Statistical Analysis Plan: J2X-MC-PYAD(c)

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

NCT04497987

Approval Date: 7-Dec-2020

1. Statistical Analysis Plan: J2X-MC-PYAD(c): 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(c)
Phase 3

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

Approval Date: 07-Dec-2020 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table of Contents

Figure **Page**

Table of Contents

Appendix **Page**

3. Revision History

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

SAP Version 4 was approved prior to the first patient visit of Part 3 of the study.

DOCUMENT HISTORY	
Document	**Date**
Version 4	7-Dec-2020
Vesion 3	12-Nov-2020
Version 2	26-Oct-2020
Original SAP	20-Jul-2020

Overall Rationale for the revision on Version 3:

The sponsor is adding Part 3 of Study PYAD. The SAP is being updated to reflect the changes implemented in protocol amendment (c).

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

Section # and Name	**Description of Change**	**Brief Rationale**
Throughout	PYAD(b) changed to PYAD(c)	Protocol Update – amendment (c).
Section 4.3 – Exploratory Endpoints	Exploratory Objectives for Part 3 added	Protocol Update – amendment (c).
5.1 – Summary of Study Design	Schema for Part 3 added.	Protocol Update – amendment (c).
5.1.1 – Screening Period	Screening period information for Part 3 added.	Protocol Update – amendment (c).
5.1.2 – Evaluation Period	Evaluation period information for Part 3 added.	Protocol Update – amendment (c).
5.1.3 – Follow-up Period	Follow-up period information for Part 3 added.	Protocol Update – amendment (c).
5.2 – Determination of Sample Size	Language discussing sample size for Part 3 added	Protocol Update – amendment (c).
5.3.2 Blinding	Added open-label language regarding Part 3	Protocol Update – amendment (c).
6.1.1 – Analysis Populations	Added Safety and Treatment populations for Part 3.	Protocol Update – amendment (c).
6.1.4 – Analysis Methods	Elaborated that only Parts 1 and 2 of the study will be controlled for multiplicity.	Protocol Update – amendment (c).

Section # and Name	Description of Change	Brief Rationale
6.10.3.5 - COVID-19-Related Deterioration (Hospitalization, Emergency Room, or Death by Day 57)	Elaborated that death also needed to be related to COVID-19 to satisfy the endpoint.	Clarification
6.16.1.3 – SARS-CoV-2 Clearance	Part 3 analysis added to description	Protocol Update – amendment (c).
6.16.2.7 – Persistently High Viral Load	Exploratory endpoint added	Protocol Update – amendment (c).

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(c)

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(c)

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(c) 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(c) 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(c) 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

Table PYAD.4.6. Exploratory Objectives of Part 3 of Study J2X-MC-PYAD(c) in Participants Positive at Baseline for SARS-CoV-2 RT-PCR and Negative at Baseline for Serology

Objectives	Endpoints
Exploratory	
Compare the frequency of hospitalization due to COVID-19	• Proportion of participants who are hospitalized or experience death 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 due to COVID-19
Characterize COVID-19 illness and severity according to NIAID ordinal scale(s)	• Worst score on a NIAID ordinal scale(s)
Characterize 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 8 or 29 days 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.
Evaluate the duration of hospitalization due to COVID-19	• Cumulative days of hospitalization in those who are hospitalized due to COVID-19.

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.

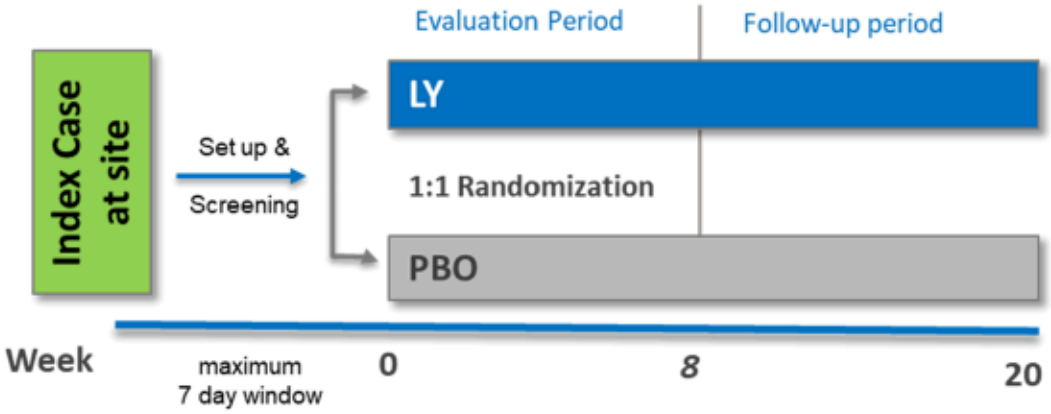

Figure PYAD.5.1. Overview of participant flow from time of Index Case at a facility to completion of follow-up for Part 1 of the study

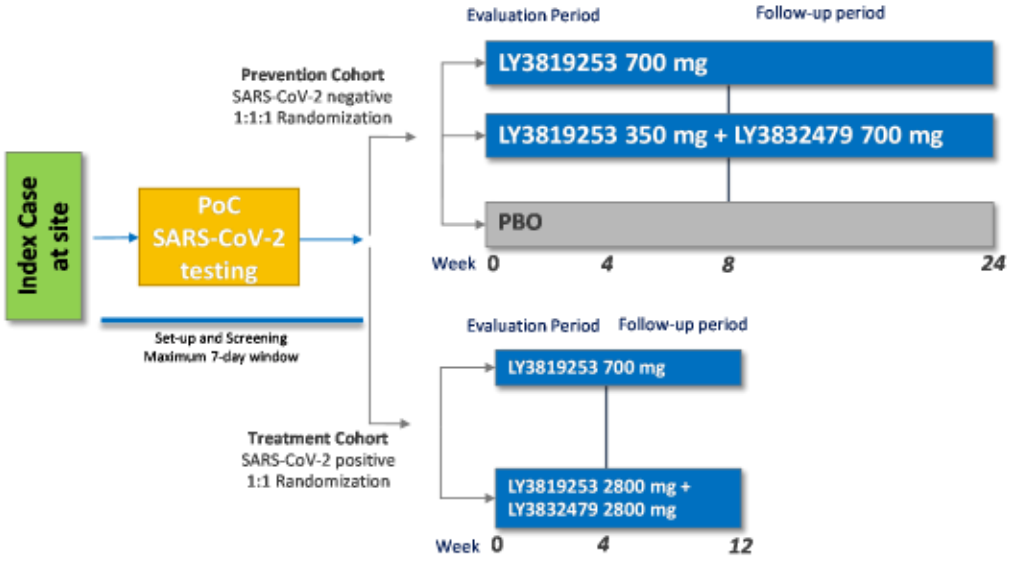

Figure PYAD.5.2. Overview of participant flow from time of Index Case at a facility to completion of follow-up for Part 2 of the study

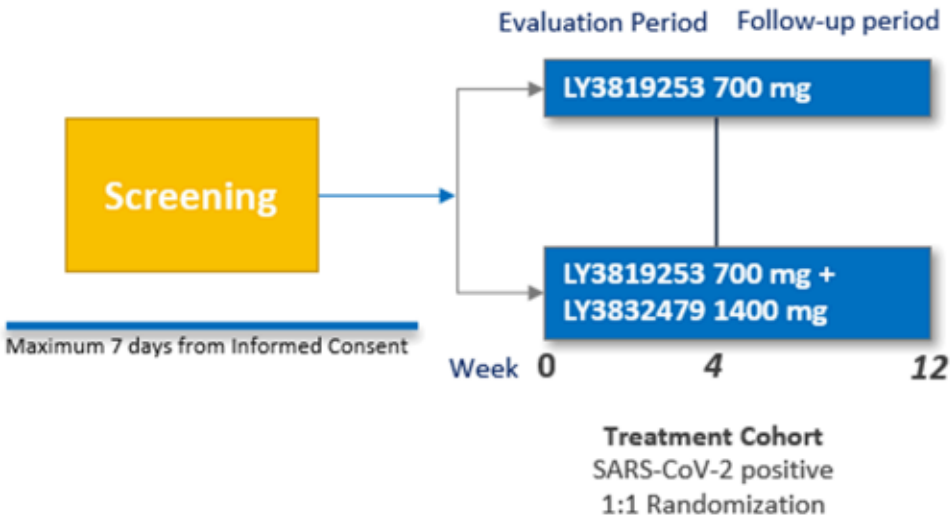

Figure PYAD.5.2. Overview of participant flow from time of Index Case at a facility to completion of follow-up for Part 2 of the study

5.1.1. Screening Period

The screening period for each site in Parts 1 and 2 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.

In Part 3, the screening period for each participant starts at the signing of the ICF. Screening, randomization, and IP administration must be completed within 7 days from signing the ICF.

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. In Part 3, participants will be randomized to 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 and for all participants in Part 3, a post-evaluation follow-up assessment will be conducted at Day 85 according to the SoA.

Strategies to manage infection risks and reduce the burden of return visits may be used by sites, such as remote visits.

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.

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

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

Parts 1 and 2 of this study are double-blinded. 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(c)

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).

Part 3 is open label.

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, including those populations from Part 3 of the study.

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
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 Treatment Cohort in Part 2 who are POC positive, RT-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 3 Treatment	**Definition:** All participants in the Enrolled/Intent-to-Treat population in Part 3 who are RT-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 and 700 mg LY3819253 + 1400mg LY3832479 **Inferential Comparisons:** LY3819253 versus LY3819253 + LY3832479 (not powered for formal inference)

Analysis Populations

Population	Description
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
Part 3 Safety	**Definition:** All participants randomly assigned and who received any amount of study intervention in Part 3. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses. **Treatment Groups (Short Label):** 700 mg LY3819253 and 700 mg LY3819253 + 1400mg LY3832479 **Inferential Comparisons:** LY3819253 versus LY3819253 + LY3832479 (not powered for formal inference)
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.

Parts 1 and 2 of the study will each 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.

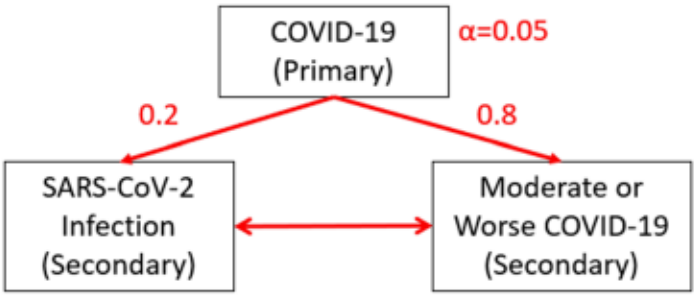

Figure PYAD.6.1. Graphical testing scheme for the primary and key secondary endpoints in Part 1

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 populations. 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 related to COVID-19

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 of 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(c) 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 and Part 3 treatment populations 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 and Part 3 treatment populations, within 8 and 29 days) of becoming SARS-CoV-2 positive will be analyzed using logistic regression to compare treatment 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.

6.16.2.7. Persistently High Viral Load

In Part 3 (and only for Part 3), for any sample with a positive CoV-2 test result, an additional normalization step will be taken in the calculation of viral load. The viral load Ct value described in the previous steps will be subtracted by (RP Ct – 26.17), where RP Ct is a measure for the amount of material in the sample, and 26.17 is a historical average value of RP Ct for this assay, used here to center the RP Ct values. The log base 10 viral load will then be calculated from the result as above.

The proportion of patients with Day 7 viral load greater than 5.27 will be summarized by treatment for participants in the Part 3 Treatment population. Additionally, the proportion of patients with Day 7 viral load greater than 5.27 may be analyzed using logistic regression to compare treatment groups, if there are sufficient data available. Missing data will be imputed using the NRI method as described in Section 6.3.3.

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