Statistical Analysis Plan (v10): J2X-MC-PYAH

A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Mono and Combination Therapy with Monoclonal Antibodies in Participants with Mild to Moderate COVID-19 Illness (BLAZE-4)

NCT04634409

Approval Date: 04-Aug-2021

1. Statistical Analysis Plan: J2X-MC-PYAH: A Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Mono and Combination Therapy with Monoclonal Antibodies in Participants with Mild to Moderate COVID-19 Illness (BLAZE-4)

LY3819253 alone and in combination with LY3832479, LY3819253 in combination with VIR-7831, LY3853113 alone and in combination with 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.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol J2X-MC-PYAH
Phase 2

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Statistical Analysis Plan Version 10 electronically signed and approved by Lilly on date provided below:

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3. Revision History

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

DOCUMENT HISTORY	
Document	**Date**
Version 10	See approval date on cover page
Version 9	31 March 2021
Version 8	16 March 2021
Version 7	22 February 2021
Version 6	21 January 2021
Version 5	13 January 2021
Version 4	14 December 2020
Version 3	30 November 2020
Version 2	11 November 2020
Original SAP	14 October 2020

Overall Rationale for Version 2:

Section # and Name	Description of Change	Brief Rationale
4.2 Secondary Objectives	Changed the time period to Day 29 from Day 22 for the clinical status objectives	Protocol revision (amendment a)
6.1.1. Analysis Populations	Removed the LY/LY2 total treatment group for the Efficacy Population	Pooled LY treatment arms will not be summarized or compared to placebo
6.10.2.1 Bayesian Modeling	Removed notation for k and γ_j	The notation is not applicable to this model
6.10.3.7 COVID-19-Related Hospitalization or Death	Changed the time period to Day 29 from Day 22	Protocol revision (amendment a)
6.10.3.7.1 Bayesian Modeling for COVID-19-Related Hospitalization or Death	Removed notation for k, β, σ_γ^2 and γ_j	The notation is not applicable to this model
6.10.3.8 COVID-19-Related Hospitalization, Emergency Room Visit, or Death	Changed the time period to Day 29 from Day 22	Protocol revision (amendment a)
6.11. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Methods	Removed content related to noncompartmental analysis methods	Descriptive analysis will be reported

Overall Rationale for Version 3:

Section # and Name	Description of Change	Brief Rationale
6.10 Efficacy Analyses	Added an additional potential exploratory PK/PD analysis	Consistency with study J2W-MC-PYAB
6.13 Subgroup Analyses	For concomitant medications of	Spelling correction

Section # and Name	Description of Change	Brief Rationale
	interest subgroup, corrected the spelling of HYDROXYCHLOROQUINE	
6.19 Analyses for the Open-Label Addendum Substudy	Added section	Protocol addendum (2)

Overall Rationale for Version 4:

Section # and Name	Description of Change	Brief Rationale
4.2 Secondary Objectives	Changed/added timepoints to some endpoints Added an endpoint for viral load AUC through Day 11	Protocol revision (b)
5.1.3 Double-Blind Treatment and Assessment Period	Updated Table PYAH.5.1 with Treatment Arm 6	Protocol revision (b)
5.2 Determination of Sample Size	Updated sample size for the addition of Treatment Arm 6	Protocol revision (b)
6.1.1 Analysis Populations	Added Treatment Arm 6 Safety analyses will compare pooled LY1/LY2 to placebo and 700 mg LY1 to placebo	Protocol revision (b) Clarification
6.3.1 Modified Non-Responder Imputation (mNRI)	Replaced the LOCF section with a mNRI section for viral clearance endpoints	Changed imputation rule such that all patients are now included in the analysis
6.3.4 Modified Last Observation Carried Forward	Added that change in symptom score will not use this imputation method	Clarification
6.10.1 Primary Outcome and Methodology	Added a name for the imputation method for PHVL	Clarification
6.10.3.1 Change from Baseline in SARS-CoV-2 Viral Load	Clarified that no missing imputations will be performed	Clarification
6.10.3.4. SARS-CoV-2 Clearance	Added timepoints for Days 22 and 29	Protocol revision (b)
6.10.3.6.4. Change in Symptom Questionnaire Score	Added timepoints for Days 22 and 29	Protocol revision (b)
6.10.3.7. COVID-19-Related Hospitalization or Death	Clarified the definition of hospitalization	Clarification
6.15.1. Interim Analyses	Added text for Treatment Arm 6	Protocol revision (b)

Overall Rationale for Version 5:

Section # and Name	Description of Change	Brief Rationale
4.1 Primary Objective	Added primary objective for Treatment Arms 7-8	Protocol revision (c)
4.2 Secondary Objectives	Added secondary objectives for Treatment Arms 7-8	Protocol revision (c)

Section # and Name	Description of Change	Brief Rationale
	Clarified that Death is Death from all causes for the overall participant clinical status objectives Added Day 22 and 29 for symptom objectives	Clarification Protocol revision (b)
4.3 Exploratory Objectives	Added exploratory objectives for Treatment Arms 7-8	Protocol revision (c)
5.1.3 Double-Blind Treatment and Assessment Period	Added Treatment Arms 7-8	Protocol revision (c)
5.2 Determination of Sample Size	Added Treatment Arms 7-8	Protocol revision (c)
6.1 General Considerations	Added subgroup analyses for females who are pregnant at baseline	Protocol revision (c)
6.1.1 Analysis Populations	Added analyses for Treatment Arms 7-8 Added a per-protocol population	Protocol revision (c) Additional sensitivity analyses
6.7 Participant Characteristics	Added analyses for females who are pregnant at baseline	Protocol revision (c)
6.10.3.4 SARS-CoV-2 Clearance	Removed Day 22 analyses	Do not collect NP swabs on Day 22
6.10.3.6.1 Symptom Resolution	Added analyses for day 22 and 29 for proportion of patients that achieve symptom resolution	Protocol revision (b)
6.10.3.6.5 Symptom Improvement	Added analyses for day 22 and 29 for proportion of patients that achieve symptom resolution	Protocol revision (b)
6.10.3.7 COVID-19-Related Hospitalization or Death From Any Cause	Clarified that Death is Death from all causes	Clarification
6.10.3.7.1 Bayesian Modeling for COVID-19-Related Hospitalization or Death From Any Cause	Clarified that Death is Death from all causes	Clarification
6.10.3.8 COVID-19-Related Hospitalization, Emergency Room Visit, or Death From Any Cause	Clarified that Death is Death from all causes	Clarification
6.12.9 Immunogenicity	Added analyses for VIR-7831	Protocol revision (c)
6.13 Subgroup Analyses	Added subgroup analyses for females who are pregnant at baseline	Protocol revision (c)
6.15.1 Interim Analyses	Added potential interim analysis for Treatment Arms 7-8 Added analyses for primary outcome	Protocol revision (c) Clarification

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Section # and Name	Description of Change	Brief Rationale
CCI [redacted]		

Overall Rationale for Version 6:

Section # and Name	Description of Change	Brief Rationale
6.1 General Considerations	Removed analyses for female participants who are pregnant at baseline	Protocol revision (d)
6.7 Participant Characteristics	Removed summary for female participants who are pregnant at baseline	Protocol revision (d)
6.10.3.6.2 Time to Symptom Resolution	Added a sentence that states patients will be censored at the date of hospitalization	Clarification
6.10.3.6.6. Time to Symptom Improvement	Added a sentence that states patients will be censored at the date of hospitalization	Clarification
6.13 Subgroup Analyses	Removed analyses for female participants who are pregnant at baseline	Protocol revision (d)

Overall Rationale for Version 7:

Section # and Name	Description of Change	Brief Rationale
6.3.4. Last Observation Carried Forward	Added section for missing data imputation for the persistently high viral load analysis	Added LOCF imputation method for the persistently high viral load analysis, after doing post hoc analyses on Treatment Arms 1-6
6.10.1 Primary Outcome Methodology	Added that the imputation method will be LOCF instead of RSI	Added LOCF imputation method for the persistently high viral load analysis, after doing post hoc analyses on Treatment Arms 1-6

Overall Rationale for Version 8:

Section # and Name	Description of Change	Brief Rationale
6.3.4 Relevance Sequence Imputation	Added section for missing data imputation for the persistently high viral load analysis for Treatment Arms 1-6.	Clarification
6.3.5 Last Observation Carried Forward	Clarified that this missing data imputation method will be used for Treatment Arms 7 and 8.	Clarification
6.10.1 Primary Outcome Methodology	Added that the imputation method will be RSI for Treatment Arms 1-6 and LOCF for Treatment Arms 7 and 8	Clarification

Overall Rationale for Version 9:

Section # and Name	Description of Change	Brief Rationale
4.1 Primary Objective	Added objectives for Arms 9-11 and 12-13	Protocol amendment (f)
4.2 Secondary Objectives	Added objectives for Arms 9-11 and 12-13	Protocol amendment (f)
4.3 Exploratory Objectives	Added objectives for Arms 9-11 and 12-13	Protocol amendment (f)
5.1 Summary of Study Design	Added design elements for Arms 9-11 and 12-13.	Protocol amendment (f)
5.1.2 Screening	Added child/adolescent assent	Protocol amendment (f)
5.1.3 Double-Blind Treatment and Assessment Period	Updated Table PYAH.5.1. to include Arms 9-11 and 12-13	Protocol amendment (f)
5.2 Determination of Sample Size	Added sample size for Arms 9-11 and 12-13	Protocol amendment (f)
5.3.1 Randomization	Added stratification factors for Arms 9-11 and 12-13	Protocol amendment (f)
6.1 General Considerations	Added a description of the analyses for Arms 1-13. Added that participants who have received a SARS-CoV-2 vaccine prior to screening may be summarized separately.	Protocol amendment (f)
6.1.1 Analysis Populations	Added treatment group descriptions for Arms 9-11 and 12-13.	Protocol amendment (f)
6.1.4 Analysis Methods	Added a description for multiplicity adjustment for the primary endpoints for Arms 9-11. Added analyses description for Arms 12-13.	Protocol amendment (f)

Section # and Name	Description of Change	Brief Rationale
6.3.5 Last Observation Carried Forward	Added Arms 9-13.	Protocol amendment (f)
6.5. Multiple Comparisons/Multiplicity	Added a description for multiplicity adjustment for the primary endpoints for Arms 9-11.	Protocol amendment (f)
6.7 Participants Characteristics	Added analyses for Arms 12-13	Protocol amendment (f)
6.10.1 Primary Outcome and Methodology	Removed the +2 day window. Added Arms 9-13 for method of handling missing data.	Protocol amendment (f)
6.10.3.1 SARS-CoV-2 Viral Load	Added section	Re-organization of secondary objectives
6.10.3.1.1 Change from Baseline in SARS-CoV-2 Viral Load	Removed the visit windows. Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.1.3 SARS-CoV-2 Viral Load AUC	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.1.4 75th Percentile of SARS-CoV-2 Viral Load	Added section for new secondary objective	Protocol amendment (f)
6.10.3.1.5 SARS-CoV-2 Clearance	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.2.1 Symptom Resolution	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.2.3 Time to Sustained Symptom Resolution	Added section for new secondary objective	Protocol amendment (f)
6.10.3.2.4 Symptom Questionnaire AUC	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.2.5 Change in Symptom Questionnaire Score	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.2.6 Symptom Improvement	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.3 Participant Clinical Status	Added section	Re-organization of secondary objectives
6.10.3.3.1 COVID-19-Related Hospitalization or Death From Any Cause	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.10.3.3.2 COVID-19-Related Hospitalization, Emergency Room Visit, or Death From Any Cause	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.11 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Methods	Added LY3853113 and VIR-7831	Protocol amendment (c) and Protocol amendment (f)

Section # and Name	Description of Change	Brief Rationale
6.12.7. Vital Signs and Other Physical Findings	Updated Table PYAH.6.10. to include criteria for adolescents	Protocol amendment (f)
6.12.9 Immunogenicity	Added LY3853113	Protocol amendment (f)
6.13 Subgroup Analyses	Added analyses for Arms 12-13	Protocol amendment (f)
6.16.2.1 SpO2 AUC	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.16.2.7 Duration of Hospitalization	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.16.2.10 Days Since Symptom Onset Cutpoint Analysis	Clarified that analyses displays will be active treatment minus placebo.	Protocol amendment (f)
6.19 Analyses for Open-Label Addendum Substudies	Added analyses for addendum (4)	Protocol Addendum (4)
7 References	Removed references that are no longer referenced	Clarification

Overall Rationale for Version 10:

Section # and Name	Description of Change	Brief Rationale
4.1 Primary Objective	Added primary objective for Arm 14	Protocol revision (g)
4.2 Secondary Objectives	Added secondary objectives for Arm 14	Protocol revision (g)
4.3 Exploratory Objectives	Added exploratory objectives for Arm 14	Protocol revision (g)
5.1.3 Double-Blind Treatment and Assessment Period	Added Arm 14 Corrected that Arm 1 is the placebo comparison for Arms 2-6	Protocol revision (g) Error
5.2 Determination of Sample Size	Added sample size for Arm 14	Protocol revision (g)
6.1 General Considerations	Added analyses for Arm 14 and for adolescents	Protocol revision (g)
6.1.1 Analysis Populations	Added Arm 14 Added an integrated population for Arms 9-14 for safety	Protocol revision (g)
6.1.4 Analysis Methods	Added Arm 14	Protocol revision (g)
6.1.2 Definition of Study Baseline	Added language for the scenario where 2 viral load samples exists with the same date and time	Clarification
6.3.3 Highest Disease States Imputation	Corrected the imputation to follow the ordinal scales	Error
6.7 Participant Characteristics	Added analyses for Arm 14	Protocol revision (g)

Section # and Name	Description of Change	Brief Rationale
	Added that high-risk status will be summarized for Arms 12-14 Clarified summaries for SARS-CoV-2 vaccinations at baseline and during the study	Clarifications
6.10.3.1.4 75th Percentile of SARS-CoV-2 Viral Load	Added that for Arm 12-14, descriptive analyses only will be done	Clarification
6.10.3.2.1 Symptom Resolution	Updated the definition for Arms 9-14 to align with the added secondary objective for sustained symptom resolution	Clarification
6.10.3.2.3 Time to Sustained Symptom Resolution	Added analyses for Arm 14	Protocol revision (g)
6.10.3.3.1 COVID-19 Related Hospitalization or Death from Any Cause	Clarified that no imputations will be performed for the analysis	Clarification
6.10.3.3.21 COVID-19 Related Hospitalization, Emergency Room Visit, or Death from Any Cause	Clarified that no imputations will be performed for the analysis	Clarification
6.12.6 Clinical Laboratory Evaluation	Added that if sites use local laboratories to analyze lab data, then the results will be standardized for analysis purposes	Clarification
6.13 Subgroup Analyses	Clarified that subgroup analyses for SARS-CoV-2 vaccination status at baseline may be performed for Arms 12-14 only Added age and BMI analyses for Arm 14	Clarification Protocol revision (g)
6.16.2.13 Variants	Added exploratory analyses	Added exploratory analyses

4. Study Objectives

4.1. Primary Objective

Treatment Arms 1-6:

The primary objective is to characterize the effect of LY2819253 alone and in combination with LY3832479 compared to placebo on SARS-CoV-2 viral load and viral clearance among participants with mild to moderate COVID-19 illness. The primary endpoint is the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days), corresponding to Ct value of less than 27.5 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 logistic regression analysis method at the 2-sided 0.05 level. 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.

Treatment Arms 7-8:

The primary objective is to characterize the effect of LY2819253 in combination with VIR-7831 compared to placebo on SARS-CoV-2 viral load and viral clearance among participants with mild to moderate COVID-19 illness. The primary endpoint is the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days), corresponding to Ct value of less than 27.5 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 logistic regression analysis method at the 2-sided 0.05 level. 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.

Treatment Arms 9-11:

The primary objective is to characterize the effect of LY3853113 alone and in combination with LY3819253 and LY3832479 after intravenous infusion compared to placebo on SARS-CoV-2 viral load with mild to moderate COVID-19 illness. The primary endpoint is the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7, corresponding to Ct value of less than 27.5 based on nasopharyngeal swab sampling for RT-PCR testing for SARS-CoV-2. Statistical hypothesis testing for the primary endpoint will be conducted using a logistic regression analysis method at the 2-sided 0.05 level. 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.

Treatment Arms 12-14:

The primary objective is to characterize the safety profile of LY3853113 alone and in combination with LY3819253 and LY3832479 after intravenous infusion for participants with mild to moderate COVID-19 illness who are at a high risk of severe COVID-19 illness and/or hospitalization.

4.2. Secondary Objectives

Table PYAH.4.1. Secondary Objectives of Study J2X-MC-PYAH, Treatment Arms 1-6

The secondary objectives are to characterize the effect of LY3819253 alone and in combination with LY3832479, compared to placebo on…	
• 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 Death from any cause
• SARS-CoV-2 viral load and viral clearance	• SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 11 • Change from baseline to o Day 3 (+1 day) o Day 5 (±2 days) o Day 7 (±2 days) o Day 11 (±2 days) • Proportion of participants with viral load greater than 5.27 on Day 7 (+2 days) among participants enrolled with ≤8 days of symptoms prior to randomization • Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11, and 29) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 11
• symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 3, 5, 7, 11, 22, and 29 • AUC from baseline to Day 11 • Change in symptom score (total of ratings) from baseline up to Day 7, 11, 22, and 29.
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 3, 5, 7, 11, 22, and 29
• safety	• Safety assessments such as AEs and SAEs
• 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 clinical status for participants	• Proportion (percentage) of participants who experience these events through Day 29: o COVID-19 related hospitalization (defined as

	≥24 hours of acute care), ○ COVID-19 related emergency room visit, or ○ Death from any cause
• characterize the pharmacokinetics of LY3819253 and LY3832479	• Mean concentration of LY3819253 and LY3832479 on Day 29

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

Table PYAH.4.2. Secondary Objectives of Study J2X-MC-PYAH, Treatment Arms 7-8

The secondary objectives are to characterize the effect of LY3819253 in combination with VIR-7831, compared to placebo on…	
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 ○ COVID-19 related hospitalization (defined as ≥24 hours of acute care) ○ Death from any cause
• SARS-CoV-2 viral load and viral clearance	• SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 11 • Change from baseline to ○ Day 3 (+1 day) ○ Day 5 (±2 days) ○ Day 7 (±2 days) ○ Day 11 (±2 days) • Proportion of participants with viral load greater than 5.27 on Day 7 (+2 days) among participants enrolled with ≤8 days of symptoms prior to randomization • Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11, and 29) • Time to SARS-CoV-2 clearance • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 11
• symptom resolution	• Time to symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 3, 5, 7, 11, 22, and 29 • AUC from baseline to Day 11 • Change in symptom score (total of ratings) from baseline up to Day 7, 11, 22, and 29.
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 3, 5, 7, 11, 22, and 29
• safety	• Safety assessments such as AEs and SAEs
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Days 22, 60, and 85 ○ COVID-19 related hospitalization

	(defined as ≥24 hours of acute care) o Death from any cause
• characterize clinical status for participants	• Proportion (percentage) of participants who experience these events through Day 29: o COVID-19 related hospitalization (defined as ≥24 hours of acute care), o COVID-19 related emergency room visit, or o Death from any cause
• characterize the pharmacokinetics of LY3819253 and VIR-7831	• Mean concentration of LY3819253 and VIR-7831 on Day 29

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

Table PYAH.4.3. Secondary Objectives of Study J2X-MC-PYAH, Treatment Arms 9-11

Secondary The secondary objectives are to characterize the effect of LY3853113 alone and in combination with LY3819253 and LY3832479 after intravenous infusion compared to placebo on…	
• 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 Death
• SARS-CoV-2 viral load and viral clearance	• Change from baseline to o Day 3 o Day 5 o Day 7 o Day 11 • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 11 • 75th Percentile of SARS-CoV-2 viral load at Day 7 • Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11, and 29) • Time to SARS-CoV-2 clearance
• symptom resolution	• Time to symptom resolution • Time to sustained symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11, 22, and 29
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11, 22, and 29
• safety	• Safety assessments such as AEs and SAEs
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 22

	○ COVID-19 related hospitalization (defined as ≥24 hours of acute care) ○ Death
• Characterize clinical status for participants	• Proportion (percentage) of participants who experience these events through Day 29: ○ COVID-19 related hospitalization (defined as ≥24 hours of acute care), ○ COVID-19 related emergency room visit, or ○ death
• Characterize the pharmacokinetics of LY3853113, LY3819253, and LY3832479	• Mean concentration of LY3853113, LY3819253, and LY3832479 on Day 29

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

Table PYAH.4.4. Secondary Objectives of Study J2X-MC-PYAH, Treatment Arms 12-14

Secondary The secondary objectives are to characterize the effect of LY3853113 alone and in combination with LY3819253 and LY3832479 after intravenous infusion on…	
• overall participant clinical status	• Proportion (percentage) of participants who experience these events by Day 29 ○ COVID-19 related hospitalization (defined as ≥24 hours of acute care) ○ Death
• SARS-CoV-2 viral load and viral clearance	• Proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 • Change from baseline to ○ Day 3 ○ Day 5 ○ Day 7 ○ Day 11 • 75th Percentile of SARS-CoV-2 viral load at Day 7 • SARS-CoV-2 viral load area under the response-time curve (AUC) assessed through Day 11 • Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11, and 29) • Time to SARS-CoV-2 clearance
• symptom resolution	• Time to symptom resolution • Time to sustained symptom resolution • Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 2-11, 22, and 29
• symptom improvement	• Time to symptom improvement • Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 2-11, 22, and 29
• overall participant clinical status	• Proportion (percentage) of participants who

	experience these events by Day 22 o COVID-19 related hospitalization (defined as ≥24 hours of acute care) o Death
• Characterize clinical status for participants	• Proportion (percentage) of participants who experience these events through Day 29: o COVID-19 related hospitalization (defined as ≥24 hours of acute care), o COVID-19 related emergency room visit, or o death
• Characterize the pharmacokinetics of LY3853113, LY3819253, and LY3832479	• Mean concentration of LY3853113, LY3819253, and LY3832479 on Day 29

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

4.3. Exploratory Objectives

Table PYAH.4.5. Exploratory Objective of Study J2X-MC-PYAH, Treatment Arms 1-6

The exploratory objective is …	
• 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

Table PYAH.4.6. Exploratory Objective of Study J2X-MC-PYAH, Treatment Arms 7-8

The exploratory objective is …	
• Characterize emergence of viral resistance to LY3819253 in combination with VIR-7831	• Comparison from baseline to the last evaluable time point up to Day 29

Table PYAH.4.7. Exploratory Objective of Study J2X-MC-PYAH, Treatment Arms 9-11

The exploratory objective is …	
• Characterize emergence of viral resistance to LY3853113	• Comparison from baseline to the last evaluable time point up to Day 29

Table PYAH.4.8. Exploratory Objective of Study J2X-MC-PYAH, Treatment Arms 12-14

The exploratory objective is …	
• Characterize emergence of viral resistance to LY3853113	• Comparison from baseline to the last evaluable time point up to Day 29

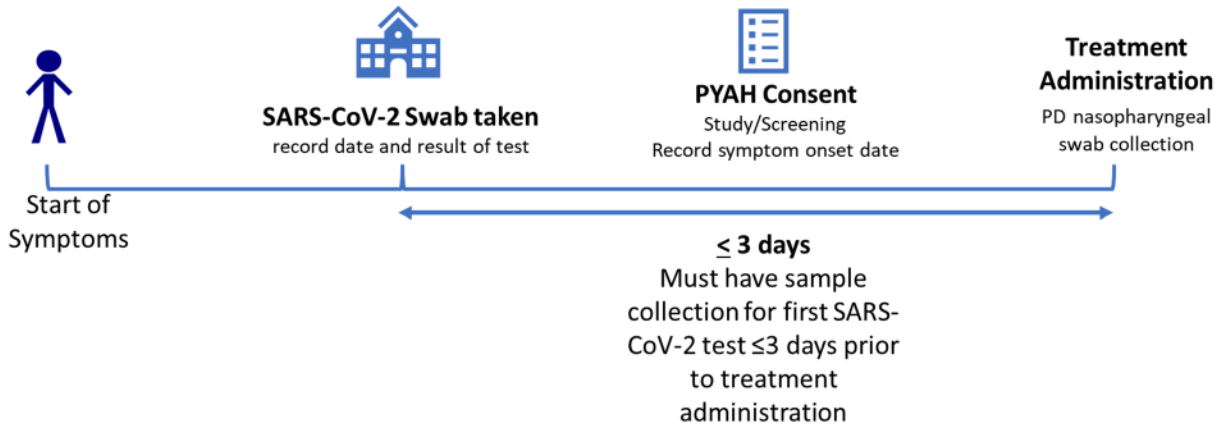
Exploratory objectives not previously defined in the protocol are described in Section 6.16.2.

5. Study Design

5.1. Summary of Study Design

This is a Phase 2, randomized, single-dose study in participants with mild to moderate COVID-19 illness. Treatment Arms 1-11 are double-blind and placebo controlled, and Treatment Arms 12 and 14 are open-label.

5.1.1. Design Outline



Abbreviations: PD = pharmacodynamic; PYAH = Study J2X-MC-PYAH; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Figure PYAH.5.1. Overview of participant flow from time of SARS-CoV-2 symptoms to treatment administration.

5.1.2. Screening

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

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

5.1.3. 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 post-infusion sample collection.

Table PYAH.5.1 describes the planned Treatment Arms.

Table PYAH.5.1. Treatment Arms of Study J2X-MC-PYAH

Treatment Arms	Dose	Intervention	Participant Population
1	---	Placebo	---
2	175 mg + 350 mg	LY3819253 + LY3832479	---
3	700 mg + 1400 mg	LY3819253 + LY3832479	---
4	2800 mg + 2800 mg	LY3819253 + LY3832479	---
5	700 mg	LY3819253	---
6	350 mg + 700 mg	LY3819253 + LY3832479	---
7	700 mg + 500 mg	LY3819253 + VIR-7831	---
8	---	Placebo	---
9	175 mg	LY3853113	Low risk
10	175 mg + 700 mg + 1400 mg	LY3853113 + LY3819253 + LY3832479	Low risk
11	---	Placebo	Low risk
12	175 mg	LY3853113	High risk[a]
13	175 mg + 700 mg + 1400 mg	LY3853113 + LY3819253 + LY3832479	High risk[a]
14	175 mg + 700 mg + 1400 mg	LY3853113 + LY3819253 + LY3832479	High risk[b]

[a] See Protocol Section 5.1, Inclusion Criteria 27 and 28, for the definition of high-risk participants applicable for Treatment Arms 12 and 13.

[b] See Protocol Section 5.1, Inclusion Criterion 30, for the definition of high-risk participants applicable for Treatment Arm 14.

Treatment Arm 1 is the corresponding placebo control for Treatment Arms 2-6.

Treatment Arm 8 is the corresponding placebo control for Treatment Arm 7.

Treatment Arm 11 is the corresponding placebo control for Treatment Arms 9 and 10.

5.1.4. Posttreatment Follow-up

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

5.2. Determination of Sample Size

Treatment Arms 1-6

The initial planned sample size is approximately 500 participants allocated across 4 Treatment Arms (Treatment Arms 1 through 5). The planned sample size is approximately 100 participants for Treatment Arm 6. Since Treatment Arm 6 begins enrollment after Treatment Arms 1-5, additional participants will be enrolled in Treatment Arm 1 to ensure at least a 50% increase in placebo participants and concurrent placebo control for the primary comparison of Treatment Arm 6. Additional participants will also be enrolled in Treatment Arm 3 to ensure at least a 50% increase in LY3819253 700 mg + LY3832479 1400 mg participants to provide concurrent enrollment of an additional treatment arm.

Up to 100 additional participants may be introduced either for each optional treatment arm or in addition to an existing treatment arm (including placebo). See Protocol Section 9.5 for details.

Sample size was determined based on pairwise comparisons of each dose compared to placebo. An assumed sample size of 100 participants in Treatment Arms 2, 4-6 and 150 participants in Treatment Arms 1 and 3 provides greater than 90% power to test the superiority of at least one dose of LY3819253 or the combination of LY3819253 and LY3832479 versus placebo at the two-sided 0.05 alpha level, adjusted for multiplicity, on the proportion of participants with SARS-CoV-2 viral load greater than 5.27 at Day 7 (+2 days). This assumes the true underlying proportion of participants meeting this endpoint is 5% in the LY3819253 arm of 700 mg, and LY38192353 + LY3832479 combination Treatment Arms for dose levels 2800 mg+2800 mg, and 700 mg+1400 mg, 7% for dose level 350 mg+700 mg and for 175 mg+350 mg, and 19% in the placebo arm.

Treatment Arms 7-8

The planned sample size is approximately 100 participants per treatment arm.

Sample size was determined based on a pairwise comparison of LY3819253 in combination with VIR-7831 compared to placebo. An assumed sample size of 100 participants in Treatment Arms 7 and 8 provides greater than 87% power to test the superiority at the two-sided 0.05 alpha level on the proportion of participants with SARS-CoV-2 viral load greater than 5.27 at Day 7 (+2 days). This assumes the true underlying proportion of participants meeting this endpoint is 5% in the LY3819253 700 mg + VIR-7831 500-mg treatment arm and 19% in the placebo arm.

The sample size calculations were performed using simulations from the software EAST© v6.5.

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

Treatment Arms 9-11

The planned sample size is approximately 122 participants per treatment arm.

Sample size was determined based on pairwise comparisons of each dose compared to placebo. An assumed sample size of 122 participants per treatment arm provides about 84% power to test the superiority of either LY3853113 alone or the combination with LY3819253 and LY3832479 versus placebo at the two-sided 0.05 alpha level on the proportion of participants with SARS-CoV-2 viral load greater than 5.27 at Day 7. This assumes the true underlying proportion of participants meeting this endpoint is 12% in both the LY3853113 alone treatment arm and the LY3853113 + LY3819253 + LY3832479 combination treatment arm, and 28% in the placebo arm.

Treatment Arms 12-14

Approximately 100 participants will be enrolled into Treatment Arm 12 and approximately 50 participants will be enrolled into Treatment Arm 13. Treatment Arm 12 includes a greater number of participants to assess the tolerability of undiluted LY3853113 administration.

Approximately 140 participants will be enrolled into Treatment Arm 14 once Treatment Arms 12 and 13 have completed enrollment.

5.3. Method of Assignment to Treatment

5.3.1. Randomization

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

For Treatment Arms 1-13, participants will be stratified by duration since symptom onset to randomization (≤8 days vs >8 days). For Treatment Arms 12-13, participants will also be stratified by 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. Periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made to in an effort to achieve an equal allocation across the Treatment Arms at the end of enrollment. Given the staggered start of Treatment Arms, additional participants may be enrolled in existing Treatment Arms and the allocation ratio may change accordingly. See Protocol Section 9.5 for details.

5.3.2. Blinding

Treatment Arms 1-11 are double-blinded. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base lock at the conclusion of the study.

Table PYAH.5.2 describes general procedures for unblinding.

Table PYAH.5.2. Unblinding Procedures for Study J2X-MC-PYAH

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

Abbreviation: IWRS = interactive web-response system.

If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the

infusion stopped. If any amount of study intervention was administered, follow procedures according to the Schedule of Activities (SoA).

6. A Priori Statistical Methods

6.1. General Considerations

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

All tables, figures, and listings will be created using the clinical trial database (unless otherwise noted), including data during study participation. While not reflected in a table, figure, or listing, any data collected after study participation (e.g., in the Eli Lilly and Company [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.

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.

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.

Analyses will be performed separately for Treatment Arms:

- 1-6
- 7 and 8,
- 9-11,
- 12 and 13, and
- 14.

For Treatment Arms 12-14, participants who have received a SARS-CoV-2 vaccine prior to screening may be summarized separately from those who have not received a SARS-CoV-2 vaccine prior to screening, for all efficacy and safety outcomes. Additionally, participants who are ≥12 and <18 years old may be summarized separately than those who are ≥18 years old.

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 PYAH.6.1 along with the analysis to be used to conduct. The treatment groups and inferential comparisons described in Table PYAH.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 PYAH.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 1-6:* 175 mg LY3819253 and 350 mg LY3832479 (175/350 LY/LY2), 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY1/LY2), 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 (700 LY), and placebo (Pbo). *Treatment Arms 7-8:* 700 mg LY3819253 and 500 mg VIR-7831 (700/500 LY/VIR), and placebo (Pbo). *Treatment Arms 9-11:* 175 mg LY3853113 (175 LY3), 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2), placebo (Pbo) *Treatment Arms 12-13:* 175 mg LY3853113 (175 LY3) and 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) *Treatment Arm 14:* 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) Additional optional combination arm may be added if decided. **Inferential Comparisons:** *Treatment Arms 1-6:* Each LY dose versus placebo *Treatment Arms 7-8:* 700/500 LY/VIR dose versus placebo *Treatment Arms 9-11:* Each LY dose versus placebo *Treatment Arms 12-14:* None
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 hospitalization or death from any cause. **Treatment Groups (Short Label):** *Treatment Arms 1-6:* 175 mg LY3819253 and 350 mg LY3832479 (175/350 LY/LY2), 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY1/LY2), 700 mg

	LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 (700 LY), LY2 total, LY1/LY2 total, and placebo (Pbo). *Treatment Arms 7-8:* 700 mg LY3819253 and 500 mg VIR-7831 (700/500 LY/VIR), and placebo (Pbo). *Treatment Arms 9-11:* 175 mg LY3853113 (175 LY3), 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2), placebo (Pbo) *Treatment Arms 12-13:* 175 mg LY3853113 (175 LY3) and 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) *Treatment Arms 14:* 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) Additional optional combination arm may be added if decided. **Inferential Comparisons:** *Treatment Arms 1-6:* LY2 total versus placebo and 700 mg versus placebo *Treatment Arms 7-8:* 700/500 LY/VIR dose versus placebo *Treatment Arms 9-11:* Each LY dose versus placebo *Treatment Arms 12-14:* None
Integrated Safety (Arms 9, 10, 12-14)	**Definition:** All participants randomly assigned and who received any amount of study intervention in Arms 9, 10, or 12-14. Participants will be analyzed according to the intervention they actually received. **Purpose:** Used for safety analyses. **Treatment Groups (Short Label):** *Treatment Arms 9 and 12:* 175 mg LY3853113 (175 LY3) *Treatment Arms 10 and 13-14:* 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) **Inferential Comparisons:** None
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 1-6:* 175 mg LY3819253 and 350 mg LY3832479 (175/350 LY/LY2), 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY1/LY2), 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 (700 LY), LY/LY2 total, and placebo (Pbo). *Treatment Arms 7-8:*

	700 mg LY3819253 and 500 mg VIR-7831 (700/500 LY/VIR), and placebo (Pbo). *Treatment Arms 9-11:* 175 mg LY3853113 (175 LY3), 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2), placebo (Pbo) *Treatment Arms 12-13:* 175 mg LY3853113 (175 LY3) and 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) *Treatment Arm 14:* 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) Additional optional combination arm may be added if decided. **Inferential Comparisons:** *Treatment Arms 1-6:* Each LY dose versus placebo *Treatment Arms 7-8:* 700/500 LY/VIR dose versus placebo *Treatment Arms 9-11:* Each LY dose versus placebo *Treatment Arms 12-14:* None
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; • did not meet an inclusion criterion; or • meet an exclusion criterion. **Purpose:** Used for sensitivity analyses for the primary endpoint and the following secondary endpoints: • change from baseline in viral load to Day 7, • if there are a sufficient number of events, COVID-19 related hospitalization or death from any cause, • if there are a sufficient number of events, COVID-19 related hospitalization, COVID-19 related emergency room visit, or death from any cause, • time to symptom resolution **Treatment Groups (Short Label):** *Treatment Arms 1-6:* 175 mg LY3819253 and 350 mg LY3832479 (175/350 LY/LY2), 350 mg LY3819253 and 700 mg LY3832479 (350/700 LY1/LY2), 700 mg LY3819253 and 1400 mg LY3832479 (700/1400 LY/LY2), 2800 mg LY3819253 and 2800 mg LY3832479 (2800/2800 LY/LY2), 700 mg LY3819253 (700 LY), and placebo (Pbo). *Treatment Arms 7-8:* 700 mg LY3819253 and 500 mg VIR-7831 (700/500 LY/VIR), and placebo (Pbo). *Treatment Arms 9-11:* 175 mg LY3853113 (175 LY3), 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2), placebo (Pbo)

	Treatment Arms 12-13: 175 mg LY3853113 (175 LY3) and 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) *Treatment Arm 14:* 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479 (LY3/LY/LY2) Additional optional combination arm may be added if decided. **Inferential Comparisons:** *Treatment Arms 1-6:* Each LY dose versus placebo *Treatment Arms 7-8:* 700/500 LY/VIR dose versus placebo *Treatment Arms 9-11:* Each LY dose versus placebo *Treatment Arms 12-14:* None

Abbreviations: LY = study drug; PD = pharmacodynamic; PK = pharmacokinetic.

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. If 2 viral load records exist with identical sample dates and times, the results for the highest viral load will be used in the analysis.

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 PYAH.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 PYAH.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 and assessment 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 and assessment 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.

All hypothesis tests will be 2-sided at an alpha level of 0.05. No adjustment for multiplicity will be performed for Treatment Arms 1-8. For Treatment Arms 9-11, a hierarchical multiple comparisons procedure, which will control type I error in the primary endpoint analysis, will be implemented, see Section 6.5.

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 PYAH.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 in the model
Nonparametric	Treatment comparison of ordinal, nominal, and non-

(e.g., Mann-Whitney or van Elteren tests)	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 a mixed-effects model repeated measures (MMRM) analysis. When MMRM is used, it includes: (a) treatment group, (b) baseline value in the model, (c) visit, and (d) 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% confidence interval (CI) will also be reported. Unless otherwise specified, for MMRM, reported data from only planned visits will be used as the primary analysis.

Treatment comparisons of continuous efficacy, safety, and health outcome variables with a single postbaseline timepoint will be made using analysis of covariance (ANCOVA) with: (a) treatment group, and (b) 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. The Firth correction can be implemented in PROC Logistic by including *'firth'* as an option in the model statement. The odds ratio 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 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.

For Treatment Arms 12-14, all safety, efficacy, and health outcome endpoints will be summarized using descriptive statistics only.

6.2. Adjustments for Covariates

Analyses may be adjusted for baseline values, where appropriate, however, analyses will not be adjusted for the stratification factor, duration since symptom onset (≤8 days vs. >8 days).

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. Modified Non-Responder Imputation

For analysis of viral clearance (yes/no), missing data will be imputed using a mNRI. Specifically, for patients that have missing postbaseline data for reverse transcription polymerase chain reaction (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.

6.3.2. 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.

6.3.3. 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 2, 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 7, the highest value for a recovery or nonhospitalized status, will be used for imputation.

6.3.4. Relevance Sequence Imputation

Analysis of persistently high viral load on Day 7 will utilize a relevance sequence imputation (RSI) for Treatment Arms 1-6. The RSI is defined as:

> If Day 7 SARS-CoV-2 viral load is missing, then Day 7 will be imputed using a relevance sequence imputation as follows:

1. Impute Day 7 SARS-CoV-2 viral load with the Day 5 measurement, if available.
2. If Day 5 SARS-CoV-2 viral load is also missing, then impute Day 7 with the Day 3 measurement, if available.
3. If Day 3 SARS-CoV-2 viral load is also missing, then impute Day 7 with the Day 11 measurement, if available.
4. If Day 11 SARS-CoV-2 viral load is also missing, then impute Day 7 with the Day 1 measurement, if available.
5. If Day 1, Day 3, Day 5, Day 7, and Day 11 measurements are all missing, the viral load will be treated as MAR in the analysis.

6.3.5. Last Observation Carried Forward

Analysis of persistently high viral load on Day 7 will utilize a last observation carried forward (LOCF) analysis for Treatment Arms 7-13. 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 1-8

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

Treatment Arms 9-11

As this is a Phase 2 (nonconfirmatory) dose-finding study, no adjustments for multiple comparisons for the secondary endpoints will be made. However, a hierarchical multiple comparisons procedure, which will control type I error in the primary endpoint analysis, will be implemented. The primary endpoints will be tested in a sequential manner at a 1-sided 0.025 significance level. The following is a list of the primary outcomes to be tested:

- Primary (Test 1) - LY3853113 in combination with LY3819253 and LY3832479 compared to placebo for the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7
- Primary (Test 2) – LY3853113 alone compared to placebo for the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7

6.6. Participant Disposition

The treatment and assessment 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 adverse events (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 PYAH.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 and assessment 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

Participant 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 PYAH.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 (<35, ≥35 to <45, ≥45 to <55, >55 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 **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 12-14: • The age groups are defined as: o 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) • The following additional groups are defined: o Baseline SARS-CoV-2 vaccine status o SARS-CoV-2 vaccination during the study
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 and assessment 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 PYAH.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.
- For any sample with a positive CoV-2 test result, an additional normalization step will be taken in the analysis. 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. This step will be skipped if a valid RP Ct value is unavailable for the sample.

- The (log base 10) viral load will be calculated from the Ct value (45-Ct)/$\log_2 10$, or (45-Ct)/3.321928.

A lower Ct value of 40 for negative CoV-2 tests may be explored as part of exploratory PK/PD exposure-response analysis (Section 6.11).

6.10.1. Primary Outcome and Methodology

The primary endpoint is the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7, corresponding to Ct value of less than 27.5 based on nasopharyngeal swab sampling for RT-PCR testing for SARS-CoV-2. Statistical hypotheses testing for the primary endpoint will be conducted using a logistic regression model at the two-sided 0.05 level.

The proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 will be statistically analyzed using a logistic regression with a Firth penalized likelihood (Firth 1993). The Firth correction can be implemented in PROC Logistic by including *'firth'* as an option in the model statement. The odds ratio 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.

If Day 7 SARS-CoV-2 viral load is missing, then Day 7 will be imputed using RSI as described in Section 6.3.4 for Treatment Arms 1-6 and LOCF described in Section 6.3.5 for Treatment Arms 7-13.

6.10.2. Additional Analyses of the Primary Outcome

6.10.2.1. Bayesian Modeling

A Bayesian logistic regression model will be fitted to evaluate the success criteria by the Lilly statistics group with the model listed below:

$$r_{ij} \sim Binomial(p_{ij}, 1)$$
$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \beta \times base_{ij} + \alpha_i$$

Where,

r_{ij} : is 0 if patient j on treatment i has a SARS-CoV-2 viral load greater than 5.27 on Day 7 and 1 otherwise
$base_{ij}$: is the baseline viral load for patient j on treatment i
β: a fixed coefficient on the covariate log base 10 baseline viral load
α_i: a parameter corresponding to treatment i (with i=1 being the placebo group).

and priors:

$$\beta \sim N(0,100^2)$$
$$\alpha_1 \sim \pi(\alpha_1)$$

At least 2 priors ($\pi(\alpha_1)$) will be considered for α_1, a diffuse $N(0,100^2)$ and an informative prior based on available information at the time of analysis.

6.10.3. Secondary Efficacy Analyses

6.10.3.1. SARS-CoV-2 Viral Load

6.10.3.1.1. Change from Baseline in SARS-CoV-2 Viral Load

Changes from baseline to Day 3, Day 5, Day 7, and 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 LS means and treatment differences (active treatment minus placebo) 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, the ratio of geometric mean ratio to baseline vs placebo, and corresponding 95% CIs will be presented. All available data will be used in the analysis.

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.

No imputations of missing data will be conducted.

6.10.3.1.2. 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.

6.10.3.1.3. SARS-CoV-2 Viral Load AUC

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) 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-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, 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 (active treatment 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, by removing the day, interaction, and within subject error term, will be applied for log base 10 transformed AUC measure analysis.

6.10.3.1.4. 75th Percentile of SARS-CoV-2 Viral Load

For treatment groups 9-11, the 75th percentile of SARS-CoV-2 viral load on Day 7 will be statistically analyzed using a quantile regression analysis. The model will contain treatment as a fixed effect. The conditional 75th percentile and treatment differences (active treatment minus placebo) will be calculated and presented with their corresponding 95% CIs.

If Day 7 SARS-CoV-2 viral load is missing, then Day 7 will be imputed using LOCF described in Section 6.3.5.

For treatment groups 12-14, the 75th percentile of SARS-CoV-2 viral load on Day 7 will be summarized descriptively.

6.10.3.1.5. SARS-CoV-2 Clearance

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 3, 5, 7, 11, and 29 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that achieve SARS-CoV-2 clearance at Days 3, 5, 7, 11, and 29 will be analyzed using logistic regression to compare active treatment versus placebo at each dose level.

6.10.3.1.6. 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 and assessment period, the patient will be censored at the date of their last visit during the treatment and assessment period.

Time to SARS-CoV-2 clearance will be evaluated during the study treatment and assessment period only, and will be summarized by treatment and listed. Cox proportional hazard model will be used.

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

6.10.3.2. Symptom Questionnaire

Participants will rate their overall clinical status and severity of symptoms associated with COVID-19 by a daily questionnaire up to Day 11 and on Days 22 and 29. See Appendix 1 for further details regarding the symptoms and overall clinical status participant questionnaire.

6.10.3.2.1. Symptom Resolution

For treatment groups 1-8, symptom resolution is defined as all symptoms (those scored 0 to 3) on the symptom questionnaire scored as absent.

For treatment groups 9-14, 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.

The proportion of participants that achieve symptom resolution at Days 3, 5, 7, 11, 22, and 29 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that achieve symptom resolution at Days 3, 5, 7, 11 22, and 29 will be analyzed using logistic regression to compare active treatment 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.

6.10.3.2.2. 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 and assessment 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 treatment and assessment period only and will be summarized by treatment and listed. Cox proportional hazard model will be used.

Time to symptom resolution will be presented graphically.

6.10.3.2.3. Time to Sustained Symptom Resolution

For treatment groups 9-14, 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)

For Treatment Arms 9-11, similar methodology, as described in Section 6.10.3.2.2, will be utilized to perform treatment group comparisons.

6.10.3.2.4. Symptom Questionnaire AUC

The AUC from Day 1 predose to Day 11 (AUC[0-D11]) 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-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 active treatment group minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.10.3.2.5. Change in Symptom Questionnaire Score

Change in symptom questionnaire score (total of ratings from those symptoms scored 0-3) from baseline to Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 22, and 29 will be analyzed using an MMRM. The model will contain baseline as a covariate, treatment, day, and treatment-by-day interaction as fixed effects. The LS means and treatment differences (each active treatment group minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.10.3.2.6. 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 3, 5, 7, 11, 22, and 29 will be summarized by treatment in frequency tables and listed.

In addition, the number of participants that achieve symptom improvement at days 3, 5, 7, 11, 22, and 29 will be analyzed using logistic regression to compare active treatment 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.

6.10.3.2.7. 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 and assessment 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 and assessment 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.

6.10.3.3. Participant Clinical Status

6.10.3.3.1. COVID-19-Related Hospitalization or Death from Any Cause

Proportion (percentage) of participants who experience any of the following by Day 29 will be analyzed:

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

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

In addition, the number of participants that experience COVID-19 hospitalization or death from any cause by Day 29 will be analyzed using logistic regression to compare active treatment versus placebo at each dose level. 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. Data will not be imputed due to dropouts or missing data.

Proportion (percentage) of participants who experience COVID-19 related hospitalization or death from any cause by Days 22, 60, and 85 will also be analyzed.

The safety population will be utilized to analyze COVID-19-related hospitalization or death from any cause.

Based on the 'Hospitalization Events' eCRF 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.

6.10.3.3.1.1. Bayesian Modeling for COVID-19-Related Hospitalization or Death From Any Cause

Additionally, a Bayesian sensitivity analysis will be performed. A Bayesian logistic regression model will be fitted to evaluate the success criteria by the Lilly statistics group with the model listed below:

$$r_{ij} \sim Binomial(p_{ij}, 1)$$

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \alpha_i$$

Where,

r_{ij}: is 1 if patient j on treatment i was hospitalized and 0 otherwise
α_i: a parameter corresponding to treatment i (with i=1 being the placebo group).

and priors:

$$\alpha_1 \sim \pi(\alpha_1)$$

At least 2 priors ($\pi(\alpha_1)$) will be considered for α_1, a diffuse $N(0,100^2)$ and an informative prior based on available information at the time of analysis.

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

6.10.3.3.2. COVID-19-Related Hospitalization, Emergency Room Visit, or Death From Any Cause

Proportion (percentage) of participants who experience any of the following by Day 29 will be analyzed:

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

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

In addition, the number of participants that experience COVID-19 related hospitalization, emergency room visit, or death from any cause by Day 29 will be analyzed using logistic regression to compare active treatment versus placebo at each dose level. 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. Data will not be imputed due to dropouts or missing data.

Proportion (percentage) of participants who experience COVID-19 related hospitalization, emergency room visit, or death from any cause by Days 22, 60, and 85 will also be analyzed.

The safety population will be utilized to analyze COVID-19 related hospitalization, emergency room visit, or death from any cause.

6.11. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic, pharmacodynamic, and PK/PD analyses are the responsibility of Lilly's PK/PD group.

A summary of LY3853113, LY3819253, LY3832479, and VIR-7831 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, and
- continuous measurements:
  - p-value based on ANCOVA:
    - model containing terms for treatment,
    - 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 PYAH.6.7 provides conceptual definitions of baseline and postbaseline by analysis type.

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

Analysis Type	Baseline	Postbaseline
TEAEs	Start of screening and ends prior to the first dose.	Starts after initiation of the first dose and ends on or prior to the day of study discontinuation
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 discontinuation. All scheduled and unscheduled measurements will be included.
Change from Baseline 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 discontinuation. 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

See Appendix 2 for the definitions of AEs and serious adverse events (SAEs).

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC), preferred term (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.

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.

Summaries of TEAEs will include the number of participants with at least 1 TEAE for each treatment group. When reporting by 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 TEAEs (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.

In an overview table, the number and percentage of participants who experienced a TEAE, a SAE, an AE related to study drug, an AE resulting in death, incomplete dose of study treatment, or discontinuation from the study due to an AE will be summarized by treatment. Treatment-emergent AEs may be reported separately for the treatment and assessment period and the follow-up period.

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

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

Event Type	Summary Method
SAEs	SAEs will be summarized for each treatment arm by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.
TEAEs Resulting in Death	If there are any TEAEs that result in death, a listing of all deaths will be provided. In addition, a summary table may also be created by PT in order of decreasing frequency of preferred term.
TEAEs Leading to Study 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.

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

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

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 treatment and assessment period) will be analyzed with the method described in Section 6.16.2.7 and Section 6.16.2.9:

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

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

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

6.12.6. Clinical Laboratory Evaluation

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol (See Protocol Appendix 2). However, unscheduled measurements of planned analytes will be included/excluded as specified in the relevant sections. Examples of unplanned

measurements include those that the clinical investigator orders as a repeat test or "retest" of a laboratory test in case of an abnormal value, and those the investigator orders for a "follow-up visit" due to clinical concerns. Some planned analytes are intended for individual case reviews and will not be included in group-level summaries.

Investigative sites may use a local laboratory instead of a central laboratory for reporting the hematology and clinical chemistry analytes. Individual laboratory results reported using a local laboratory will be transformed such that a standardized result is used in the analysis. The transformation will be made using the calculation below:

$$s = L_s + (x - L_x)\frac{U_s - L_s}{U_x - L_x}$$

Where,

- S = the transformed individual laboratory value to a common standard laboratory reference range
- x = the individual local laboratory value
- L_x and U_x = lower and upper limits of normal range for the corresponding laboratory analyte, and
- L_s and U_s = lower and upper limits of normal range for the corresponding laboratory analyte from the central laboratory.

6.12.7. Vital Signs and Other Physical Findings

The planned summaries are provided in Table PYAH.6.9. 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 PYAH.6.10.

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

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

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

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

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

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

Parameter	Age Group	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	12 years	≤85 and decrease from baseline ≥20	≥126 and increase from baseline ≥20
	13-17 years	≤90 and decrease from baseline ≥20	≥129 and increase from baseline ≥20
	≥18 years	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	12 years	≤50 and decrease from baseline ≥10	≥82 and increase from baseline ≥10
	13-17 years	≤50 and decrease from baseline ≥10	≥86 and increase from baseline ≥10
	≥18 years	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	12 years	<60 and decrease from baseline ≥25	>140 and increase from baseline ≥25
	13-17 years	<50 and decrease from baseline ≥15	>120 and increase from baseline ≥15
	≥18 years	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Temperature	All	<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 LY3853113, LY3819253, LY3832479, and/or VIR-7831 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 LY3853113, LY3819253, LY3832479, and/or VIR-7831 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 (<35, ≥35 to <45, ≥45 to <55, >55 years old)
- gender (male, female)
- race
- ethnicity
- baseline weight (<60 kg, ≥60 to <100 kg, ≥100 kg)
- baseline body mass index (underweight to normal: <25 kg/m^2, overweight: ≥25 to <30 kg/m^2 and obese: ≥30 kg/m^2)
- concomitant medication of interest use (yes/no)

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; i.e., 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 PYAH.6.11.

Table PYAH.6.11. 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 12-14

Subgroup analyses (≥12 and <18 years old versus ≥18 years old) may be performed on all analyses and include descriptive statistics only. Subgroup analyses for SARS-CoV-2 vaccine status may be performed.

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 (based on Centers for Disease Control and Prevention (CDC) growth charts)
  - 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
      - For Treatment Arms 12-13, BMI <35 kg/m^2, or for Treatment Arm 14, BMI <25 kg/m^2
      - For Treatment Arms 12-13, BMI ≥35 kg/m^2, or for Treatment Arm 14, BMI ≥25 kg/m^2
  - Group 2:
    - age <18 years old and
      - Underweight (BMI <5th percentile)
      - Normal (BMI 5th percentile to < 85th percentile)
      - Overweight (BMI 85th percentile to <95th percentile)
      - Obese (BMI ≥95th percentile)
    - age ≥18 years old and
      - Underweight or normal (BMI <25 kg/m^2)
      - Overweight (BMI ≥25 to <30 kg/m^2)
      - Obese (BMI ≥30 to <40 kg/m^2), and
      - Extreme obese (BMI ≥40 kg/m^2)

Subgroup analyses for high-risk status will not be performed. Other subgroup analyses may be conducted if there is sufficient sample size within the subgroups.

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 "PYAH 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

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 starting after approximately 150 participants are enrolled and have had an opportunity to reach Day 4 to monitor participant safety. These initial ongoing individual reviews of unblinded safety data will subsequently occur at least every 30 days. 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.

An interim analysis is planned when approximately 75 participants in each arm (Treatment Arms 1-5) reach Day 7. An additional interim analysis may be conducted when at least 50% of participants in Treatment Arm 6 reach Day 7 and also when at least 33% of participants in Treatment Arms 7 and 8 reach Day 7.

The primary outcome may be analyzed first when the data is available, i.e. once all patients in Treatment Arms 1-6 reach Day 7 and/or once all patients in Arms 7 and 8 reach Day 7. Periodic adjustments to the allocation ratio may be made to achieve the planned allocation across Treatment Arms at the conclusion of enrollment. If additional placebo participants are enrolled, then the allocation ratio may change accordingly.

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

6.15.2. Data Monitoring Committee/Assessment Committee

The sponsor will form an AC to analyze the interim study data. To minimize any bias introduced into the analysis of the study results, analysis plans will be finalized and approved prior to the interim analyses.

The primary goal of the AC is to review the interim results regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. Information that

may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded. If necessary to inform time critical decisions of additional dose(s) to be studied in the program, in order to more effectively address unmet medical needs, questions with simple (e.g. yes/no) answers may be posed to the AC. These questions will be specified in the AC Charter, and the AC will communicate recommendations to the senior management designee.

Overall committee structure information is in Protocol Section 10.1.5. Details of the AC will be provided in the AC charter. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

6.16. Planned Exploratory Analyses

6.16.1. Protocol-Defined Exploratory Endpoint

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

6.16.2. Additional Exploratory Analyses Not Defined in the Protocol

6.16.2.1. SpO_2 AUC

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 active treatment minus placebo) will be calculated and presented with their corresponding 95% CIs. All available data will be used in the analysis.

6.16.2.2. Symptom Questionnaire

See Appendix 1 for further details regarding the symptoms and overall clinical status participant questionnaire.

6.16.2.2.1. Loss of Appetite and Changes in Taste and Smell

Participants will rate the loss of appetite and changes in taste and smell with yes/no responses. Responses at Days 3, 5, 7, 11, 22, and 29 will be summarized by treatment in frequency tables and listed.

6.16.2.2.2. Overall Clinical Status

Participants will complete questions about their overall clinical status. Responses at Days 3, 5, 7, 11, 22, and 29 will be summarized by treatment in frequency tables and listed.

6.16.2.3. NIAID Score

See Appendix 3 for further details regarding the NIAID scoring scale.

6.16.2.3.1. Worst NIAID Score

The lowest daily value from Day 1 through Day 11 for a patient on the NIAID ordinal scale will be summarized by treatment groups. Mean value by treatment group will be plotted over time.

6.16.2.3.2. Clinical Worsening Based on the NIAID Scale

Clinical worsening is defined as the proportion (percentage) of participants with any worsening on the NIAID ordinal scale from baseline to Days 3, 5, 7, 11, 22, and 29.

6.16.2.4. National Early Warning Score (NEWS2)

See Appendix 4 for further details regarding the NEWS2 scoring scale.

6.16.2.4.1. Highest Daily NEWS2 Score

The highest daily value from Day 1 through Day 11 for a patient on the NEWS2 ordinal scale will be summarized by treatment groups. Mean value by treatment group will be plotted over time.

6.16.2.4.2. NEWS2 Consciousness Level

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

6.16.2.5. NIAID/NEWS2 Overall Improvement

Overall improvement on the ordinal scales (NIAID, NEWS2) will be summarized by treatment group from baseline to Days 3, 5, 7, 11, and 29.

6.16.2.6. 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 and assessment period.

Time to hospitalization will be evaluated during the study treatment and assessment period only and will be summarized by treatment and listed. Cox proportional hazard model will be used.

Time to hospitalization may be presented graphically.

6.16.2.7. Duration of Hospitalization

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

6.16.2.8. 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 and assessment period.

Time to ICU will be summarized by treatment group for those patients who are admitted to the ICU.

Time to ICU may be presented graphically.

6.16.2.9. 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") will be summarized separately by treatment group. These endpoints will be evaluated thru Days 7, 11, 15, 22, and 29.

If an event (hospitalization, ICU, or Mechanical Ventilation) occurs, the participant will be defined as having had the event for all subsequent timepoints evaluated. For example, if a participant experiences a hospitalization on day 8, their hospitalization status would be defined as:

- 'No' for the evaluation of hospitalization thru day 7, and
- 'Yes' for hospitalization thru Days 11, 15, 22, 29.

No imputation will be used as these endpoints are based on running records; i.e., an event is only reported if they are observed.

6.16.2.10. 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 active treatment and placebo.

6.16.2.11. SpO2 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 as a fixed effect and baseline SpO_2 as a covariate in the model. Missing values will be considered to be missing completely at random (MCAR).

6.16.2.12. Viral Load Plots

The 7th octile (87.5th percentile) for the observed viral load data will be plotted across Days 1, 3, 5, 7, and 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 Days 1, 3, 5, 7, and 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.

6.16.2.13. Variants

Baseline and treatment-emergent variants may be identified, and the results may be described descriptively by treatment group. Additionally, subgroup analyses may be performed by baseline variants.

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).
- AE reporting is consistent with other document disclosures (e.g., the CSR, manuscripts, and so forth).

6.19. Analyses for the Open-Label Addendum Substudies

6.19.1. General Considerations

Data from participants in the substudies will be summarized separately from participants in the main PYAH study and separately for each addendum. 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 substudy will not include inferential analyses.

This table defines the populations for the analysis of the substudies.

Population	Description
Entered - Addendum	**Definition**: All participants who sign the informed consent form for the addendum. **Purpose**: Used for disposition analysis. **Treatment Groups**: None **Inferential Comparisons**: None

Efficacy - Addendum	**Definition**: All participants who were allocated and received study intervention in the addendum and provided at least one postbaseline measure for the relevant endpoint. Participants will be analyzed according to the intervention to which they were allocated (intention to treat).
	Purpose: Used for efficacy and pharmacodynamic variables analyses.
	Treatment Groups (Short Label):
	Addendum (2):
	700 mg LY3819253, 15-minute infusion (700 LY, 15-min), 700 mg LY3819253 and 1400 mg LY3832479, 30-minute infusion rate (700/1400 LY/LY2, 30-min), 700 mg LY3819253 and 1400 mg LY3832479, 15-minute infusion rate (700/1400 LY/LY2, 15-min).
	CCI [redacted]
	Addendum (4):
	• Arm A – intravenous (IV)
	  • 70 mg LY3853113, 140 mg/min (Dose A-1), placebo (Dose A-1 Pbo)
	  • 175 mg LY3853113, 140 mg/min (Dose A-2a), placebo (Dose A-

	2a Pbo) • 175 mg LY3853113, 350 mg/min (Dose A-2b), placebo (Dose A-2b Pbo) • 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479, 350 mg/min (Dose A-2c), placebo (Dose A-2c Pbo) • 1750 mg LY3853113, 350 mg/min (Dose A-3), placebo (Dose A-3 Pbo) • Arm B – subcutaneous (SC) • 280 mg LY3853113 (Dose B-1), placebo (Dose B-1 Pbo) • 560 mg LY3853113 (Dose B-2), placebo (Dose B-2 Pbo) Additional optional arms may be added if decided. **Inferential Comparisons**: None
Safety - Addendum	**Definition**: All participants allocated to treatment in the addendum and who received study intervention. Participants will be analyzed according to the intervention they actually received. **Purpose**: Used for safety analyses, analyses of COVID-19-related hospitalization or death from any cause. **Treatment Groups (Short Label)**: *Addendum (2):* 700 mg LY3819253, 15-minute infusion (700 LY, 15-min), 700 mg LY3819253 and 1400 mg LY3832479, 30-minute infusion rate (700/1400 LY/LY2, 30-min), 700 mg LY3819253 and 1400 mg LY3832479, 15-minute infusion rate (700/1400 LY/LY2, 15-min), CCI [redacted] • Arm A – intravenous (IV) • 70 mg LY3853113, 140 mg/min (Dose A-1), placebo (Dose A-1 Pbo) • 175 mg LY3853113, 140 mg/min (Dose A-2a), placebo (Dose A-2a Pbo) • 175 mg LY3853113, 350 mg/min (Dose A-2b), placebo (Dose A-2b Pbo) • 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479, 350 mg/min (Dose A-2c), placebo (Dose A-2c Pbo) • 1750 mg LY3853113, 350 mg/min (Dose A-3), placebo (Dose A-3 Pbo) • Arm B – subcutaneous (SC) • 280 mg LY3853113 (Dose B-1), placebo (Dose B-1 Pbo) • 560 mg LY3853113 (Dose B-2), placebo (Dose B-2 Pbo) Additional optional arms may be added if decided. **Inferential Comparisons**: None

Pharmacokinetic - Addendum	**Definition**: All participants who were allocated and received study intervention in the addendum and have evaluable pharmacokinetic sample. Participants will be analyzed according to the intervention they received.
	Purpose: Used for pharmacokinetic analyses.
	Treatment Groups (Short Label):
	Addendum (2):
	700 mg LY3819253, 15-minute infusion (700 LY, 15-min), 700 mg LY3819253 and 1400 mg LY3832479, 30-minute infusion rate (700/1400 LY/LY2, 30-min), 700 mg LY3819253 and 1400 mg LY3832479, 15-minute infusion rate (700/1400 LY/LY2, 15-min).
	CCI [redacted]
	Addendum (4):
	• Arm A – intravenous (IV)
	  • 70 mg LY3853113, 140 mg/min (Dose A-1), placebo (Dose A-1 Pbo)
	  • 175 mg LY3853113, 140 mg/min (Dose A-2a), placebo (Dose A-2a Pbo)
	  • 175 mg LY3853113, 350 mg/min (Dose A-2b), placebo (Dose A-2b Pbo)
	  • 175 mg LY3853113 + 700 mg LY3819253 + 1400 mg LY3832479, 350 mg/min (Dose A-2c), placebo (Dose A-2c Pbo)
	  • 1750 mg LY3853113, 350 mg/min (Dose A-3), placebo (Dose A-3 Pbo)
	• Arm B – subcutaneous (SC)
	  • 280 mg LY3853113 (Dose B-1), placebo (Dose B-1 Pbo)
	  • 560 mg LY3853113 (Dose B-2), placebo (Dose B-2 Pbo)
	Additional optional arms may be added if decided.
	Inferential Comparisons: None

Participant disposition will be summarized by treatment group and infusion rate and/or administration route in a similar manner as the main study (see Section 6.6).

Participant characteristics will be summarized by treatment group and infusion rate and/or administration route in a similar manner as the main study (see Section 6.7).

Treatment compliance will be summarized by treatment group and infusion rate and/or administration route in a similar manner as the main study (see Section 6.8).

Prior medication(s) and concomitant therapies summarized by treatment group and infusion rate and/or administration route in a similar manner as the main study (see Section 6.9).

The primary objective for the substudies is to characterize the safety and tolerability of LY3819253 alone, and in combination with LY3832479; and LY3853113 alone, and in

combination with LY3819253 and LY3832479. Safety endpoints include safety assessments such as AEs and SAEs. All safety analyses will be summarized by treatment group and infusion rate and/or administration route in a similar manner as the main study (see Section 6.12).

The secondary PK objective for the substudies is to characterize the PK of LY3819253 alone, and in combination with LY3832479 and LY3853113 alone, and in combination with LY3819253 and LY3832479. The secondary PK endpoint is mean concentration of LY3819253 alone, and in combination with LY3832479 and LY3853113 alone, and in combination with LY3819253 and LY3832479 on Day 29. The PK endpoint will be summarized by treatment group and infusion rate and/or administration route in a similar manner as the main study (see Section 6.11).

The secondary efficacy objective for the substudies is to characterize the SARS-CoV-2 viral load and viral clearance for participants who received LY3819253 alone, and in combination with LY3832479; and LY3853113 alone, and in combination with LY3819253 and LY3832479. The following are the secondary efficacy endpoints:

- Change from baseline in SARS-CoV-2 viral load to:
  - Day 3
  - Day 5
  - Day 7
  - Day 11
- Proportion of participants with viral load greater than 5.27 on Day 7
- Time to SARS-CoV-2 clearance
- SARS-CoV-2 viral load AUC assessed through Day 11
- For addendum (2)[redacted]:
  - Proportion of participants with viral load greater than 5.27 on Day 7 among participants enrolled with ≤8 days of symptoms prior to randomization
  - Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11, and 29)

The secondary efficacy endpoints will be summarized by treatment group and infusion rate and administration, as appropriate, in a similar manner as the main study (see Section 6.10).

The exploratory efficacy objectives for the substudies are to characterize overall participant clinical status, viral load, and symptom resolution and improvement. The following are the exploratory efficacy endpoints:

- For addendum (2)[redacted]:
  - Proportion (percentage) of participants who experience these events by Day 22, 29, 60, and 85
    - COVID-19 related hospitalization (defined as ≥24 hours of acute care)
    - Death from any cause
  - Proportion (percentage) 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
    - Time to symptom resolution
    - Proportion of participants demonstrating symptom resolution via the symptom questionnaire on Days 3, 5, 7, 11, 22, and 29
    - Change in symptom score (total of ratings) from baseline up to Days 7, 11, 22, and 29.
    - Time to symptom improvement
    - Proportion of participants demonstrating symptom improvement via the symptom questionnaire on Days 3, 5, 7, 11, 22, and 29
- For addendum (4):
    - Duration, in days, of hospitalizations,
    - Proportion of participants admitted to the ICU
    - Proportion of participants requiring mechanical ventilation
    - Proportion of participants that achieve SARS-CoV-2 clearance (Days 3, 5, 7, 11, and 29)
    - 75th percentile of SARS-CoV-2 viral load at Day 7
    - Characterize emergence of viral resistance to LY3853113

The exploratory efficacy endpoints will be summarized by treatment group and infusion rate and/or administration route in a similar manner as the main study (see Section 6.10).

Additional analyses may be performed for the substudies.

An interim analysis of safety data may be conducted at any time for participants who have reached Day 3.

7. References

Firth D. Bias reduction of maximum likelihood estimates. *Biometrika.* 1993;80(1):27-38. https://doi.org/10.2307/2336755

8. Appendices

Appendix 1. Symptoms and Overall Clinical Status Participant Questionnaire

Participants will rate their overall clinical status and severity of symptoms associated with COVID-19 by a 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 by the participant as experienced during the past 24 hours.

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).

Appendix 2. Definitions of Adverse Events and Serious Adverse Events

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

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

Events NOT Meeting the AE Definition
• The following study-specific clinical events related to COVID-19 are exempt from adverse event reporting unless the investigator deems the event to be related to the

administration of study drug:

- Hypoxemia due to COVID-19 requiring supplemental oxygen;
- Hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen devices;
- Respiratory failure due to COVID-19 requiring invasive mechanical ventilation or ECMO

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

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE

should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

Appendix 3. 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.1.2. 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: NIAID = National Institute of Allergy and Infectious Diseases.

Appendix 4. 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 the hospital. Six simple physiological parameters form the basis of the scoring system:

- respiration rate
- oxygen saturation
- systolic blood pressure
- pulse rate
- level of consciousness or new confusion
- temperature

Figure APP.1.1. NEWS2 Scoring

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.1.2. NEWS2 Scoring Clinical Risk Thresholds

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.

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).

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