. Similar summaries will be made for the proportion of patients in the Part 2 Treatment population that achieve SARS-CoV-2 clearance within 8 and 29 days of becoming SARS-CoV-2 positive.

In addition, the number of patients that achieve SARS-CoV-2 clearance within 1, 2, or 3 weeks (or, for the Part 2 Treatment population, within 8 and 29 days) of becoming SARS-CoV-2 positive will be analyzed using logistic regression to comparetreatment groups, if there are sufficient data available. Missing data will be imputed using the NRI method as described in Section 6.3.3. This comparison will be made on the Prevention and Treatment populations.

6.16.1.4. Time to SARS-CoV-2 Clearance

See Section 6.16.1.3 for more details on the definition of viral clearance and date of viral clearance.

Time to SARS-CoV-2 clearance is defined (in days) as:

(Date of first negative SARS-CoV-2 RT-PCR test – Date of first positive SARS-CoV-2 RT-PCR test + 1)

Only patients who have at baseline or later develop SARS-CoV-2 infection will be included in the analysis. If a patient has not experienced SARS-CoV-2 clearance by completion or early discontinuation of the evaluation period, the patient will be censored at the date of their last visit during the evaluation period.

Time to SARS-CoV-2 clearance will be evaluated during the study evaluation period only and will be summarized by treatment group, and listed for the Prevention and Treatment populations. Cox proportional hazard methodology will be used.

Time to SARS-CoV-2 clearance will be presented graphically.

6.16.1.5. Viral Resistance

If appropriate, the evaluation of viral resistance will be conducted as described in a separate bioanalytical analysis plan for the Prevention and Treatment populations.

6.16.1.6. Duration of Hospitalization

Treatment comparisons of the mean DOH (in days) due to COVID-19 will be compared between each study intervention and placebo using a nonparametric rank-sum test (such as Mann-Whitney or van Elteren test) adjusting for facility and for the randomization stratification factors. This comparison will be made on the Prevention and Treatment populations.

6.16.2. Additional Exploratory Analyses not Defined in the Protocol

In addition to the protocol defined endpoints, additional sensitivity analyses may be performed if deemed appropriate.

Additional analyses include:

6.16.2.1. SARS-CoV-2 Viral Load over Time

For quantitative viral load endpoints in the trial, the Ct values will be utilized with the following considerations:

- Two Ct values will be provided on 2 different genes: N1 and N2. N1 will be used as the primary measure; N2 will only be used when the Ct value for N1 is not available.
- Ct values range between 0 and 45.
- Negative SARS-CoV-2 tests will be associated with a Ct value of 45.
- The (log base 10) viral load will be calculated from the Ct value $(45\text{-Ct})/\log_2 10$, or (45-Ct)/3.321928.

For participants who are SARS-CoV-2 positive at baseline or at any time during the Evaluation Period, change from the date of confirmed infection to the end of the Evaluation Period of SARS-CoV-2 viral load data in the log base 10 scale will be statistically analyzed using a MMRM analysis method. The model will contain log base 10 transformed viral load at time of confirmed infection as a covariate, treatment, days since confirmed infection (day), treatment-by-day interaction, facility, and the randomization stratification factors as fixed effects.

6.16.2.2. Clinical Worsening based on the NIAID Scale

Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to the end of the Evaluation Period. Treatment group comparisons will be analyzed using logistic regression, if there are sufficient data available. Missing data will be imputed using the NRI method as described in Section 6.3.3.

6.16.2.3. Time to Hospitalization from first positive SARS-CoV-2 test

Time to Hospitalization is defined (in days) as:

(First study day when hospitalized status is changed to "Yes" – Date of first positive SARS-CoV-2 test +1)

Only patients who have at baseline or later develop SARS-CoV-2 infection will be included in the analysis. If a patient has not been admitted to the hospital or ICU by completion or early discontinuation of the evaluation period, the patient will be censored at the date of their last visit during the evaluation period.

Time to hospitalization will be evaluated during the study evaluation period only and will be summarized by treatment group, and listed for the Prevention and Treatment populations. Cox proportional hazard methodology will be used.

Time to hospitalization may be presented graphically.

6.16.2.4. Time to Admission to ICU from first positive SARS-CoV-2 test

Time to ICU is defined (in days) as:

(First study day when ICU status is changed to "Yes" – Date of first positive SARS-CoV-2 test +1)

Only patients who have at baseline or later develop SARS-CoV-2 infection will be included in the analysis. If a patient has been admitted to the hospital or ICU by completion or early discontinuation of the evaluation period, the patient will be censored at the date of their last visit during the evaluation period.

Time to ICU will be evaluated during the study evaluation period only and will be summarized by treatment, and listed for the Prevention and Treatment populations. Cox proportional hazard methodology will be used.

Time to ICU may be presented graphically.

6.16.2.5. Proportions of Patients Hospitalized, Admitted to the ICU, Requiring Mechanical Ventilation

The proportion of patients hospitalized, admitted to the ICU, requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation") will be evaluated separately using a logistic regression analysis with treatment, facility, and randomization stratification in the model. Missing data will be imputed using the NRI method as described in Section 6.3.3. These endpoints will be evaluated for the Prevention and Treatment populations at Day 57.

6.16.2.6. All Cause Mortality

The proportion of patients that experience death after randomization will be summarized by treatment in frequency tables and listed for participants in the Safety Populations.

Additionally, at the End of Evaluation Database Lock, the number of patients who experienced death anytime after randomization will be analyzed to compare each study intervention versus placebo in the Prevention and Treatment populations, if there are sufficient data available. In addition, the number of patients that experience death after randomization will be analyzed using logistic regression to compare each study intervention versus placebo at each dose level, if there are sufficient data available.

6.17. Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.18. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (e.g., the CSR, manuscripts, and so forth).

7. References

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

Rao, C.R. Large sample tests of statistical hypotheses concerning several parameters with applications to problems of estimation. Proc. Cambridge Philos. Sco. 44. 50-57

8. Appendices

Appendix 1. NIAID Scoring Scale

The National Institute of Allergy and Infectious Diseases (NIAID) scoring scale will be assessed daily and defined as the lowest score achieved for that day.

The scoring is based on the clinical status of the patient as described below.

NIAID Score	Description
1	Death
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
3	Hospitalized, on noninvasive ventilation or high flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
7	Not hospitalized, limitation on activities and/or requiring home oxygen
8	Not hospitalized, no limitations on activities