Statistical Analysis Plan J2W-MC-PYAB (V8)

A Randomized, Double-blind, Placebo-Controlled, Phase 2/3 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness

NCT04427501

Approval Date: 17-Mar-2021

1. Statistical Analysis Plan: J2W-MC-PYAB: A Randomized, Double-Blind, Placebo-Controlled, Phase 2/3 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness

LY3819253 and LY3832479 - Mild to Moderate COVID-19 Illness

This is a Phase 2, randomized, double-blind, placebo-controlled, single-dose study in participants with mild to moderate COVID-19 illness to evaluate the efficacy and safety of LY3819253.

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Protocol J2W-MC-PYAB
Phase 2/3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 19-June-2020
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 31-July-2020
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly: 08 September 2020
Statistical Analysis Plan Version 4 electronically signed and approved by Lilly: 18-September-2020
Statistical Analysis Plan Version 5 electronically signed and approved by Lilly: 17-December-2020
Statistical Analysis Plan Version 6 electronically signed and approved by Lilly: 13-January-2021
Statistical Analysis Plan Version 7 electronically signed and approved by Lilly: 09-March-2021
Statistical Analysis Plan Version 8 electronically signed and approved by Lilly on date provided below.

Approval Date: 17-Mar-2021 GMT

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3. Revision History

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

DOCUMENT HISTORY	
Document	**Date**
Version 8	See approval date on cover page
Version 7	09-Mar-2021
Version 6	13-Jan-2021
Version 5	17-Dec-2020
Version 4	18-Sep-2020
Version 3	08-Sep-2020
Version 2	31-Jul-2020
Original SAP	19-Jun-2020

Overall Rationale for the Revision on Version 1:

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

Section # and Name	Description of Change	Brief Rationale
4 Study Objectives	Added text for the combination with LY3832479 in objectives	For the addition of LY3832479
4 Study Objectives	Updated PK objective and endpoints	For the addition of LY3832479
5.1.3 Double-Blind Treatment and Assessment Period	Updated text, moved text around and updated the treatment table	Moved text for better flow of information. Updated text and table for the addition of the new combination treatment
5.2 Determination of Sample Size	Added text	Addition of new treatment arms
5.3.1 Randomization	Added text	Addition of new treatment arms
6.1 General Considerations	Added text	Addition of generalized linear model as an optional method for a longitudinal binary endpoint
6.1.1 Analysis Populations	Added text	Addition of new treatment arms
6.1.4 Analysis Methods	Replaced health outcome with pharmacodynamic	For consistency with protocol of health outcome.
6.3.2 Last Observation Carried Forward (LOCF)	Added text	To add an alternative missing data imputation strategy
6.3.5 Modified Last Observation Carried Forward	Added section	To describe an alternative missing data imputation strategy
6.7 Participant Characteristics	Updated text	To add categories on age grouping, symptom onset, SpO_2, and prior therapy of interest
6.10.1 Primary Outcome and Methodology	Removed text: symptom onset strata from the model, imputation of 1 if viral load value of 0.	To avoid collinearity between symptom onset strata and baseline viral load. Viral load data is not going to impute which will be calculated

Section # and Name	Description of Change	Brief Rationale
		from cycle threshold.
6.10.2.1 Dose Response Modeling	Added text	To add more details for candidate models for dose response.
6.10.3.2 SARS-CoV-2 Viral Load AUC	Added text	AUC0-11(day)
6.10.3.4 Time to SARS-CoV-2 Clearance	Modified definition of time to clearance to reference infusion date as opposed to randomization date.	Time to SARS-CoV-2 clearance definition clarified
6.10.3.4 Time to SARS-CoV-2 Clearance	'methodology' changed to 'model'	Clarification of text
6.10.3.6 Time to Symptom Resolution	'methodology' changed to 'model'	Clarification of text
6.10.3.10 Change in Symptom Questionnaire Score	Changed scoring from 0-4 to 0-3	Clarification of text
6.11 Health Outcomes and Quality of Life Analyses	Removed	It is not in protocol
6.12 Safety Analyses	Added text	Added stratification factor in the model
6.12.5 Hospitalization, Clinical Events, Clinical Status, and Environmental Risk Factors	Updated text	Referred to Section 6.16.2.6 and Section 6.16.2.8 for analysis method.
6.12.7 Vital Signs and Other Physical Findings	Added text	Added SpO_2, respiratory rate, FiO2
6.12.9 Immunogenicity	Added text	For the addition of LY3832479
6.13 Subgroup Analyses	Added text	Added age grouping and the definition of COVID-19 disease severity.
6.15.1 Interim Analyses	Updated text	For consistency with protocol Section 9.5
6.16.1.2	Added new endpoint	For addition of SpO_2 AUC(0-D11)
6.16.1.3	Added new endpoint	For addition of symptoms AUC(0-D11)
6.16.2.5 Time to Hospitalization	'methodology' changed to 'model'	Clarification of text
6.16.2.7 Time to Admission to ICU	'methodology' changed to 'model'	Clarification of text
6.16.2.10	Added new endpoint	For the addition of new SpO2 endpoint using different cutoffs

Overall Rationale for the Revision on Version 2:

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

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

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

Section # and Name	Description of Change	Brief Rationale
Ventilation		
6.6.2.11 Viral Load Plots	Added text	Added exploratory viral load plots
Appendix 1. NEWS2 Scoring Scale	Added text.	Added text to clarify how missing consciousness data will be handled in the analysis.

Overall Rationale for the Revision on Version 3:

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

Section # and Name	Description of Change	Brief Rationale
6.1.1 Analysis Populations	• Clarified definition of the efficacy population to be consistent with what is defined in the protocol. • Clarified use of safety population to include deterioration and hospitalization events in the population table.	Alignment with protocol. Clarification of text.
6.1.4 Analysis Methods	Clarified that patients with missing baseline measures will be excluded from the corresponding analyses of change from baseline.	Clarification of text describing methodology.
6.3.3 Mixed-Effects Model Repeated Measures (MMRM)	Clarified that patients with missing baseline measures will be excluded from the corresponding analyses of change from baseline.	Clarification of text describing methodology.
6.10.3.9 COVID-19-Related Deterioration	Clarified that the safety population will be utilized to analyze COVID-19-related deterioration.	Clarification of text.
6.10.3.11 Additional Secondary Efficacy Analyses for Treatment Arms 7 and 8	Clarified that the safety population will be utilized to analyze COVID-19-related deterioration.	Clarification of text.
6.16.2 Additional Exploratory Analyses not Defined in the Protocol	Clarified that the analyses of hospitalization events will utilize the safety population.	Clarification of text.

Overall Rationale for the Revision on Version 4:

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

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

Section # and Name	Description of Change	Brief Rationale
		amendments f-j.
5.1.3 Double-Blind Treatment and Assessment Period	Added treatment arm 9.	Alignment with protocol amendment i.
5.2 Determination of Sample Size	Added sample size for treatment arm 9.	Alignment with protocol amendment i.
5.3.1 Randomization	Added randomization for treatment arms 7-9	Alignment with protocol amendments f-i.
5.3.2 Blinding	Clarified text	Alignment with protocol amendment i.
6.1. General Considerations	Added descriptive statistics for adolescent versus adult participants. Clarified that BMI criteria for high-risk status is ≥30.	Inclusion of adolescent participants in the protocol amendment f-i.
6.1.1 Analysis Populations	Add treatment arm 9.	Alignment with protocol amendment i.
6.1.4 Analysis Methods	Added Bayesian methodology and added that multiplicity adjustments will be done for treatment arms 7-9	Alignment with protocol amendment i.
6.3.2 Last Observation Carried Forward (LOCF)	Removed section	Not needed
6.3.2 Modified Non-Responder Imputation (mNRI)	Added section	Clarified this is used in viral clearance analyses
6.3.5 Modified Last Observation Carried Forward	Clarified that this imputation is not used in change from baseline symptom score analyses.	Clarification
6.5 Multiple Comparisons/Multiplicity	Added that multiplicity is done from treatment arms 7-9	Added for Phase 3 endpoints.
6.7 Participant Characteristics	Clarified analyses for adolescents.	Inclusion of adolescent participants in the protocol amendment f.
6.10 Efficacy Analyses	Removed duplicated text	Removed duplicated text
6.10.1 Primary Outcome and Methodology	Added analysis methodology for treatment arms 7-9.	Alignment with protocol amendment f-i.
6.10.2.1 Dose Response Modeling for Treatment Arms 1-4 and 6	Clarified this is only for treatment arms 1-4 and 6	Clarification
6.10.2.2 Bayesian Modeling	Added text for treatment arms 7-9	Alignment with protocol amendment i.
6.10.3.11 Secondary Efficacy Analyses for Treatment Arms 7-9	Updated section to align with the secondary objectives for treatment arms 7-9	Alignment with protocol amendment f-i.
6.11 Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods	Removed content related to noncompartmental analysis methods	Descriptive analysis will be reported
6.12 Safety Analyses	Clarified text	Clarified text
6.13 Subgroup Analyses	• Clarified analyses for adolescents. • Clarified analyses for treatment arms 7-9	Alignment with protocol amendment f-i.
6.15.1 Interim Analyses	Updated text for Treatment arms 7-9	Alignment with protocol amendment f-i.
6.15.2 Data Monitoring	Updated text for Treatment arms 7 and 8	Alignment with protocol

Section # and Name	Description of Change	Brief Rationale
Committee/Assessment Committee		amendment f-i.
6.16.2.11 Viral Load Plots	Clarified text	Clarified text
6.16.2.12 Proportion of Participants with Symptom Resolution on Days 22 and 29	Added Section	Moved to exploratory analyses
6.16.2.13 Proportion of Participants with Symptom Improvement on Days 22 and 29	Added Section	Moved to exploratory analyses

Overall Rationale for the Revision on Version 5:

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

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

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

Overall Rationale for the Revision on Version 6:

New pediatric treatment arm 15 added from the Protocol addendum (2) and new treatment arms 18 and 19 added from Protocol amendment (l). Arms 16 and 17 were added from Protocol amendment (l) and subsequently removed from Protocol amendment (m). Additionally, Protocol amendment (l) reduced the sample size for treatment arms 13 and 14, and Protocol amendment

(m) updated the objectives for treatment arms 13 and 14. Protocol amendment (k) allowed for participants with prior vaccine use to be included in treatment arms 13-14, 18-19.

Section # and Name	Description of Change	Brief Rationale
4.1. Primary Objective	Updated the primary objective for treatment arms 7-9. Added and updated the primary objective for treatment arms 13-14, 18-19.	Protocol Amendment (l) Protocol Amendment (m)
4.2. Secondary Objectives	Added and updated the secondary objectives for treatment arms 13-14, 18-19.	Protocol Amendment (l), Protocol Amendment (m)
4.3. Exploratory Objectives	Added and updated the exploratory objectives for treatment arms 13-14, 18-19.	Protocol Amendment (l), Protocol Amendment (m)
5.2. Design Outline	Updated the design outline.	Protocol Amendment (l)
5.2.2. Double-Blind Treatment and Assessment Period	Updated language for postdose sample collection. Updated the treatment arms. Corrected language for treatment arm 5 and added text for treatment arms 2-4.	Protocol Amendment (l) Protocol Amendment (l), Protocol Amendment(m) Correction
5.3. Determination of Sample Size	Added stratification for those participants with a prior SARS-CoV-2 vaccine use. Added that there is no set sample size for participants with a prior SARS-CoV-2 vaccine use. Updated language for treatment arms 13 and 14. Sample size was reduced for treatment arms 13 and 14. Added sample size for treatment arms 18-19.	Protocol Amendment (k) Protocol Amendment (k) Protocol Amendment (l), Protocol Amendment (m)
5.4.1. Randomization	Added stratification for those participants with a prior SARS-CoV-2 vaccine use.	Protocol Amendment (k)
5.4.2. Blinding	Updated for treatment arms 1-14. Treatment arms 18-19 are unblinded.	Protocol Amendment (l)
6.1. General Considerations	Clarified that subgroup analyses for adolescents and pregnant females may be performed as appropriate.	Clarification
6.1.1. Analysis Populations	Updated the populations for treatment arms 13-14, 18-19.	Protocol Amendment (l)
6.1.4. Analysis Methods	Updated language for multiplicity for treatment arms 13-14, 18-19. Updated the MMRM model for stratification factors. Updated the criteria (observed events instead	Protocol Amendment (l), Protocol Amendment (m) Correction

Section # and Name	Description of Change	Brief Rationale
	of sample size) for using an exact test rather than logistic regression.	
6.3.1. Non-Responder Imputation	Corrected a grammatical error.	Correction
6.3.5. Last Observation Carried Forward	Added section for missing data imputation for PHVL.	Addition
6.5. Multiple Comparisons/Multiplicity	Added multiplicity scheme for treatment arms 13-14, 18-19.	Protocol Amendment (l), Protocol Amendment (m)
6.7. Participant Characteristics	Added analysis for pregnancy and baseline vaccine use for treatment arms 13-14, 18-19.	Protocol Amendment (l)
6.10. Efficacy Analyses	Added treatment arms 13-14, 18-19.	Protocol Amendment (l)
6.10.1. Primary Outcome and Methodology	Updated methodology for treatment arms 7-9. Added methodology for treatment arms 13-14, 18-19.	Protocol Amendment (l) Protocol Amendment (l), Protocol Amendment (m)
6.10.3.6. Time to Symptom Resolution	Clarified that patients who are hospitalized are censored at the date of hospitalization.	Clarification
6.10.3.8. Time to Symptom Improvement	Clarified that patients who are hospitalized are censored at the date of hospitalization.	Clarification
6.10.3.11. Secondary Efficacy Analyses for Treatment Arms 7-9	Section was updated to remove analyses for treatment arms 13-14.	Protocol Amendment (l)
6.10.3.11.1. SARS-CoV-2 Viral Load >5.27 on Day 7 (+2 Days)	Section was updated to remove analyses for treatment arms 13-14.	Protocol Amendment (l)
6.10.3.12. Secondary Efficacy Analyses for Treatment Arms 13-14	Added section for the secondary analyses for treatment arms 13-14	Protocol Amendment (l), Protocol Amendment (m)
6.12.3. Adverse Events	Added analyses for infusion reactions and injection-site reactions.	Protocol Amendment (l)
6.13. Subgroup Analyses	Added analyses for baseline vaccine use.	Protocol Amendment (l)
6.15.1. Interim Analyses	Added possible interim analyses for treatment arms 13 and 14, 18-19.	Protocol Amendment (l)
6.15.2. Data Monitoring Committee/Assessment Committee	Added possible interim analyses for treatment arms 13 and 14, 18-19.	Protocol Amendment (l)
6.16.1.5. COVID-19-Related Deterioration (COVID-19-Related Hospitalization or Death from Any Cause) by Days 22, 60, and 85	Updated to add analyses for treatment arms 13-14, 18-19.	Protocol Amendment (l), Protocol Amendment (m)
6.16.2.8. Proportions of Participants Hospitalized, Admitted to ICU, Requiring Mechanical Ventilation	Removed analyses by visit and added analyses at any time.	Clarification
6.19. Analyses for the Pediatric Open-Label Addendum	Added section.	Protocol Addendum (2)
6.20. Analyses for the Faster Intravenous Infusion Addendum	Added section.	Protocol Addendum (3)
7. References	Added references.	Addition

Overall Rationale for the Revision on Version 7:

New revisions to the pediatric addendum, addendums 2.1 and 2.2.

Section # and Name	Description of Change	Brief Rationale
1. Statistical Analysis Plan: J2W-MC-PYAB: A Randomized, Double-Blind, Placebo-Controlled, Phase 2/3 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness	Made title changes Added LY3832479 and Phase 3	Protocol Amendment (i)
6.19.1 Sample Size	Modified the sample size for the pediatric addendum	Protocol Addendum 2.2
6.19.2 General Considerations	Modified the age groups for the pediatric addendum Updated the treatment arm number for the pediatric addendum Updated the treatment arm labels for the output displays	Protocol Addendum 2.2
6.19.4 Addendum Secondary Analyses	Removed the visit windows from the secondary objectives	Protocol Addendum 2.2
6.19.6. Addendum Exploratory Analyses	Added exploratory objectives	Protocol Addendum 2.2
6.19.7 Addendum Interim Analyses	Updated the interim analyses language to include all regulatory interactions and not just for a biologics license application	Protocol Addendum 2.2

4. Study Objectives

4.1. Primary Objective

Treatment Arms 1-4, and 6

The primary objective of this trial is to characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on upper respiratory tract severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load and viral clearance among participants with mild to moderate COVID-19 illness. The primary endpoint is the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load based on nasopharyngeal swab sampling for reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. Statistical hypothesis testing for the primary endpoint will be conducted using a mixed-effects model repeated measures (MMRM) analysis method at the 2-sided 0.05 level.

Treatment Arms 7-9

The primary objective is to characterize the effect of LY3819253 in combination with LY3832479 compared to placebo on overall participant clinical status. The primary endpoint is the proportion of participants who experience COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29. Statistical hypothesis testing for the primary endpoint will be conducted using a logistic regression with a primary success criterion of a 1-sided alpha level 0.0025.

Treatment Arms 13-14

The primary objective is to characterize the effect of 350 mg LY3819253 in combination with 700 mg LY3832479 (treatment arm 14) on persistently high SARS-CoV-2 viral load compared to treatment arm 13. The primary endpoint is the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7. Statistical hypothesis testing for the primary endpoint will be conducted using a logistic regression with a primary success criterion of a 1-sided alpha level of 0.025.

Treatment Arms 18-19

The primary objective is to demonstrate non-inferiority (NI) of treatment arm 19 on persistently high SARS-CoV-2 viral load compared to the active comparator treatment arm 18. The primary endpoint is the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7. Statistical hypothesis testing for the primary endpoint will be conducted using a logistic regression with a primary success criterion of the upper bound of the 95% confidence interval (CI) ≤1.96.

4.2. Secondary Objectives

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

Objectives	Endpoints
Secondary for Treatment Arms 1-4 and 6 Characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on:	
• safety	• Safety assessments such as AEs and SAEs
• SARS-CoV-2 viral load among participants with ≤8 days since symptom onset	• Change from baseline to Day 11 (±4 days) in SARS--CoV-2 viral load among participants enrolled with ≤8 days of symptoms prior to randomization
• symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 7, 11, 15, and 22 • Change in symptom score (total of ratings) from baseline to Days 7, 11, 15, and 22
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 7, 11, 15, and 22
• SARS-CoV-2 viral load and viral clearance	• Proportion of participants that achieve SARS-CoV-2 clearance (Days 7, 11, 15, and 22) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 29
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 o COVID-19-related hospitalization (defined as ≥24 hours of acute care) o a COVID-19-related emergency room visit, or o death.
Additional Secondary for Treatment Arms 1-4 and 6	
Characterize the pharmacokinetics of LY3819253 and LY3819253 in combination with LY3832479	• Mean concentration of LY3819253 alone and in the presence of LY3832479 on Day 29 • Mean concentration of LY3832479 in presence of LY3819253 on Day 29

Key Secondary for Treatment Arms 7-9 **The key secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on:**	
• the reduction of SARS-CoV-2 viral load	• Change from baseline to Day 7 (±2 days)
• persistently high SARS-CoV-2 viral load	• Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 o COVID-19-related hospitalization (defined as ≥24 hours of acute care), or o COVID-19-related emergency room visit, or o death from any cause.
• Sustained symptom resolution	• Time to sustained symptom resolution
Other Secondary for Treatment Arms 7-9 **The secondary objectives are to characterize the effect of LY3819253 in combination with LY3832479, compared to placebo on:**	
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• Time to sustained complete symptom resolution • Time to complete symptom resolution • Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs
Key Secondary for Treatment Arms 13-14:	
Reduction of SARS-CoV-2 viral load for treatment arms 14 compared to treatment arm 13	Change from baseline to Day 7
Clinical status for treatment arm 14 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29

Additional Secondary for Treatment Arms 13-14:	
Clinical status for treatment arm 14 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience these events by Day 29 • COVID-19-related hospitalization (defined as ≥24 hours of acute care), or • a COVID-19-related emergency room visit, or • death from any cause
Treatment arm 13 compared to treatment arm 14:	
• sustained symptom resolution	• Time to sustained symptom resolution
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 o Day 5 • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• Time to symptom resolution • Time to complete symptom resolution • Time to sustained complete symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs, including date and time of events
Key Secondary for treatment arms 18-19:	
Reduction of SARS-CoV-2 viral load for treatment arm 19 compared to treatment arm 18	Change from baseline to Day 7
Overall participant clinical status for treatment arm 19 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29
Additional Secondary for treatment arms 18-19	
Clinical status for treatment arm 19 compared to all high-risk placebo participants in treatment arms 8 and 13	Proportion (percentage) of participants who experience these events by Day 29 • COVID-19-related hospitalization (defined as ≥24 hours of acute care)

	• a COVID-19-related emergency room visit, or • death from any cause
Treatment arm 19 compared to treatment arm 18 on…	
• sustained symptom resolution	• time to sustained symptom resolution
• SARS-CoV-2 viral load reduction	• Change from baseline to o Day 3 o Day 5 • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 7
• SARS-CoV-2 viral clearance	• Time to SARS-CoV-2 clearance
• symptom resolution	• Time to symptom resolution • Time to complete symptom resolution • Time to sustained complete symptom resolution Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11
• safety	• Safety assessments such as AEs and SAEs, including date and time of events

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

4.3. Exploratory Objectives

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

Objectives	Endpoints
Exploratory for Treatment Arms 1-4 and 6	
Characterize emergence of viral resistance to LY3819253 and LY3819253 in combination with LY3832479	• Comparison from baseline to the last evaluable time point up to Day 29
Characterize the effect of LY3819253 and LY3819253 in combination with LY3832479 compared to placebo on:	
• SpO_2 over time	• SpO_2 AUC assessed through Day 29
• symptom severity	• Symptom severity as assessed by mean AUC through Day 29 of symptom questionnaire
• overall improvement on the NIAID Ordinal Scale	• Comparison of the mean worst daily NIAID ordinal scale values at Days 7, 11, 15, and 22
Exploratory for Treatment Arms 7-9	
• Overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60, and 85 o COVID-19-related hospitalization (defined as ≥24 hours of acute care) o death from any cause
Characterize the pharmacokinetics of LY3819253 in combination with LY3832479	• Mean concentration of LY3832479 in presence of LY3819253 on Day 29
Exploratory for Treatment Arms 13-14	
Treatment arm 14 compared to treatment arms 13 and 8 on overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60, and 85 o COVID-19-related hospitalization (defined as ≥24 hours of acute care), or o death from any cause
Characterize the pharmacokinetics of LY3819253 in combination with LY3832479	Mean concentration of LY3832479 in presence of LY3819253 on Day 29
Exploratory for Treatment Arms 18-19	
Treatment arm 19 compared to treatment arms 13 and 8 on overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60, and 85 o COVID-19-related hospitalization (defined as ≥24 hours of acute care), or o death from any cause
Characterize the pharmacokinetics of LY3819253 in	Mean concentration of LY3832479 in presence of

combination with LY3832479	LY3819253 on Day 29

Abbreviations: AUC = area under the response-time curve; COVID-19 = coronavirus disease 2019; NIAID = National Institute of Allergy and Infectious Diseases; SpO_2 = saturation of peripheral oxygen.

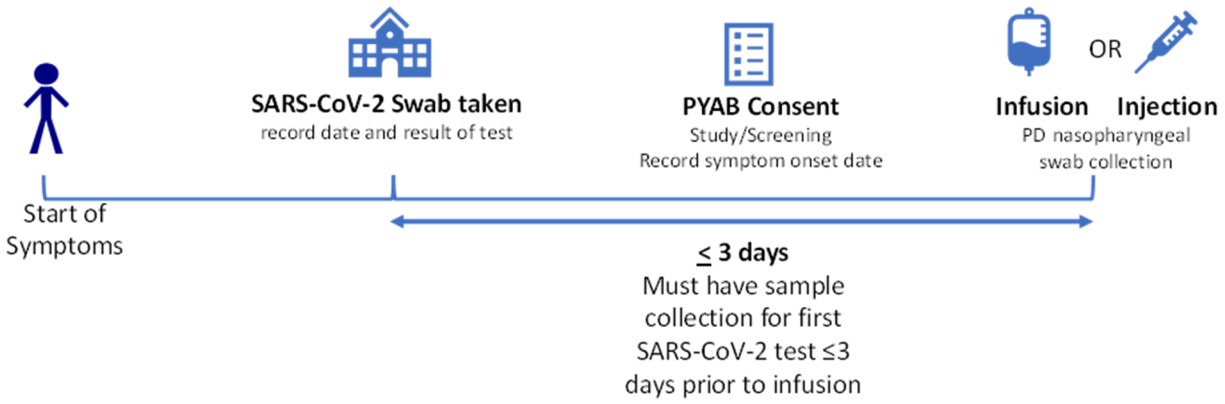
Additional exploratory objectives not previously defined in the protocol are described in Section 6.16.2.

5. Study Design

5.1. Summary of Study Design

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

5.2. Design Outline



Abbreviations: IV = intravenous; PD = pharmacodynamic; PYAB = Study J2W-MC-PYAB; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

5.2.1. Screening

Interested participants will sign the appropriate informed consent document(s) prior to completion of any procedures. The participant may enter the study with a previous positive SARS-CoV-2 viral test result from an external testing facility. This test result must be the first time the patient has tested positive for SARS-CoV-2.

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

5.2.2. Double-Blind Treatment and Assessment Period

This is the general sequence of events during the treatment and assessment period:

- complete baseline procedures and sample collection
- participants are randomized to an intervention group
- participants receive study intervention, and
- complete all safety monitoring and postdose sample collection.

Table PYAB.5.1 describes the planned treatment arms.

Table PYAB.5.1. Treatment Arms of Study J2W-MC-PYAB

Treatment Arms	Dose	Intervention	Route of Administration
1	---	placebo	Intravenous
2	700 mg	LY3819253	
3	2800 mg	LY3819253	
4	7000 mg	LY3819253	
Optional 5	To Be Determined	LY3819253	
6	2800 mg + 2800 mg	LY3819253+LY3832479	
7	2800 mg + 2800 mg	LY3819253+LY3832479	
8	---	placebo	
9	700 mg + 1400 mg	LY3819253+LY3832479	
13	---	placebo	
14	350 mg + 700 mg	LY3819253+LY3832479	
18	700 mg + 1400 mg	LY3819253+LY3832479	
19	CCI	LY3819253+LY3832479	Subcutaneous

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

As LY3819253 dose levels in Study J2W-MC-PYAA are determined to be safe, treatment arms 2-4 may be introduced in Study PYAB.

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

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

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

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

Treatment arms 18-19 are open-label.

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

5.2.3. Posttreatment Follow-up

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

5.3. Determination of Sample Size

Sample Size

Treatment arms 1-4 and 6

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

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

Treatment arms 7-9

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

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

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

Treatment arms 13 and 14

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

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

Treatment arm 18

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

Treatment arm 19

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

Stratification

Participants will be stratified by

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

Treatment Arms 1 Through 4 and 6

Simulations

A viral dynamic model was used to simulate viral loads over time for participants treated with LY3819253 and placebo. This simulated population and Monte Carlo methods were used to estimate statistical power associated with the comparison of change from baseline of interest in SARS-CoV-2 viral load between LY3819253 and placebo.

The mean log change from baseline to Day 11 for LY3819253 and placebo in the simulated population were approximately 4.38 and -3.48 (standard deviation [SD] 1.9), respectively, representing an average of 87% viral load reduction.

Given these assumptions, an assumed sample size of 100 participants per arm provides approximately 91% power to test superiority of intervention group versus placebo in effect on viral load, as measured by change from baseline to Day 11 (±4 days), at the 2-sided 0.05 alpha level.

Periodic adjustments to the allocation ratio of participants will be informed by planned interim analyses. See Protocol Section 9.5 for details.

Treatment Arms 7 Through 9

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

Treatment Arms 13-14

Sample size justification for these arms is based on the endpoint of proportion of participants with persistently high SARS-CoV-2 viral load at Day 7. A sample size of approximately 400 participants per treatment arm provides greater than 90% power to demonstrate that LY3819253 in combination with LY3832479 is statistically significantly better than placebo. This sample size calculation assumed a placebo event rate of 30% and a relative reduction of 60% for LY3819253 in combination with LY3832479, which were informed from available data on rates of persistently high SARS-CoV-2 viral load.

Treatment Arms 18-19

The primary objective for these treatment arms is to demonstrate NI of treatment arm 19 compared to the active comparator treatment arm 18 for Day 7 in persistently high viral load (PHVL). A NI boundary of 1.96 will be used, which is approximately the square root of the observed OR for treatment arm 7 and 8.

Treatment Arms	Dose	Intervention	Observed PHVL Proportion	Observed Odds Ratio	Square Root of the Odds Ratio
7	2800 mg + 2800 mg	LY3819253+LY3832479	50/508	3.83	1.96
8	---	Placebo	147/499	---	---

Abbreviation: PHVL = persistently high viral load.

The NI margin of 1.96 ensures preservation of at least 50% of the treatment effect, estimated using the observed OR. The randomization of approximately 920 participants across treatment arms 18 and 19 provides 85% power to establish NI of treatment arm 19 compared to treatment arm 18. If Day 7 PHVL status has an OR of 1 for the comparison of arm 14 combined with arms 16 and 17 to treatment arm 18, the upper bound of the 95% CI of the OR is ≤1.96.

5.4. Method of Assignment to Treatment

5.4.1. Randomization

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

Participants will be stratified by

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

All eligible participants will be randomized, initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made in an effort to achieve an equal allocation across the treatment arms at the end of enrollment. If additional placebo participants are enrolled, then the allocation ratio may change accordingly.

5.4.2. Blinding

For the blinded treatment arms (arms 1-14), neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base lock at the conclusion of the study.

Table PYAB.5.2 describes general procedures for unblinding.

Table PYAB.5.2. Unblinding Procedures for Study J2W-MC-PYAB

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

Abbreviation: IWRS = interactive web-response system.

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

6. A Priori Statistical Methods

6.1. General Considerations

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

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

Unless otherwise noted, displays will include columns for each treatment group, and in case of multiple doses of investigational product (IP), another column for IP doses combined will be displayed. A column that combines IP groups with placebo and/or active controls (i.e., a total column) will not be created.

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

Analyses will be performed separately for treatment arms

- 1-4 and 6,
- 7 and concurrently enrolled 8,
- 8 and 9,
- 13 and 14, and
- 18-19 for the NI analyses

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

For treatment arms 7-9 and 13-14, subgroup analyses (≥12 and <18 years old versus ≥18 years old) will be performed as appropriate and include descriptive statistics only. For treatment arms 13-14 and 18-19, subgroup analyses may be performed on all female participants who are pregnant at baseline and will include descriptive statistics only.

For a binary endpoint collected in a longitudinal fashion, a generalized linear mixed-effect model may be applied assuming missing at random (MAR) if deemed appropriate.

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

6.1.1. Analysis Populations

Patient populations are defined in Table PYAB.6.1 along with the analysis to be used to conduct. The treatment groups and inferential comparisons described in Table PYAB.6.1 will be used

unless otherwise specified. Also, unless otherwise specified, for all populations/analysis, participants will be analyzed according to the treatment to which they were assigned.

Table PYAB.6.1. Analysis Populations

Population	Description
Entered	**Definition:** All participants who signed informed consent. **Purpose:** Used for disposition analysis. **Treatment Groups:** None **Inferential Comparisons:** None
Efficacy	**Definition:** All randomized participants who received study intervention and provided at least 1 postbaseline measure viral load measurement. Participants will be analyzed according to the intervention to which they were randomized (Intention to treat). **Purpose:** Used for efficacy and pharmacodynamic variables analyses. **Treatment Groups (Short Label):** *Treatment arms 1-4 and 6:* 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), LY total, and placebo (Pbo). *Treatment arms 7-8:* 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) and placebo (Pbo). *Treatment arms 8-9:* 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2) and placebo (Pbo). *Treatment arms 13-14:* 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2) and placebo (Pbo). *Treatment arms 18-19:* CCI [redacted] and 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2). Additional optional combination arms may be added if decided. **Inferential Comparisons:** *Treatment arms 1-4, 6, 7-14:* • Each LY dose versus Pbo • Each LY/LY2 dose versus Pbo *Treatment arms 18-19:* • CCI [redacted] versus 700/1400 LY/LY2
Safety	**Definition:** All participants randomly assigned and who received any amount of study intervention. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses, analyses of COVID-19-related deterioration and hospitalization events. **Treatment Groups (Short Label):**

Population	Description
	Treatment arms 1-4 and 6: 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), LY total, and placebo (Pbo). *Treatment arms 7-8:* 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) and placebo (Pbo). *Treatment arms 8-9:* 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2) and placebo (Pbo). *Treatment arms 13-14:* 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2) and placebo (Pbo). *Treatment arms 14, 16-18:* CCI [redacted] and 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2). Additional optional combination arms may be added if decided. **Inferential Comparisons:** *Treatment arms 1-4, 6, 7-14:* • LY total versus placebo • LY/LY2 total versus placebo *Treatment arms 18-19:* • No inferential comparisons • For overall clinical status endpoints: o CCI [redacted] versus Pbo (high-risk participants from treatment arms 1, 8, and 13 combined)
Pharmacokinetic and PK/PD (exposure-response relationships)	**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):** *Treatment arms 1-4 and 6:* 700 mg LY3819253 (700 LY), 2800 mg LY3819253 (2800 LY), 7000 mg LY3819253 (7000 LY), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), and placebo (Pbo). *Treatment arms 7-8:* 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) and placebo (Pbo). *Treatment arms 8-9:* 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2) and placebo (Pbo).

Population	Description
	Treatment arms 13-14: 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2) and placebo (Pbo). *Treatment arms 18-19:* CCI [redacted] and 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2). Additional optional combination arm may be added if decided. **Inferential Comparisons:** *Treatment arms 1-4, 6, 7-14:* • Each LY dose versus Pbo • Each LY/LY2 dose versus Pbo *Treatment arms 18-19:* • CCI [redacted] versus 700/1400 LY/LY2
Per-Protocol	**Definition:** All participants in the efficacy population who do not meet any of the following criteria: • received medication other than the medication the participant was randomized to receive; • did not meet an inclusion criterion; or • met an exclusion criterion. **Purpose:** Used for sensitivity analyses for the primary and key secondary endpoints. **Treatment Groups (Short Label):** *Treatment arms 7-8:* 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) and placebo (Pbo). *Treatment arms 8-9:* 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2) and placebo (Pbo). *Treatment arms 13-14:* 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2) and placebo (Pbo). *Treatment arms 18-19:* CCI [redacted] and 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2). Additional optional combination arms may be added if decided. **Inferential Comparisons:** *Treatment arms 1-4, 6, 7-14:* • LY total versus placebo • LY/LY2 total versus placebo

Population	Description
	Treatment arms 18-19: • CCI [redacted] versus 700/1400 LY/LY2 • For overall clinical status endpoints: o CCI [redacted] versus Pbo (treatment arms 8 and 13 combined)

Abbreviations: COVID-19 = coronavirus disease 2019; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous.

6.1.2. Definition of Study Baseline

Unless otherwise specified, for efficacy and health outcome, baseline is defined as the last nonmissing assessment recorded on, or prior to, the date of the first study drug administration at study Day 1.

Baseline for safety analysis is described in the safety section.

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

6.1.3. Study Time Intervals

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

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

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 PYAB.6.2 should be understood to mean "the day before" while the words "after" should be understood to mean "the day after." For the purpose of determining whether a date/time lies within an interval, these words are intended to convey whether the start or end of the period is inclusive of the specified date.

Table PYAB.6.2. Definition of Study Period Time Intervals

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

6.1.4. Analysis Methods

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

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

No adjustment for multiplicity will be performed for treatment arms 1 through 6. For treatment arms 7-9, 13-14, and 18-19, a multiple testing procedure that controls the familywise error rate at the 1-sided 0.025 level will be applied to the primary and key secondary endpoints.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Additional exploratory analyses of the data may be conducted as deemed appropriate, including pharmacokinetic/pharmacodynamic (PK/PD) model-based exposure-response analyses.

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

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

Treatment comparisons of continuous efficacy, and pharmacodynamic variables with multiple postbaseline measurements will be made using MMRM analysis. When MMRM is used, it includes: (a) treatment group, (b) stratification factor of duration since symptom onset to randomization (≤8 days versus >8 days), unless otherwise noted, (c) baseline value in the model, (d) visit, and (e) the interactions of treatment-by-visit as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The first structure to yield convergence will be used for inference. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Unless otherwise specified, for MMRM, reported data from only planned visits will be used as the primary analysis.

Treatment comparisons of continuous efficacy, safety, and health outcome variables with a single postbaseline timepoint will be made using analysis of covariance (ANCOVA) with:- (a) treatment group, (b) stratification factor of duration since symptom onset to randomization (≤8 days versus >8 days), and (c) baseline value in the model. Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value-, and 95% CI, unless otherwise specified, will also be reported. Missing data imputation method for the ANCOVA model is specified in Section 6.3.

Treatment comparisons for binary endpoints will be made using logistic regression with a Firth penalized likelihood (Firth 1993). The model will include the treatment groups and duration since symptom onset to randomization category (≤8 days versus >8 days), unless otherwise noted. The Firth correction can be implemented in PROC Logistic by including *'firth'* as an option in the model statement. The OR and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be reported. If the number of observed events is less

than 5 in any treatment arm an exact test (i.e., Fisher's exact) will be conducted instead of using a logistic regression.

The Kaplan-Meier (KM) product limit method will be used for time-to-event analyses. The hazard ratio and log-rank test, stratified by duration since symptom onset to randomization (≤8 days versus >8 days), will be reported. Time for all analyses will be described in units of days.

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

6.2. Adjustments for Covariates

Unless otherwise specified, efficacy analyses will adjust for the baseline value of the endpoint and by the randomization stratification factor, duration since symptom onset to randomization (≤8 days versus >8 days), when modeling estimates and calculating p-values.

6.3. Handling of Dropouts or Missing Data

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

6.3.1. Non-Responder Imputation

For analysis of categorical efficacy and pharmacodynamic variables, missing data will be imputed using a non-responder imputation (NRI) method. Participants will be considered non-responders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest.

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

6.3.2. Modified Non-Responder Imputation

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

- If a participant has previously achieved viral clearance (i.e., the participant previously had 2 consecutive negative tests), then viral clearance will be imputed as "Yes."
- If a participant has not previously achieved viral clearance (i.e., the participant does not have 2 consecutive previous negative tests), then viral clearance will be imputed as "No."

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

6.3.3. Mixed-Effects Model Repeated Measures

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

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

6.3.4. Highest Disease States Imputation

For the analyses related to National Institute of Allergy and Infectious Diseases (NIAID)/World Health Organization (WHO) ordinal scales, the following imputation will be considered if applicable.

For participants whose data is missing during the hospitalization period (not yet recovered), a score of 7, which is the highest value for a hospitalization status, will be used for imputation.

For participants whose data is missing after recovery or discharged, a score of 3, the highest value for a recovery or nonhospitalized status, will be used for imputation.

6.3.5. Last Observation Carried Forward

Analyses of PHVL on Day 7 will utilize a last observation analysis (LOCF). The LOCF method is performed by carrying forward the last nonmissing assessment. If only the baseline viral load is nonmissing, then the baseline is carried forward.

6.3.6. Modified Last Observation Carried Forward

Analyses of symptom data, with the exception of change in symptom score, will utilize a modified last observation analysis (mLOCF). The mLOCF method is performed by carrying forward the last nonmissing postbaseline assessment to the subsequent missing assessments for analysis. For patients who die, all missing collection time points subsequent to the date of death will be imputed to Severe.

After mLOCF imputation, data from participants with nonmissing baseline and at least 1 postbaseline observation will be included in the analyses. The mLOCF imputation helps ensure that the maximum number of randomized participants who were assessed postbaseline will be included in the analyses and unfavorable terminal events are represented.

6.4. Multicenter Studies

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

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

6.5. Multiple Comparisons/Multiplicity

Treatment Arms 1-4, and 6

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

Treatment Arms 7-9

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

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

Treatment Arms 13-14

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

- Primary (Test 1) – proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 for treatment arm 14 versus treatment arm 13 (primary objective)
- Key Secondary (Test 2) – change from baseline to Day 7 in viral load for treatment arm 14 versus treatment arm 13

- Key Secondary (Test 3) – proportion of participants who experience these events by Day 29:
  - COVID-19-related hospitalization (defined as ≥24 hours of acute care), or
  - Death from any cause

  Note: This key secondary endpoint will compare treatment arm 14 versus treatment arms 8 and 13 combined. The success criterion will be a posterior probability ≥97.5 for OR <1, relative to placebo.

Treatment Arms 18-19

- Primary (Test 1) – noninferiority in the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 for treatment arm 19 versus treatment arm 18. The success criterion will be the upper bound of the 95% CI ≤1.96.
- Key Secondary (Test 2) – comparison in the change from baseline to Day 7 in viral load for treatment arms 19 combined versus treatment arm 18.
- Key Secondary (Test 3) – comparison in the proportion of participants who experience these events by Day 29:
  - COVID-19-related hospitalization (defined as ≥24 hours of acute care), or
  - Death from any cause

  Note: This analysis will compare treatment arm 19 versus treatment arms 1, 8, and 13 combined (all high-risk placebo).

6.6. Participant Disposition

The treatment period disposition and study disposition will be summarized for the safety population. Disposition summaries will be by treatment group. Summaries will also include reason for discontinuation from the study tabulated by treatment group.

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

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

Table PYAB.6.4. Tables and Figures Related to Disposition

Analysis	Details
Patient Disposition	Number and percentage of participants by reason for • study discontinuation and • study treatment period discontinuation A column that combines all treatment groups (i.e., a total column) will be included (applicable to controlled analysis sets) No inferential statistics
Listing of study and study treatment disposition	--
Listing of participants discontinuing due to a decision-related reason (loss to follow-up, patient decision, or investigator decision)	Variables included the reason for study discontinuation, the text collected in the specify field associated with the reasons for discontinuation, and the dates of discontinuation The text in the specified field should provide information to support that the reason is unrelated to efficacy or safety
Time to early discontinuation of study treatment due to adverse events (AEs)	Presented as a figure (if necessary)

6.7. Participant Characteristics

Patient demographic variables and baseline characteristics will be summarized by treatment and overall for the safety population. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline covariates across treatment groups will be performed. By-patient listings of basic demographic characteristics (i.e., age, sex, race, racial subgroup, ethnicity, and body weight) for the efficacy population will be provided.

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

Analysis	Details
Baseline Demographic Characteristics	**Variables to be included:** • Age • Age groups (<65, ≥65 years old), (<35, ≥35 to <45, ≥45 to <55, ≥55 to <65, ≥65 years old), and (<65, ≥65 to <75, ≥75 to <85, ≥85 years old) • Sex • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported) • Height • Weight • Body mass index (BMI), and • Days since COVID-19 symptom onset. • Days since COVID-19 symptom onset (≤8 days, >8 days) • SpO_2 • SpO_2 category (<96%, ≥96%) • COVID-19 disease severity category • High-risk status for severe COVID-19 illness (Age ≥ 55 or BMI ≥ 30 or a medical history event of interest) **Statistics to be included:** Continuous: Mean, standard deviation, min, max, median, and first quartile and third quartile 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 For treatment arms 7-9, the age groups are defined as: • Age groups (<65, ≥65 years old), (≥12 to <18, ≥18 to <35, ≥35 to <45, ≥45 to <55, ≥55 to <65, ≥65 years old), (<65, ≥65 to <75, ≥75 to <85, ≥85 years old), and (≥12 to <18, ≥18 years old) High-Risk status will not be summarized for treatment arms 7-9. For treatment arms 13-14, 18-19, the following additional group is defined as: • If female, pregnant (yes/no) For treatment arms 13-14, 18-19, the following additional group is defined as: • SARS-CoV-2 vaccine status • Number of SARS-CoV-2 vaccinations (none, partial, full)
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 total arm Preexisting conditions are defined as those conditions with a start date prior to the first dose of the study drug and stop dates that are at or after the informed consent date or have no stop date (i.e., are ongoing).
Prior Therapy of Interest	Number and percentage of participants with prior medication of interest will be displayed as "Prior medications"
Listing demographics	--

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

6.8. Treatment Compliance

As all study drug doses will be administered at the study site, treatment compliance will not be reported.

6.9. Prior Medication and Concomitant Therapy

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

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

For all summary tables of concomitant medications, Preferred Terms of concomitant medication will be sorted by descending frequency in the LY total arm.

Table PYAB.6.6. Summary Tables Related to Concomitant Medications

Analysis	Details
Prior medications	Number and percentage of participants using Preferred Terms of prior medication • Ordered by decreasing frequency No inferential statistics
Concomitant medications	Number and percentage of participants using Preferred Terms of concomitant medication • Ordered by decreasing frequency No inferential statistics

6.10. Efficacy Analyses

The analysis of the viral load lab results will utilize the following conventions:

For qualitative endpoints in the trial (viral clearance yes/no, time to viral clearance) the lab determination of "positive"/ "negative" will be used. SARS-CoV-2 clearance (yes/no) is defined as 2 consecutive negative tests for the SARS-CoV-2 virus. The date of viral clearance is defined as the earliest date of the 2 consecutive negative tests.

For quantitative endpoints in the trial (change from baseline, area under the response viral load curve [AUC]), the viral load will be derived based on cycle threshold (Ct) values with the following considerations:

- Two Ct values will be provided on 2 different genes: N1 and N2. N1 will be used as the primary measure; N2 will only be used when the Ct value for N1 is not available.
- Ct values range between 0 and 45.

- Negative CoV-2 tests will be associated with a Ct value of 45.
- The (log base 10) viral load will be calculated from the Ct value (45-Ct)/$\log_2 10$, or (45-Ct)/3.321928.

For Treatment Arms 7-9, 13-14, and 18-19

In addition to the considerations above, treatment arms 7-9, 13-14, and 18-19 will also include a normalization step for any sample with a positive SARS-CoV-2 test result. The viral load Ct value described in the previous steps will be subtracted by (RP Ct – 26.17), where RP Ct is a measure for the amount of material in the sample and 26.17 is a historical average value of RP Ct for this assay, used here to center the RP Ct values.

6.10.1. Primary Outcome and Methodology

Treatment Arms 1-4, and 6

Primary endpoint is the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load. Statistical hypothesis testing for the primary endpoint will be conducted using an MMRM analysis method at the 2-sided 0.05 level.

SARS-CoV-2 viral load, including changes from baseline, will be summarized and plotted by treatment and listed. Baseline is defined as the Day 1 predose assessment.

Changes from baseline to Day 11 in SARS-CoV-2 viral load data in the log base 10 scale will be statistically analyzed using a linear mixed-effect model. The model will contain log base 10 transformed baseline as a covariate, treatment, day, treatment-by-day interaction) as fixed effects. The symptom onset stratification factor is not included in order to avoid the collinearity with the baseline viral load. The LS means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. In addition, the geometric mean ratio to baseline and corresponding standard error for each treatment, and ratio of geometric mean ratio to baseline versus placebo, and corresponding 95% CIs will be presented. All available data will be used in the analysis.

If Day 11 SARS-CoV-2 viral load is missing, the earliest measurement closest to the Day 11 visit, but within 4 days (Day 7 through Day 15), will be used for the Day 11 value. If no measurements are available, the Day 11 viral load will be treated as MAR in the analysis.

Treatment Arms 7-9

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

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

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

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

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

In addition, the number of participants that experience COVID-19-related hospitalization or death from any cause by Day 29 will be analyzed using logistic regression to compare LY3819253 and LY3819253 in combination with LY3832479 versus concurrently enrolled placebo for treatment arm 8 and versus all placebo data for treatment group 9. The model will include duration since symptom onset (≤8 days versus >8 days) and age at the time of screening (<18 years of age versus ≥18 years of age).

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

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

- 'Reason for Health Care Visit' of 'Primary Study Condition'

AND

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

  OR
- 'Emergency Room' with a duration of ≥24 hours.

Treatment Arms 13-14

For treatment arm 14, the hypothesis is whether there is a difference in the proportion of participants with persistently high SARS-CoV-2 viral load at Day 7 (+2 days) compared to concurrently enrolled placebo data from treatment arm 8.

The proportion of participants with SARS-CoV-2 viral load greater than 5.27 (PHVL) on Day 7 (+2 days), corresponding to Ct value of 27.5 based on nasopharyngeal swab sampling for RT-PCR testing for SARS-CoV-2 will be statistically analyzed using a logistic regression with a Firth penalized likelihood (Firth 1993). The model will contain a covariate for treatment arms. The Firth correction can be implemented in PROC Logistic by including 'firth' as an option in the model statement. The OR and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be reported. The primary success criterion will be based on a 1-sided significance level of 0.025. The proportion of participants with PHVL will also be summarized by treatment arm.

If Day 7 (±2 days) SARS-CoV-2 viral load is missing, it will be imputed using the LOCF method as described in Section 6.3.5.

Treatment Arms 18-19

For treatment arms 18-19, the hypothesis is NI in the proportion of participants with persistently high SARS-CoV-2 viral load at Day 7 (+2 days) between treatment arm 19 and treatment arm 18.

The proportion of participants with SARS-CoV-2 viral load greater than 5.27 (PHVL) on Day 7 (+2 days), corresponding to Ct value of 27.5 based on nasopharyngeal swab sampling for RT-PCR testing for SARS-CoV-2 will be statistically analyzed using a logistic regression with a Firth penalized likelihood (Firth 1993). The model will contain a covariate for treatment arms. The Firth correction can be implemented in PROC Logistic by including 'firth' as an option in the model statement. The OR and the corresponding CIs, as well as the treatment differences and the corresponding CIs, will be reported. The primary success criterion will be the upper bound of the 95% CI of the OR ≤1.96. The proportion of participants with PHVL will also be summarized by treatment arm.

If Day 7 (±2 days) SARS-CoV-2 viral load is missing, it will be imputed using the LOCF method as described in Section 6.3.5.

6.10.2. Additional Analyses of the Primary Outcome

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

A Bayesian model averaging approach may be explored to estimate the dose-response relationship with change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load being the response variable of interest. This Bayesian model averaging approach is the Bayesian analog of the Multiple Comparisons - Modeling (MCP-Mod) methodology (Bretz et al. 2005), and the Qualification of the MCP-Mod procedure (OCP 2015) is supportive in the use of MCP-Mod or Bayesian model averaging to assist in dose selection decisions.

Bayesian model averaging is a general mixture distribution, where each mixture component is a different parametric model. Prior weights are placed on each model and the posterior model weights are updated based on how well each model fits the data. Let $\mu(d)$ represent the mean of the dose response curve at dose d, $y = \{y_1, \ldots, y_n\}$ be the observed data, and $m \in \{1, \ldots, M\}$ be an index on the M parametric models. Then the posterior of the dose response curve, $\mu(d)$, of the Bayesian model averaging model is

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

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

where $p(\mu(d) \mid y, m)$ is the posterior mean dose response curve from model m, $p(m \mid y)$ is the posterior weight of model m, $p(y \mid m)$ is the marginal likelihood of the data under model m, and $p(m)$ is the prior weight assigned to model m. In cases where $p(y \mid m)$ is difficult to compute, Gould (2019) proposes using the observed data's fit to the posterior predictive

distribution as a surrogate in calculating the posterior weights; this is the approach used in this analysis.

Similar dose response methodology may be applied to additional efficacy endpoints as appropriate.

6.10.2.2. Bayesian Modeling

Treatment Arms 1-4, and 6

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

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

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

μ: a constant common to all observations

α: a fixed coefficient on the covariate log base 10 baseline viral load

α_i: a parameter corresponding to treatment i

β_k: a parameter corresponding to day k

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

ε_{ij}, ε_{ijk}: random error for between- and within-subject variability

prior μ, α, α_i, β_k, $(\alpha\beta)_{ik}$ ~*N(0, 100)*

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

σ_1, σ_2 ~*uniform(0, 100) or igamma(0.01,0.01)*

Treatment Arms 7-9

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

$$y_i \sim Binomial(n_i, p_i)$$

with

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

where α is the log odds of the placebo rate and β is the log OR of the treatment relative to the control.

A mixture prior will be used for the log OR β for hospitalization/death:

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

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

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

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

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

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

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

6.10.3. Secondary Efficacy Analyses

6.10.3.1. SARS-CoV-2 Viral Load Among Participants Enrolled with ≤8 Days of Symptoms Prior to Randomization

Similar methodology, as described in Section 6.10.1, will be utilized on the subset of participants enrolled with ≤8 days of symptoms prior to randomization.

6.10.3.2. SARS-CoV-2 Viral Load AUC

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) will be also calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification. No imputations of missing data will be conducted. No AUC(0-D11) values will be calculated when Day 1 predose and/or Day 11 values are missing, or if more than 1 value is missing in the profile.

The AUC will be summarized and plotted by treatment and listed.

Additionally, AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, log base 10 transformed baseline viral load as a covariate. The least square (LS) means and treatment differences (LY3819253 minus placebo at each dose level) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

If deemed appropriate, the data may be log-transformed prior to analysis, and the LS means, and treatment differences will be back-transformed.

A similar Bayesian model listed in Section 6.10.2.2, by removing the day, interaction, and within subject error term, will be applied for log base 10 transformed AUC measure analysis.

6.10.3.3. SARS-CoV-2 Clearance at Days 7, 11, 15, and 22

See Section 6.10 for more details on the definition of viral clearance.

The proportion of participants that achieve SARS-CoV-2 clearance at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that achieve SARS-CoV-2 clearance at Days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

6.10.3.4. Time to SARS-CoV-2 Clearance

See Section 6.10 for more details on the definition of viral clearance and date of viral clearance.

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

(Date when SARS-CoV-2 clearance status is first changed to "Yes" – Infusion Date + 1)

If a patient has not experienced SARS-CoV-2 clearance by completion or early discontinuation of study/study treatment period, the patient will be censored at the date of their last visit during the treatment period.

Time to SARS-CoV-2 clearance will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days versus >8 days).

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

6.10.3.5. Symptom Resolution

Symptom resolution is defined as all symptoms (those scored 0-3) on the symptom questionnaire scored as absent.

The proportion of participants that achieve symptom resolution at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables, and listed.

In addition, the number of participants that achieve symptom resolution at Days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

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

6.10.3.6. Time to Symptom Resolution

Time to symptom resolution is defined (in days) as:

(First study day when symptom resolution status is changed to "Yes" – Infusion Date + 1)

If a patient has not experienced symptom resolution by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period. If a patient is hospitalized, the patient will be censored at the date of hospitalization.

Time to symptom resolution will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days versus >8 days).

Time to symptom resolution will be presented graphically.

6.10.3.7. Symptom Improvement

Symptom improvement is defined as a patient experiencing both:

- Symptoms on the symptom questionnaire scored as moderate or severe at baseline are subsequently scored as mild or absent, AND
- Symptoms on the symptom questionnaire scored as mild or absent at baseline are subsequently scored as absent.

The proportion of participants that achieve symptom improvement at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables, and listed.

In addition, the number of participants that achieve symptom improvement at days 7, 11, 15, and 22 will be analyzed using logistic regression to compare LY3819253 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

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

6.10.3.8. Time to Symptom Improvement

Time to symptom improvement is defined (in days) as:

(Date when symptom improvement status is changed to "Yes" – Infusion Date + 1)

If a patient has not experienced symptom improvement by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period. If a patient is hospitalized, the patient will be censored at the date of hospitalization.

Time to symptom improvement will be evaluated during the study treatment period only and will be summarized by treatment and listed. In addition, a graphical presentation of the symptom improvement will be provided using a KM plot.

6.10.3.9. COVID-19-Related Deterioration (COVID-19-Related Hospitalization, Emergency Room Visit, or Death from Any Cause by Day 29, 60, and 85)

Proportion (percentage) of participants who experience deterioration by Day 29 will be analyzed and is defined as:

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

The proportion of participants that experience deterioration by Day 29 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that experience deterioration by Day 29 will be analyzed using logistic regression to compare LY3819253 and LY3819253 in combination with LY3832479 versus placebo at each dose level.

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

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

6.10.3.10. Change in Symptom Questionnaire Score

Change in symptom questionnaire score (total of ratings from those symptoms scored 0-3) from baseline to Days 7, 11, 15, and 22 will be analyzed using an MMRM. The model will contain baseline as a covariate, symptom onset strata, treatment, day, and treatment-by-day interaction as fixed effects. The LS means and treatment differences (each dose or dose combination group minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.10.3.11. Secondary Efficacy Analyses for Treatment Arms 7-9

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

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

The proportion of participants with SARS-CoV-2 viral load greater than 5.27 (PHVL) on Day 7 (+2 days) will be analyzed in a similar manner as described in Section 6.10.1 (treatment arms 14, 16-18). Superiority will be tested between treatment arms 7 and 8 and treatment arms 9 and 8.

For treatment arms 7 and 8, if Day 7 (±2 days) SARS-CoV-2 viral load is missing, it will be imputed using the first available measurement after Day 7. If no measurements are available, the viral load will be treated as MAR in the analysis. For treatment arms 9 and 8, if Day 7 (±2 days) SARS-CoV-2 viral load is missing, it will be imputed using the LOCF method as described in Section 6.3.5.

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

Bayesian Analyses

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

$$y_i \sim Binomial(n_i, p_i)$$

with

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

where α is the log odds of the placebo rate and β is the log OR of the treatment relative to the control.

Weakly informative distributions are used for PHVL:

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

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

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

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

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

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

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

Similar to the methodology described in Section 6.10.3.2, the AUC from Day 1 predose to Day 7 (AUC[0-D7]) will be calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load-time values above the lower limit of quantification. No imputations of missing data will be conducted. No AUC(0-D7) values will be calculated when Day 1 predose and/or Day 7 values are missing, or if more than 1 value is missing in the profile.

6.10.3.11.4. Time to SARS-CoV-2 Clearance

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

6.10.3.11.5. Time to Sustained Symptom Resolution

Sustained symptom resolution is defined as 2 consecutive assessments with a score of 0 for shortness of breath, feeling feverish, body aches and pains, sore throat, chills, and headache; and

a score of 0 or 1 for cough and fatigue on the symptom questionnaire. Time to sustained symptom resolution is defined (in days) as:

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

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

6.10.3.11.6. Time to Sustained Complete Symptom Resolution

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

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

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

6.10.3.11.7. Time to Complete Symptom Resolution

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

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

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

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

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

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

6.10.3.11.9. Time to Symptom Resolution

Time to symptom resolution is defined (in days) as:

(First study day when symptom resolution status is changed to "Yes" – Infusion Date + 1)

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

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

Symptom improvement is defined as a patient experiencing both:

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

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

6.10.3.11.11. Time to Symptom Improvement

Time to symptom improvement is defined as:

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

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

6.10.3.12. Secondary Efficacy Analyses for Treatment Arms 13-14

6.10.3.12.1. SARS-CoV-2 Viral Load on Days 3, 5, and 7

Change from baseline to Day 3 (+1 day), Day 5 (±2 days), and Day 7 (±2 days) in SARS-CoV-2 viral load will be analyzed in a similar manner as described in Section 6.10.1 (treatment arms 1-4, and 6). Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.2. SARS-CoV-2 Viral Load AUC from Day 1 to Day 7

The AUC from Day 1 predose to Day 7 (AUC[0-D7]) will be analyzed in a similar manner as described in Section 6.10.3.11.3. Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.3. Time to SARS-CoV-2 Clearance

Time to SARS-CoV-2 clearance will be analyzed using similar methodology as described in Section 6.10.3.4. Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.4. COVID-19-Related Deterioration (COVID-19-Related Hospitalization or Death from Any Cause) by Days 22, 29, 60, and 85

The proportion of patients with COVID-19-related hospitalization or death from any cause will be analyzed using similar methodology as described in Section 6.10.1 for treatment arms 7-9. Superiority will be tested between:

- treatment arm 14 and all high-risk participants from arms 8 and 13 combined.

The success criterion will be a posterior probability ≥97.5 for OR <1, relative to placebo.

A Bayesian network meta-analysis will be used to perform the comparisons. The binary model with logistic link with random relative treatment effects is used as described in Dias et al. (2013). The model is

$$\mathrm{y_{ij}} \sim \mathrm{Binomial}(\zeta_{ij}, \mathrm{n_{ij}})$$

$$logit(\zeta_{ij}) = \phi_i + \delta_{ij}$$

$$\phi_i \sim Normal(m, \sigma_m^2)$$

$$\mathrm{m} \sim Normal(0, \tau_m^2)$$

$$\sigma_m \sim Uniform(0, b_{\sigma_m})$$

$$\delta_{\mathrm{ij}} \sim Normal\left(s_i + d_{t_{ij}} - d_{t_{i1}}, \sigma^2/2\right), \mathrm{i} = 1, \ldots, \mathrm{N};\ \mathrm{j} > 1$$

$$\delta_{i1} = 0$$

$$s_i \sim N(0, \sigma^2/2)$$

$$d_1 = 0$$

$$\mathrm{d_k} \sim (0, \sigma_{\mathrm{d}}^2), \mathrm{k} = 2, \ldots, \mathrm{N_a}$$

$$\sigma \sim Uniform(0, b_\sigma)$$

where ϕ_i is the log odds of the placebo arm in group i, δ_{ij} is the log-OR of treatment j in group i, n_{ij} is the number of patients in group i, arm j, t_{ij} is the treatment index, s_i is a group-level random treatment effect, d_k is the hierarchical average log odds over all groups for the N_a unique arms (excluding baseline/placebo) in the analysis, and N is the number of groups.

The following hyperparameters were used, creating diffuse priors on m and the d_k's:

$$\tau_m^2 = 100^2$$

$$\sigma_d^2 = 40^2$$

Weakly informative priors on the standard deviation of the log odds of the placebo arms, σ_m, and the standard deviation of the random treatment effects, σ, were specified by setting

$$b_{\sigma_m} = 0.90$$

$$b_\sigma = 0.25$$

The weakly informative priors were chosen by fitting the Bayesian network meta-analysis model to the arms for which data was already available. For the arms which were still enrolling, estimated sample sizes were used based on current enrollment and it was assumed that their response rates were the same as the most recently observed arms. The upper bounds on the uniform priors were chosen as the smallest values such that there was a negligible effect on the posterior means and variances of the d_k's and ϕ_i's. The success criterion in terms of this model is $P(\delta_{ij} < 0) \geq 0.975$.

If the Markov chain Monte Carlo algorithm fails to converge adequately, a fixed treatment effect will be used in the meta-analysis, i.e., $\delta_{ij} = d_{t_{ij}} - d_{t_{i1}}$ for $j > 1$ and the s_i's will be omitted from the model.

6.10.3.12.5. COVID-19-Related Deterioration (COVID-19-Related Hospitalization, Emergency Room Visit, or Death from any Cause) by Days 22, 29, 60, and 85

The proportion of patients with COVID-19-related hospitalization, COVID-19-related emergency room visit, or death from any cause will be analyzed using similar methodology as described in Section 6.10.3.12.4.

Superiority will be tested between:

- treatment arm 14 and all high-risk participants from arms 8 and 13 combined.

The success criterion will be a posterior probability ≥97.5 for OR <1, relative to placebo.

6.10.3.12.6. Time to Sustained Symptom Resolution

Similar methodology, as described in Section 6.10.3.11.5, will be utilized to analyze time to sustained symptom resolution. Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.7. Time to Symptom Resolution

Similar methodology, as described in Section 6.10.3.11.9, will be utilized to analyze time to symptom resolution. Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.8. Time to Complete Symptom Resolution

Similar methodology, as described in Section 6.10.3.11.7, will be utilized to analyze time to complete symptom resolution. Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.9. Time to Sustained Complete Symptom Resolution

Similar methodology, as described in Section 6.10.3.11.6, will be utilized to analyze time to sustained complete symptom resolution. Superiority will be tested between treatment arms 13 and 14.

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

Similar methodology, as described in Section 6.10.3.11.8, will be utilized to analyze the proportion of participants with symptom resolution. Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.11. Time to Symptom Improvement

Similar methodology, as described in Section 6.10.3.11.11, will be utilized to analyze time to symptom improvement. Superiority will be tested between treatment arms 13 and 14.

6.10.3.12.12. Proportion of Participants with Symptom Improvement on Days 2-11

Similar methodology, as described in Section 6.10.3.11.10, will be utilized to analyze the proportion of participants with symptom improvement. Superiority will be tested between treatment arms 13 and 14.

6.10.4. Symptoms and Overall Clinical Status Participant Questionnaire

Participants will rate their overall clinical status and severity of symptoms associated with COVID-19 by a daily questionnaire. This questionnaire is for outpatient participants only.

Participants will complete 3 questions about their overall clinical status daily, including

- severity of symptoms
- general physical health, and
- change in overall health

The questionnaire contains these symptoms:

- cough
- shortness of breath
- feeling feverish
- fatigue
- body aches and pain
- sore throat
- chills
- headache
- loss of appetite (yes/no), and
- changes in taste and smell (yes/no)

Each symptom will be scored daily by the participant as experienced during the past 24 hours.

Table PYAB.6.7. Symptom and Clinical Status Questionnaire Scores

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

The Total Symptom Questionnaire score is the sum of the symptoms (excluding the loss of appetite and changes in taste and smell symptoms).

Participants will rate the loss of appetite and changes in taste and smell with yes/no responses. Responses at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

Participants will complete questions about their overall clinical status. Responses at Days 7, 11, 15, and 22 will be summarized by treatment in frequency tables and listed.

Further details regarding the analysis of endpoints based on the symptom questionnaire are described in Section 6.10.2.2.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

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

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

6.12. Safety Analyses

Percentages will be calculated using the safety population as the denominator. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex.

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

- percentage-based analyses:
  - p-values based on Fisher's exact test
- continuous measurements:
  - p-value based on ANCOVA:
    - model containing terms for treatment,
    - factor of symptom onset (≤8 and >8 days) and the continuous covariate of baseline measurement, and
    - Type III sums of squares will be used.

6.12.1. Baseline and Postbaseline Definitions for Safety Groups

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

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

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

Abbreviation: TEAE = treatment-emergent adverse event.

6.12.2. Extent of Exposure

Exposure to therapy will be represented as the total number of complete and incomplete infusions, and will be summarized using descriptive statistics.

6.12.3. Adverse Events

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

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

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

Treatment-Emergent Adverse Events

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

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

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

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

Additional Types of Adverse Events to be Summarized

Event Type	Summary Method
Infusion Reactions	Treatment-emergent infusion reactions will be summarized for all treatment arms excluding treatment arm 19 by PT within high level term (HLT).
Injection-Site Reactions	For treatment arm 19, treatment-emergent injection-site reactions will be summarized by PT within HLT.

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

SOC Mapping

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

Events Not Summarized

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

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

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

- deaths
- serious adverse events, and
- discontinuations of study treatment due to AEs.

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

Safety topics of interest are not considered notable events, unless 1 of the above criteria is met. Displays with individual patient-level data will be created for safety topics of interest using various formats such as a customized listing and/or a customized graphical patient profile as specified in the section associated with the safety topic of interest. Medical case summaries/vignettes will be provided if deemed relevant for the discussion of the safety topic of interest.

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

The following events (observed at any time point during the study treatment period) will be analyzed with the method described in Section 6.16.2.6 and Section 6.16.2.8:

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

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

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

6.12.6. Clinical Laboratory Evaluation

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

6.12.7. Vital Signs and Other Physical Findings

The planned summaries are provided in Table PYAB.6.10. The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, weight, peripheral oxygen saturation (SpO_2), respiratory rate, fraction of inspired oxygen (FiO_2), and temperature if data warrant.

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

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

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

Analysis Type	Analysis Details
Box plots for observed values by visit	• 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 versus Max:** Maximum baseline versus maximum postbaseline. • **Min versus Min:** Minimum baseline versus minimum postbaseline.

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

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

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

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Temperature	<96°F (<35.6°C) and decrease ≥2°F (≥1.1°C) from baseline	≥101°F (≥38.3°C) and increase ≥2°F (≥1.1°C) from baseline

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

6.12.8. Electrocardiograms

Results of electrocardiograms (ECGs) performed during the study will not be reported.

6.12.9. Immunogenicity

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

Treatment-emergent ADAs are defined as participants

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

The frequency and percentage of participants with preexisting ADAs and who are TE-ADA positive (TE-ADA+) to LY3819253 and/or LY3832479 may be tabulated.

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

The relationship between the presence of antibodies and PK parameters, efficacy response, or safety to LY3819253 and/or LY3832479 may also be assessed.

6.13. Subgroup Analyses

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

Subgroup analyses will be conducted for the primary endpoint. Subgroups may include

- time from symptom onset to study randomization
- baseline severity of COVID-19

- age group (<65, ≥65 years old), (<35, ≥35 to <45, ≥45 to <55, ≥55 to <65, ≥65 years old), and (<65, ≥65 to <75, ≥75 to <85, ≥85 years old)
- gender (male, female)
- race
- ethnicity
- baseline weight (<60 kg, ≥60 to <100 kg, ≥100 kg)
- baseline body mass index (BMI) (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2 to <40 kg/m^2, and ≥40 kg/m^2)
- concomitant medication of interest use (yes/no)
- high-risk status for severe COVID-19 illness

Treatment group differences will be evaluated within each category of the subgroup regardless of whether the interaction is statistically significant. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided, that is, no inferential testing.

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

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

Baseline severity of COVID-19 will be defined using the following definition.

- Severity will be defined to be **Moderate** if the participant demonstrates the following at baseline:
  - Symptoms:
    - Shortness of breath (with symptom questionnaire severity score ≥1)

      OR

    - Symptoms of moderate illness with COVID-19, (any symptom questionnaire score >1, excluding loss of appetite)

    AND

  - Clinical signs suggestive of moderate illness with COVID-19, such as:
    - Respiration rate ≥20 breaths per minute

      OR

- Pulse ≥ 90 beats per minute.

- Else, severity will be defined to be **Mild**.

Concomitant therapies of interest include remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine, anticoagulants, dexamethasone, or other investigational interventions. Details of the medications included in this subgroup are provided below in Table PYAB.6.12.

Table PYAB.6.12. Concomitant Medications of Interest Subgroup

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

Abbreviation: ATC = anatomical therapeutic chemical.

Treatment Arms 7-9, 13-14

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

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

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

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

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

Subgroup analyses for SARS-CoV-2 vaccine status will be performed for treatment arms 13-14.

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

6.14. Protocol Violations

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

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

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

A by-patient listing of IPDs will be provided.

6.15. Interim Analyses and Data Monitoring

6.15.1. Interim Analyses

Monotherapy LY3819253

The ongoing study may be modified based on planned interim analyses. Based on the observed data at the time of the interim analyses, the study may

- suspend enrollment to any treatment arm (or arms) demonstrating lack of efficacy, and/or
- initiate/expand enrollment to an additional/existing treatment arm (or arms).

The modifications proposed are done so to ensure participants are being exposed to treatment with an acceptable risk-benefit profile during the ongoing trial. Additionally, the potential modifications will provide information to more fully characterize the dose response profile.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will occur throughout the study and will be conducted by Assessment Committee (AC) members. The AC will review rolling safety data after approximately 20, 40, and 60 participants are enrolled and have had an opportunity to reach Day 4 to monitor participant safety. These initial individual reviews of unblinded safety data will occur no less often than every 30 days, in case of slower than anticipated enrollment. This is intended as an individual AC member review and does not require a formal meeting. However, any AC member can ask for a full AC meeting based on the rolling review at any time.

The AC will initially review summary unblinded data after approximately 25% (100) participants have had an opportunity to reach Day 11. It is anticipated that subsequent interim analyses will occur after approximately 50%, 75%, and all participants have had an opportunity to reach Day 11. Safety will be evaluated at each of these interim analyses and benefit/risk of LY3819253 will be assessed if needed. An additional interim analysis is planned when approximately 40% participants in the 7000 mg arm have had an opportunity to reach Day 11. However, this analysis may be combined with the approximately 50% interim analysis if possible.

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

Additionally, the pre-planned interim analysis at 40% of participants in the 7000 mg arm completing 11 days will inform potential modification to the PYAB study. These modifications include:

- Dropping the 700 mg dose arm if either of these 2 conditions hold:

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

or

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

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

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

Note: Δ represents viral load change from baseline in log base 10 scale at Day 11. Details of the Bayesian methodology associated with the SARS-CoV-2 viral load can be found in Section 6.10.2.2.

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

The AC will review rolling safety data after approximately 25 participants are enrolled and have had an opportunity to reach Day 2 to monitor participant safety. The individual AC member reviews of unblinded safety data doesn't require a formal meeting.

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

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

Treatment Arm 6

The interim analyses to evaluate the benefit/risk of the combination therapy may occur after approximately 75, 150, and all participants have had an opportunity to reach Day 11.

Periodic adjustments to the allocation ratio may be made to achieve an equal allocation across treatment arms at the conclusion of enrollment. If up to 50 additional placebo participants are enrolled, then the allocation ratio may change accordingly.

Treatment Arms 7-9, 13-14, 18-19

Unblinded assessments of efficacy will be done separately for treatment arms 7-8; 8-9; 13-14; and 18-19.

Treatment Arms 7 and 8

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

Treatment Arms 8 and 9

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

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

Treatment Arms 13 and 14

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

Treatment Arms 18 and 19

Assessments will begin when all participants for treatment arm 18 and participants from treatment arm 19 complete the Day 29 visit.

Safety Reviews

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

PK/PD

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

Unblinding

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

6.15.2. Data Monitoring Committee/Assessment Committee

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

Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Unblinding details are specified in a separate unblinding plan document.

Treatment Arms 1-4, and 6

The sponsor will form an AC to analyze the interim study data. The primary goal of the AC is to review the interim results regarding the continuing safety of study participants and the continuing validity and scientific merit of the study.

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

Treatment Arms 7-9

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

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

Treatment Arms 13-14, 18-19

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

6.16. Planned Exploratory Analyses

6.16.1. Protocol-Defined Exploratory Endpoints

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

6.16.1.1. Viral Resistance

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

6.16.1.2. SpO_2 AUC Assessed through Day 29

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the daily SpO_2 values. If multiple values are collected on a given day, the average will be used. No imputations of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) will also be calculated according to the linear trapezoidal rule using the mean daily SpO_2 values. No imputations of missing data will be conducted. No AUC(0-D11) values will be calculated when Day 1 predose and/or Day 11 values are missing, or if there are more than 1 value missing in the profile.

The AUC will be summarized and plotted by treatment, and listed.

Additionally, SpO_2 AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, SpO2 baseline measurement as a covariate, and oxygen source. The LS means and treatment differences (each intervention arm minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.16.1.3. Symptom Questionnaire AUC through Day 29

The AUC from Day 1 predose to Day 29 (AUC[0-D29]) will be calculated according to the linear trapezoidal rule using the mean daily Symptom Questionnaire total score. No imputations

of missing data will be conducted. No AUC(0-D29) values will be calculated when Day 1 predose and/or Day 29 values are missing, or if there are more than 3 values missing in the profile.

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) will also be calculated according to the linear trapezoidal rule using the mean daily Symptom Questionnaire total score. No imputations of missing data will be conducted. No AUC(0-D11) values will be calculated when Day 1 predose and/or Day 11 values are missing, or if there are more than 1 value missing in the profile.

The Symptom Questionnaire AUC will be summarized and plotted by treatment, and listed.

Additionally, Symptom Questionnaire AUC data will be statistically analyzed using a linear model. The model will contain treatment as a fixed effect, baseline symptom total score as a covariate. The LS means and treatment differences (each non-placebo group minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.16.1.4. Worst NIAID Score

The lowest daily value from Day 1 through Day 29 for a patient on the NIAID ordinal scale will be analyzed using the van Elteren test adjusting for the randomization stratification factors. Mean values will be calculated and differences in treatment effect estimates at Days 7, 11, 15, and 22 will be analyzed. Mean value by treatment group will be plotted over time.

6.16.1.5. COVID-19-Related Deterioration (COVID-19-Related Hospitalization or Death from Any Cause) by Days 22, 60, and 85

The proportion of patients with COVID-19-related hospitalization or death from any cause will be analyzed using similar methodology as described in Section 6.10.1 for treatment arms 7-9, treatment arms 13-14, and treatment arm 19 compared to all high-risk placebo patients in treatment arms 8 and 13.

6.16.2. Additional Exploratory Analyses not Defined in the Protocol

In addition to the protocol defined endpoints, additional sensitivity analyses may be performed if deemed appropriate. Analyses of hospitalization events will be performed utilizing the safety population.

Additional analyses include:

6.16.2.1. Clinical Worsening Based on the NIAID Scale

Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Days 7, 11, 15, and 22.

6.16.2.2. National Early Warning Score

The highest daily value from Day 1 through Day 29 for a patient on the National Early Warning Score (NEWS2) ordinal scale will be analyzed using the van Elteren test adjusting for the randomization stratification factors. Mean values will be calculated and differences in treatment

effect estimates at Days 7, 11, 15, and 22 will be analyzed. Mean value by treatment group will be plotted over time.

6.16.2.3. NEWS2 Consciousness Level

Consciousness level assessed by NEWS2 will be summarized using a logistic regression analysis as described in Section 6.1.4.

6.16.2.4. NIAID/NEWS2 Overall Improvement

Treatment comparisons for overall improvement on the ordinal scales (NIAID, NEWS2) between LY3819253 and placebo will be made using proportional odds model with baseline stratification factor and treatment group in the model. Overall improvement will be evaluated at Days 7, 11, 15, and 22.

6.16.2.5. Time to Hospitalization

Time to Hospitalization is defined (in days) as:

(First study day when hospitalized status is changed to "Yes" – Infusion Date +1)

If a patient has been admitted to the hospital or ICU by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to hospitalization will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days versus >8 days).

Time to hospitalization may be presented graphically.

6.16.2.6. Duration of Hospitalization

Treatment comparisons of the mean DOH (in days) will be compared between LY3819253 and placebo will be made using nonparametric rank-sum test (such as Mann-Whitney or van Elteren test).

6.16.2.7. Time to Admission to ICU

Time to ICU is defined (in days) as:

(First study day when ICU status is changed to "Yes" – Infusion Date +1)

If a patient has been admitted to the hospital or ICU by completion or early discontinuation of study/study treatment, the patient will be censored at the date of their last visit during the treatment period.

Time to ICU will be evaluated during the study treatment period only and will be summarized by treatment, and listed. Cox proportional hazard model will be used, stratified by duration since symptom onset to randomization category (≤8 days versus >8 days).

Time to ICU may be presented graphically.

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

The proportion of participants hospitalized, admitted to the ICU, requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation") at any time will be evaluated separately using a logistic regression analysis with treatment and baseline stratification in the model.

No imputation will be used as these endpoints are based on running records, that is, an event is only reported if they are observed. Outcomes may be summarized by COVID-19-related events and by any cause events if appropriate.

6.16.2.9. Days Since Symptom Onset Cutpoint Analysis

An exploratory cutpoint analysis may be performed to determine the number of days since symptom onset maximizes the change from baseline to Day 11 (±4 days) in SARS-CoV-2 viral load between treatment with LY3819253, LY3819253/LY3832479, and placebo.

6.16.2.10. SpO_2 Measurements of Interest

The proportion of participants experiencing an SpO_2 measurement of interest (<96%, ≥ 96%), (<92%, ≥92%) through Day 11 and through Day 29 will be evaluated separately using a logistic regression analysis with treatment and baseline stratification as fixed effects and baseline SpO_2 as a covariate in the model. Missing values will be considered to be missing completely at random (MCAR).

6.16.2.11. Viral Load Plots

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

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

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

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

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

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

6.17. Annual Report Analyses

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

6.18. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

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

6.19. Analyses for the Pediatric Open-Label Addendum

6.19.1. Sample Size

The planned sample size is approximately 85 participants with a minimum of 5 participants in each of these age groups:

- 0 to <2
- 2 to <6
- 6 to <12 years.

Participant PK profiles were simulated using the current PK model with established allometric relationships (Betts et al. 2018) for a typical monoclonal antibody to enable a Monte Carlo assessment to achieve adequate power of the trial to estimate population PK model in pediatrics across the weight range.

6.19.2. General Considerations

Unless otherwise specified, all endpoints will be summarized descriptively. Descriptive summaries will include:

- number of participants
- mean, standard deviation, median, minimum, and maximum for continuous measures; and
- frequency counts and percentages for categorical measures.

Analyses will be performed overall and separately by age group. The age groups are defined as

- 0 to <2
- 2 to <6
- 6 to <12, and
- 12 to ≤17 years.

The definition of study baseline and study time intervals will be the same as defined for the main study (see Sections 6.1.2 and 6.1.3). Additionally, the handling of dropouts and missing data will be similar to that described for the main study (see Section 6.3) with the exception of the mixed-effects model for repeated measures, as the data from the addendum will not include inferential analyses.

For endpoints that are common between the main study treatment arms 7-9, 13-14, and 18-21 and the addendum treatment arm 22, analyses will also be performed by treatment arm.

Participants in the open-label addendum will be pooled across all weight ranges and summarized as treatment arm 22 (open-label weight-based dose of LY3819253 and LY3832479). The pediatric populations for analysis include the adolescent participants from the main study and the addendum participants who are ≤17 years old at the time of screening. The table below defines the pediatric populations for analysis.

Population	Description
Pediatric Entered	**Definition:** All pediatric participants who signed informed consent in either the main study or the addendum. **Purpose:** Used for disposition analysis. **Treatment Groups:** None **Inferential Comparisons:** None
Pediatric Efficacy	**Definition:** All pediatric participants who received study intervention in either the main study or the addendum and provided at least 1 postbaseline measure for the relevant endpoint. Participants will be analyzed according to the intervention to which they were randomized or assigned. **Purpose:** Used for efficacy and PD variables analyses. **Treatment Groups (Short Label):** *Treatment arms 8 and 13:* placebo (Pbo) *Treatment arm 7:*

Population	Description
	2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) *Treatment arms 9 and 18:* 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2) *Treatment arm 14:* 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2) *Treatment arm 19:* CCI [redacted] *Treatment arms 20-21:* 5-minute administration rate 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2, 5-min), and 3-minute administration rate 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2, 3-min) *Treatment arm 22:* open-label weight-based dose of LY3819253 and LY3832479 (OL WBD LY/LY2) **Inferential Comparisons:** None
Pediatric Safety	**Definition:** All pediatric participants who received study intervention in either the main study or the addendum. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses, analyses of COVID-19-related deterioration and hospitalization events. **Treatment Groups (Short Label):** *Treatment arms 8 and 13:* placebo (Pbo) *Treatment arm 7:* 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) *Treatment arms 9 and 18:* 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2) *Treatment arm 14:* 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2) *Treatment arm 19:* CCI [redacted] *Treatment arms 20-21:* 5-minute administration rate 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2, 5-min), and 3-minute administration rate 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2, 3-min) *Treatment arm 22:* open-label weight-based dose of LY3819253 and LY3832479 (OL WBD LY/LY2)

Population	Description
	Inferential Comparisons: None
Pediatric Pharmacokinetic and PK/PD	**Definition:** All pediatric participants who received study intervention in either the main study or the addendum and have evaluable PK sample. **Purpose:** Used for PK analyses. **Treatment Groups (Short Label):** *Treatment arms 8 and 13:* placebo (Pbo) *Treatment arm 7:* 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2) *Treatment arms 9 and 18:* 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2) *Treatment arm 14:* 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2) *Treatment arm 19:* CCI [redacted] *Treatment arms 20-21:* 5-minute administration rate 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2, 5-min), and 3-minute administration rate 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY/LY2, 3-min) *Treatment arm 22:* open-label weight-based dose of LY3819253 and LY3832479 (OL WBD LY/LY2) **Inferential Comparisons:** None

Abbreviations: COVID-19 = coronavirus disease 2019; PD = pharmacodynamic; PK = pharmacokinetic.

6.19.3. Addendum Primary Analysis

The primary objective is to assess PK in the pediatric PK population. The primary parameter for analysis is the AUC from 0 to infinity. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported. A comparison of pediatric exposures to adult exposures will be performed to demonstrate similarity between adults and pediatrics and confirm the pediatric dose.

6.19.4. Addendum Secondary Analyses

The secondary efficacy objectives for the addendum is to characterize the effect of LY3819253 in combination with LY3832479 after intravenous (IV) infusion on the following endpoints:

- Safety assessments such as AEs and SAEs
- Proportion of participants who experience COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29
- Change from baseline in SARS-CoV-2 viral load to:

  - Day 3
  - Day 5
  - Day 7
- Proportion of participants with viral load greater than 5.27 on Day 7
- SARS-CoV-2 viral load AUC assessed through Day 7
- Time to SARS-CoV-2 clearance
- Proportion of participants who experience these events by Day 29:
  - COVID-19-related hospitalization (defined as ≥24 hours of acute care)
  - a COVID-19-related emergency room visit, or
  - death from any cause
- Presence or absence of a symptom
- Absence of all symptoms
- Time to absence of all symptoms
- Time to sustained absence of all symptoms
- Proportion of participants demonstrating absence of symptoms on Days 2 through 11

The secondary efficacy endpoints will be summarized using descriptive statistics only in a similar manner as the main study (see Section 6.10). Summaries will be performed overall by treatment group and also by age and treatment groups.

6.19.5. Addendum Pharmacokinetic and Pharmacodynamic Analyses

LY3819253 and LY3832479 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. In addition, the effects of participant factors, such as weight and age on PK parameters may be evaluated. If antidrug antibody is detected from immunogenicity testing, its impact on LY3819253 and LY3832479 PK may also be evaluated.

Pharmacodynamic endpoints will be summarized using descriptive methodology. The SARS-CoV-2 viral dynamics will include evaluation of

- change from baseline in SARS-CoV-2 viral load (Days 3, 5, and 7)
- AUC, and
- time to SARS-CoV-2 clearance.

Additional PK/PD concentration-response analysis may be performed.

6.19.6. Addendum Exploratory Analyses

The exploratory objectives for the addendum are to characterize the effect of LY3819253 in combination with LY3832479 after IV infusion on the following endpoints:

- Proportion of participants who experience COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Days 22, 60, and 85
- Proportion of participants who experience multisystem inflammatory syndrome in children (MIS-C)
- Comparison from baseline to last evaluable time point up to Day 29 in the emergence of viral resistance

The exploratory efficacy endpoints will be summarized using descriptive statistics only in a similar manner as the main study (see Section 6.10). Summaries will be performed overall by treatment group and also by age and treatment groups.

Additional exploratory analyses may be performed.

6.19.7. Addendum Interim Analyses

An interim analysis may occur to evaluate safety or efficacy in support of regulatory interactions. This interim may include all pediatric data available at that time and relevant analyses.

Early review of PK data may be planned but is not considered a formal interim analysis.

6.20. Analyses for the Faster Intravenous Infusion Addendum

6.20.1. Sample Size

The planned sample size for treatment arm 20 (5-minute IV Push) is approximately 30 participants.

The planned sample size for treatment arm 21 (3-minute IV Push) is approximately 270 participants.

6.20.2. General Considerations

Unless otherwise specified, all endpoints will be summarized descriptively. Descriptive summaries will include:

- number of participants
- mean, standard deviation, median, minimum, and maximum for continuous measures; and
- frequency counts and percentages for categorical measures.

The definition of study baseline and study time intervals will be the same as defined for the main study (see Sections 6.1.2 and 6.1.3, respectively). Additionally, the handling of dropouts and missing data will be similar to that described for the main study (see Section 6.3) with the exception of the MMRM, as the data from the addendum will not include inferential analyses.

6.20.3. Addendum Primary Analysis

The primary objective is to assess the safety and tolerability of LY3819253 in combination with LY3832479 administered by IV push. Safety analyses will be conducted for all participants who receive study infusion.

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with intervention as perceived by the investigator. Adverse events reported prior to randomization

will be distinguished from those reported as new or increased in severity during the study postrandomization.

Safety parameters that will be assessed include, but are not limited to, safety laboratory parameters, vital signs, and reported AEs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Postadministration observations will be evaluated.

6.20.4. Addendum Secondary Analyses

The secondary efficacy objective for the addendum is to characterize the effect of LY3819253 in combination with LY3832479 after IV infusion on the proportion of participants who experience COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29. Results will be summarized descriptively by treatment arm for all participants who receive study infusion.

6.20.5. Addendum Interim Analyses

Interim analyses may occur to assess the safety and tolerability of LY3819253 in combination with LY3832479 administered by IV push. The first interim analysis may be conducted when approximately 150 participants complete the Day 2 visit. Other interim analyses may be scheduled as needed.

Monitoring of unblinded safety data (including AEs, SAEs, and selected laboratory measurements) will be conducted by AC members.

Any of the arms in this addendum may be stopped due to an unacceptable safety signal.

7. References

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8. Appendices

Appendix 1. NEWS2 Scoring Scale

The National Early Warning Score 2 (NEWS2) is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice, when participants present to, or are being monitored in hospital. Six simple physiological parameters form the basis of the scoring system:

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

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Abbreviations: CVPU =Confusion, Voice, Pain, Unresponsive; NEWS2 = National Early Warning Score 2; SpO2 = oxygen saturation.

Figure APP.1.1. NEWS2 scoring.

NEW score	Clinical risk
Aggregate score 0–4	Low
Red score Score of 3 in any individual parameter	Low–medium
Aggregate score 5–6	Medium
Aggregate score 7 or more	High

Abbreviation: NEWS2 = National Early Warning Score 2.

Figure APP.1.2. NEWS2 scoring clinical risk thresholds.

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

Appendix 2. 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.

Table APP.1.1. NIAID Clinical Status Scoring

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

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

Leo Document ID = 0368ff3a-6ffd-4826-975d-f4adfb7fe4a9

Approver: PPD

Approval Date & Time: 17-Mar-2021 20:08:06 GMT

Signature meaning: Approved