J2W-MC-PYAB Statistical Analysis Plan Addendum 4

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

NCT04427501

Approval Date: 15-Aug-2022

1. Supplemental Statistical Analysis Plan: J2W-MC-PYAB: A Randomized, Double-Blind, Placebo-Controlled, Phase 2/3 Study to Evaluate the Efficacy and Safety of LY3819253 and LY3832479 in Participants with Mild to Moderate COVID-19 Illness; Addendum 4

LY3853113 - Mild to Moderate COVID-19 Illness

This addendum is a Phase 2, single-arm, open label, uncontrolled, single-dose study in participants with mild to moderate COVID-19 illness to evaluate the pharmacokinetics and safety of bebtelovimab (LY3853113) in the pediatric population.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol J2W-MC-PYAB
Phase 2/3

Supplemental Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on date provided below.

Approved on 15 Aug 2022 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table of Contents

Figure **Page**

Table of Contents

Appendix **Page**

3. Revision History

Supplemental Statistical Analysis Plan (SAP) Version 1 was approved prior to initial enrollment of Addendum 4.

DOCUMENT HISTORY	
Document	**Date**
Original Supplemental SAP	See approval date on cover page

Overall Rationale for the Supplemental SAP:

Addendum 4.2 added a new treatment arm to this study to evaluate bebtelovimab in pediatric patients 0 (≥ 38 weeks gestational age and ≥ 3.3 kg) to less than 12 years of age OR 12 to 17 and weigh <40kg. This supplemental SAP summarizes the set of analyses for this cohort.

4. Study Objectives

4.1. Primary Objective

The primary objective of this trial addendum is to characterize the pharmacokinetics of bebtelovimab after intravenous injection among pediatric participants with mild to moderate COVID-19 illness. The primary endpoint is the area under the concentration-time curve (AUC) from 0 to infinity for bebtelovimab.

4.2. Secondary Objectives

4.3. Secondary Objectives

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

Objectives	Endpoints
Safety description	Safety assessments such as AEs and SAEs

Abbreviations: AE = adverse event; SAE = serious adverse event.

4.4. Exploratory Objectives

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

Objectives	Endpoints
Overall participant clinical status	Proportion (percentage) of participants who experience the following events by Days 22, 29, 60 and 85 COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death from any cause Proportion (percentage) of participants who experience the following events by Day 29 a COVID-19 related emergency room visit, or COVID-19 related hospitalization (defined as ≥24 hours of acute care), or death from any cause
SARS-CoV-2 viral load reduction	Change from baseline to Day 5 Day 7 Day 11 SARS-CoV-2 viral load area under the response-time curve (AUC)
Symptoms and resolution	Time to absence of all symptoms Time to sustained absence of all symptoms Proportion of participants demonstrating absence of symptoms
Characterize emergence of viral resistance to bebtelovimab	Comparison from baseline to the last evaluable time point
Safety	Proportion (percentage) of participants who experience MIS-C

Abbreviations: AUC = area under the response-time curve; COVID-19 = coronavirus disease 2019; MIS-C = multisystem inflammatory syndrome in children; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

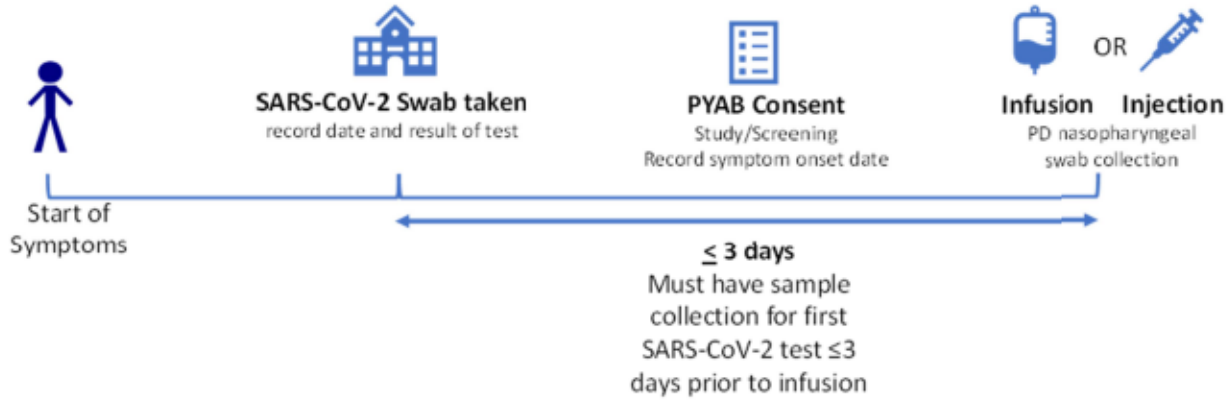
Additional exploratory objectives not previously defined in the protocol are described in Section 6.16.2.

5. Study Design

5.1. Summary of Study Design

This is a Phase 2, single-arm, open-label, single-dose study in pediatric participants with mild to moderate COVID-19 illness.

5.2. Design Outline



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

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

5.2.1. Screening

The participant or legally authorized representative will sign the appropriate informed consent and/or assent document(s) prior to completion of any procedures. The participant may enter the study with a first positive result sample of current SARS-CoV-2 viral infection within 3 days of study treatment administration.

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

5.2.2. 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 enrolled in the intervention group
participants receive study intervention, and
complete all safety monitoring and post-dose sample collection.

Table PYAB.5.1 describes the weight-based dosing for the planned treatment arm (Arm 23) for Addendum 4.

Table PYAB.5.1. Weight Group Doses for Treatment Arm 23 of Study J2W-MC-PYAB

Weight Group	Bebtelovimab Dose
≥3.3 to ≤12 kg	3 mg/kg
>12 to ≤20 kg	43.75 mg
>20 to <40 kg	87.5 mg
≥40 kg	175 mg

5.2.3. Posttreatment Follow-up

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

5.3. Determination of Sample Size

Sample Size

There is an urgent unmet need among pediatric patients since there are no approved vaccines for the prevention of COVID-19 in pediatric patients <6 months of age and no FDA-approved therapies effective for treatment of the Omicron variant in patients <12 years or outside the existing bebtelovimab EUA criteria. Consequently, this study will include SARS-CoV-2 positive pediatric patients with mild to moderate disease that are 0 (≥38 weeks gestational age and ≥ 3.3 kg) to <12 years of age, or 12 to 17 years of age and weighing <40 kg.

The planned sample size is approximately 50 participants that are 0 (≥38 weeks gestational age and ≥ 3.3 kg) to 12 years of age, with a minimum of 5 participants in each of these age groups

0 to <2
2 to <6 years, and
6 to <12 years

Participants who are 12 to 17 years of age and weighing less than 40 kg can be enrolled into the study until approximately 50 participants that are 0 (≥38 weeks gestational age and ≥ 3.3 kg) to 12 years of age are fully enrolled.

Fifty participants would provide adequate study power to target a 95% confidence interval within 60% to 140% of the geometric mean estimates of clearance and volume of distribution (Wang et al. 2012) for bebtelovimab as can be seen in Figure PYAB.5.2.

Participants who are 12 to 17 years (and weighing <40 kg) can be enrolled, up to approximately 20 participants. Enrollment for this group may continue (up to 20 participants) until approximately 50 participants <12 years have been fully enrolled.

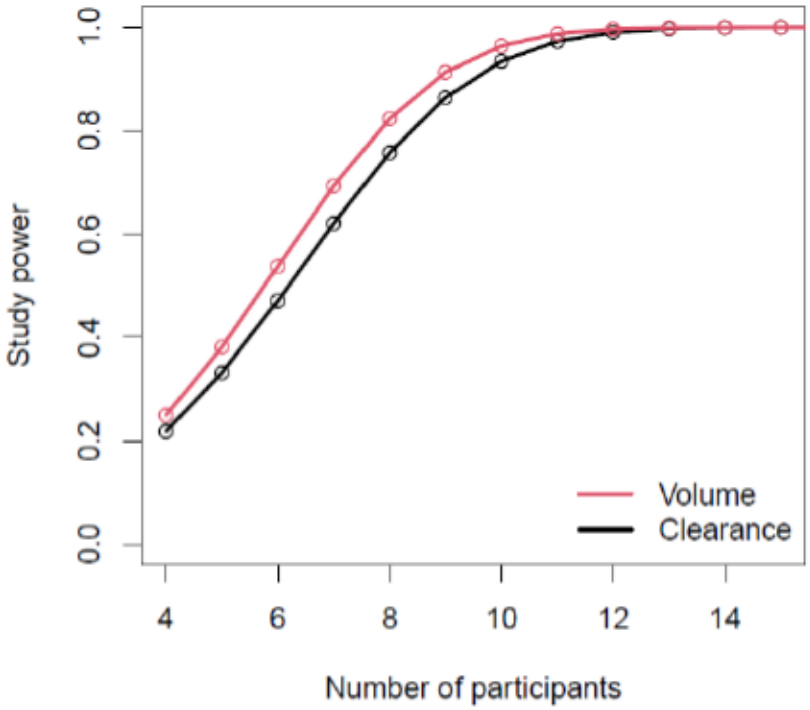


Figure PYAB.5.2. Estimated study power to target a 95% confidence interval within 60% to 140% of the geometric mean estimates of clearance and volume of distribution.

Stratification

As this is a single-arm cohort, participants will be stratified for analysis only. Participants will be stratified by

age at the time of screening (0 to <2, 2 to <6 years, 6 to <12 years, and 12 <18 years of age),
weight category (≥3.3 to ≤12 kg, >12 to ≤20 kg, >20 to <40 kg, and ≥40 kg), and
whether a participant received a SARS-CoV-2 vaccine or not prior to screening.

5.4. Method of Assignment to Treatment

5.4.1. Randomization

This is a single-arm cohort, so randomization is not applicable.

5.4.2. Blinding

As a single-arm cohort, treatment assignment will be unblinded.

6. A Priori Statistical Methods

6.1. General Considerations

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

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

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.

Subgroup analyses (by age and weight categories, see Section 5.3) will be performed as appropriate and include descriptive statistics only.

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

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

Any analyses of exploratory endpoints or sensitivity analyses will be done only if considered warranted by the team, based upon sufficient sample size.

6.1.1. Analysis Populations

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

Table PYAB.6.1. Analysis Populations

Population	Description
Entered	**Definition:** All participants who signed informed consent/assent. **Purpose:** Used for disposition analysis. **Treatment Groups:** None **Inferential Comparisons:** None
Per-Protocol	**Definition:** All participants in the efficacy population who do not meet any of the following criteria: did not meet an inclusion criterion; or met an exclusion criterion. **Purpose:** Used for sensitivity analyses for the primary and key secondary endpoints. **Treatment Groups (Short Label):** Bebtelovimab weight-based dosing. **Inferential Comparisons:** None, as this is a single-arm cohort.
Efficacy	**Definition:** All enrolled participants who received study intervention and provided at least 1 postbaseline efficacy measurement. **Purpose:** Used for efficacy variable analyses. **Treatment Groups (Short Label):** Bebtelovimab weight-based dosing. **Inferential Comparisons:** None, as this is a single-arm cohort
Safety	**Definition:** All enrolled participants who received any amount of study intervention. **Purpose:** Used for safety analyses, analyses of COVID-19-related deterioration and hospitalization events. **Treatment Groups (Short Label):** Bebtelovimab weight-based dosing. **Inferential Comparisons:** None, as this is a single-arm cohort.
Pharmacokinetic and PK/PD (exposure-response relationships)	**Definition:** All enrolled participants who received study intervention and have at least 1 post dose PK sample. **Purpose:** Used for PK analyses. **Treatment Groups (Short Label):** Bebtelovimab weight-based dosing. **Inferential Comparisons:** None, as this is a single-arm cohort.

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

6.1.2. Definition of Study Baseline

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

Baseline for safety analyses is described in the safety section.

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

6.1.3. Study Time Intervals

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

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

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

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

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

Table PYAB.6.2. Definition of Study Period Time Intervals

Study Period	Interval Start Definition	Interval End Definition
Screening: All participants who sign informed consent/assent are considered as entering the Screening Period.	Informed consent/assent date	Prior to the start of Treatment and Assessment Period.
Treatment and Assessment Period: All participants who have treatment initiated are considered as entering the Treatment Period.	At the start of study drug administration date/time.	The minimum of treatment period discontinued date, study discontinuation date, or first Post-Treatment Follow-Up visit date.
Post-Treatment Follow-Up: All participants who had a follow-up visit are considered as entering follow-up period.	After the Treatment and Assessment Period ends.	The maximum of the last study visit date or study disposition date.

6.1.4. Analysis Methods

Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. SARS-CoV-2 viral load data will be evaluated in log base 10 scale. The parametric approach will be employed by default for statistical analysis except when nonparametric

analysis, such as by a rank-based method, Mann-Whitney, or van Elteren tests, is deemed to be more appropriate.

Unless otherwise specified, confidence intervals for estimated values using frequentist approaches will be at a 95% level.

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

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

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

Visit-wise estimates of continuous efficacy, and pharmacodynamic variables with multiple postbaseline measurements will be made using MMRM analysis. When MMRM is used, it includes: (a) baseline value in the model, and (b) visit. 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. Statistical comparisons and relevant degrees of freedom estimation method are not relevant. Unless otherwise specified, for MMRM, reported data from only planned visits will be used as the primary analysis.

Estimates of continuous efficacy, safety, and health outcome variables with a single postbaseline timepoint will be made using analysis of covariance (ANCOVA) with baseline value in the model. The LS mean, standard error, and 95% CI, unless otherwise specified, will also be reported. Missing data imputation method for the ANCOVA model is specified in Section 6.3.

Estimates of binary endpoints will be made using logistic regression. The model will include the weight range groups used for dosing, unless otherwise noted. The CIs of any rate estimates will be reported.

The Kaplan-Meier (KM) product limit method will be used for time-to-event analyses. Time for all analyses will be described in units of days.

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

6.2. Adjustments for Covariates

Unless otherwise specified, efficacy analyses will adjust for the baseline value of the endpoint and by dosing weight category when modeling estimates.

6.3. Handling of Dropouts or Missing Data

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

6.3.1. Non-Responder Imputation

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

6.3.2. Modified Non-Responder Imputation

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

If a participant has previously achieved viral clearance (i.e., the participant previously had 2 consecutive negative tests), then viral clearance will be imputed as "Yes."

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

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

6.3.3. Mixed-Effects Model Repeated Measures

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

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

6.3.4. Highest Disease States Imputation

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

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

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

6.3.5. Last Observation Carried Forward

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

6.3.6. Modified Last Observation Carried Forward

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

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

6.4. Multicenter Studies

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

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

6.5. Multiple Comparisons/Multiplicity

Treatment Arm 23

Control for multiplicity is not applicable as this is a single-arm cohort.

6.6. Participant Disposition

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

All participants who are treated and discontinued from study treatment or from the study will be listed, and the timing of discontinuing the study (from treatment date) 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 treatment to early permanent discontinuation of study or study treatment due to AEs may be generated if there are a substantial number of such events.

Table PYAB.6.4. Tables and Figures Related to Disposition

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

6.7. Participant Characteristics

Patient demographic variables and baseline characteristics will be summarized 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. By-patient listings of basic demographic characteristics (i.e., age, sex, race, racial subgroup, ethnicity, and body weight) for the efficacy population will be provided.

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

Analysis	Details
Baseline Demographic Characteristics	**Variables to be included:** • Age • Age groups (<2, ≥2 to <6, ≥6 to <12, and ≥12 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 • SpO_2 • SpO_2 category (<96%, ≥96%) • COVID-19 disease severity category • High-risk status for severe COVID-19 illness (BMI ≥ 30 or a medical history event of interest) • SARS-CoV-2 vaccine status (none, partial, full, boosted) **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)
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 Preexisting conditions are defined as those conditions with a start date prior to the first dose of the study drug and stop dates that are at or after the informed consent date or have no stop date (i.e., are ongoing).
Prior Therapy of Interest	Number and percentage of participants with prior medication of interest will be displayed as "Prior medications"
Listing demographics	--

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

6.8. Treatment Compliance

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

6.9. Prior Medication and Concomitant Therapy

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

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

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

Table PYAB.6.6. Summary Tables Related to Concomitant Medications

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

6.10. Efficacy Analyses

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

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

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

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

- A normalization step will also be applied. The viral load Ct value described in the previous steps will be subtracted by (RP Ct – 26.17), where RP Ct is a measure for the amount of material in the sample and 26.17 is a historical average value of RP Ct for this assay, used here to center the RP Ct values.

6.10.1. Primary Outcome and Methodology

Treatment Arm 23

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

6.10.2. Additional Analyses of the Primary Outcome

Not applicable for this cohort.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

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

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

A limited number of pre-identified individuals may gain access to interim data prior to the primary lock, in order to initiate the population PK/PD model development processes.

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

change from baseline in SARS-CoV-2 viral load (Days 5, 7, and 11)
AUC, and
time to SARS-CoV-2 clearance.

Additional PK/PD concentration-response analysis may be performed.PK/PD analyses on adolescents in the study will be treated as secondary to support the pediatric analyses.

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.

6.12.1. Baseline and Postbaseline Definitions for Safety Groups

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

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

Abbreviation: TEAE = treatment-emergent adverse event.

6.12.2. Extent of Exposure

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

6.12.3. Adverse Events

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

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

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

Treatment-Emergent Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The

maximum severity for each LLT during the baseline period will be used as baseline. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the baseline period, it will be treated as "mild" in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment emergence will be determined by comparing with baseline severity. Missing severity will be reported as missing, without imputation, for data listing.

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

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

Event Type	Summary Method
SAEs	SAEs will be summarized 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 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 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, when not counting the serious TEAEs, will be tabulated by SOC and PT. These reports will also present the total number of TEAEs for each SOC and PT.

Additional Types of Adverse Events to be Summarized

Event Type	Summary Method
Infusion Reactions	Treatment-emergent infusion reactions will be summarized by PT within high level term (HLT).

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

SOC Mapping

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

Events Not Summarized

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

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

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

deaths

serious adverse events, and

discontinuations of study treatment due to AEs.

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

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

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

The following events (observed at any time point during the study treatment period) will be summarized as described in Sections 6.16.2.1, 6.16.2.2, 6.16.2.3, and Section 6.16.2.4.

proportion of participants hospitalized

duration of hospitalization (DOH; in days)

proportion (percentage) of participants admitted to Intensive Care Unit (ICU), and proportion (percentage) of participants requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation")

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

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

6.12.6. Clinical Laboratory Evaluation

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

6.12.7. Vital Signs and Other Physical Findings

The planned summaries are provided in Table PYAB.6.9. 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 PYAB.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 PYAB.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 PYAB.6.9. Tables and Figures Produced to Support Vital Signs and Physical Characteristics

Analysis Type	Analysis Details
Box plots for observed values by visit	Includes participants who have both a baseline and a postbaseline measurement from a planned visit. Unplanned measurements will be excluded. Last baseline will be used. Descriptive summary statistics will be included in a table below the box plot. No inferential statistics.
Box plots for change from baseline values by visit	Includes participants who have both a baseline and a postbaseline planned measurement. Unplanned measurements will be excluded. Last baseline will be used. Descriptive summary statistics will be included in a table below the box plot. Change from last baseline to last postbaseline will also be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot along with a p-value using the ANCOVA model.
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	Each study individually and studies combined will be displayed. Includes participants who have both a baseline and postbaseline observation. Unplanned measurements will be included. Lines indicating the reference limits will be included. **Max versus Max:** Maximum baseline versus maximum postbaseline. **Min versus Min:** Minimum baseline versus minimum postbaseline.
Summary tables for shifts to high/low	Limits provided by the central lab service will be used to define low and high. **Normal/high to low:** Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum postbaseline result is low. Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 postbaseline result. **Normal/low to high:** Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum postbaseline result is high. Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period. ☐ Statistical comparisons will be included.

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

Table PYAB.6.10. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement in Pediatric Individuals

Age		Systolic BP, mm Hg (supine or sitting forearm at heart level)	Diastolic BP, mm Hg (supine or sitting forearm at heart level)	Pulse/HR bpm (supine or sitting)
Infant <2	Low High[a]	≤70 and decrease ≥15 ≥108 and increase ≥15	≤35 and decrease ≥10 ≥74 and increase ≥10	<70 and decrease ≥25 >190 and increase ≥25
Child 2-4	Low High[a]	≤75 and decrease ≥15 ≥110 and increase ≥15	≤40 and decrease ≥10 ≥76 and increase ≥10	<60 and decrease ≥25 >160 and increase ≥25
Child 5-9	Low High[a]	≤80 and decrease ≥15 ≥119 and increase ≥15	≤45 and decrease ≥10 ≥78 and increase ≥10	<60 and decrease ≥25 >150 and increase ≥25
Child 10-12	Low High[a]	≤85 and decrease ≥20 ≥126 and increase ≥20	≤50 and decrease ≥10 ≥82 and increase ≥10	<60 and decrease ≥25 >140 and increase ≥25
Adolescent >13	Low High[a]	≤90 and decrease ≥20 ≥129 and increase ≥20	≤50 and decrease ≥10 ≥86 and increase ≥10	<50 and decrease ≥15 >120 and increase ≥15

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

[a]The high limit values shown in this table correspond to 95th percentile for the age group under the 2017 ACC/AHA Task Force on Clinical Practice Guidelines revised criteria for hypertension. Values higher than 95th percentile are consistent with Stage 1 or Stage 2 hypertension. Under some circumstances it may be appropriate to conduct analyses considering only the change from baseline reference limit.

6.12.8. Electrocardiograms

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

6.12.9. Immunogenicity

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

Treatment-emergent ADAs are defined as participants

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

with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

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

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

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

6.13. Subgroup Analyses

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

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

time from symptom onset to study treatment

baseline severity of COVID-19

age group (<2, 2 to <6, 6 to <12, 12 years and older)

gender (male, female)

race

ethnicity

baseline weight (≥3.3 to ≤12 kg, >12 to ≤20 kg, >20 to <40 kg, ≥40 kg)

concomitant medication of interest use (yes/no)

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

Concomitant therapies of interest include remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine, anticoagulants, dexamethasone, or other investigational interventions. Details of the medications included in this subgroup are provided below in Table PYAB.6.11.

Table PYAB.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.

6.14. Protocol Violations

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

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

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

A by-patient listing of IPDs will be provided.

6.15. Interim Analyses and Data Monitoring

6.15.1. Interim Analyses

No formal interim analyses are planned for this cohort.

Unblinding

This is an open-label, single-arm cohort, so unblinding is not applicable. However, only a limited number of individuals will have access to aggregated summary data prior to the final DBL for this cohort. To minimize any bias introduced into the analysis of the study results, the initial version of this SAP will be finalized and approved prior to initiating enrollment to this cohort.

6.15.2. Data Monitoring Committee/Assessment Committee

No data monitoring committee or assessment committee is planned for this cohort, as there are no preplanned interim analyses.

6.16. Planned Exploratory Analyses

6.16.1. Protocol-Defined Exploratory Endpoints

Protocol defined exploratory endpoints are described in Section 4.4 and analysis details are provided in the following sections.

6.16.1.1. SARS-CoV-2 Viral Load

Change in viral load from baseline to Days 5, 7, and 11 will be assessed. An MMRM analysis will be employed to estimate the mean at each day, accounting for the effects of any missing data via the intrapatient covariance structure.

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

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

The AUC will be summarized and plotted for the cohort and listed.

6.16.1.2. Symptom Resolution

Participants will be assessed for the presence of symptoms associated with COVID-19 by a daily questionnaire. This questionnaire is for outpatient participants only.

The questionnaire contains these symptoms:

shortness of breath or difficulty breathing

congestion or runny nose

fever

chills

sore throat

stomachache

nausea

vomiting

diarrhea

cough

tiredness

muscle or body aches and pains

headache

loss of taste

loss of smell

poor appetite or poor feeding

The presence or absence of symptoms associated with COVID-19 within the past 24 hours will be collected from participants or their parents/legal guardian.

Symptom resolution is defined as all symptoms on the symptom questionnaire scored as absent.

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

6.16.1.3. Time to Symptom Resolution and Sustained Symptom Resolution

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

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

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

Time to symptom resolution will be evaluated during the study treatment period only and will be summarized and listed.

Time to symptom resolution will be presented graphically.

Sustained symptom resolution occurs at the first visit where symptom resolution is observed without reoccurrence at any subsequent visits. Time to sustained symptom resolution in the same manner as described for initial symptom resolution and will be analyzed and summarized in the same way.

6.16.1.4. COVID-19-Related Deterioration (COVID-19-Related Hospitalization, or Death from Any Cause)

The proportion (percentage) of participants who experience COVID-19 related deterioration, defined as experiencing either of the following events by Day 22, 29, 60 and 85 will be analyzed:

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

In addition, the proportion (percentage) of participants who experience any of the following events by Day 29 will be analyzed:

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

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

6.16.1.5. Viral Resistance

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

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

Additional analyses include:

6.16.2.1. Time to Hospitalization

Time to Hospitalization is defined (in days) as:

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

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

Time to hospitalization will be evaluated during the study treatment period only, summarized with the Kaplan-Meier survival plot and listed.

6.16.2.2. Duration of Hospitalization

Durations of hospitalization, for those admitted to a hospital after treatment will be listed.

6.16.2.3. Time to Admission to ICU

Time to ICU is defined (in days) as:

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

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

Time to ICU will be evaluated during the study treatment period only and summarized with a Kaplan Meier plot and listed.

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

The proportion of participants hospitalized, admitted to the ICU, requiring mechanical ventilation (oxygen source = "Intubation/Mechanical Ventilation") at any time may be summarized with those having an event also listed.

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

6.16.2.5. SpO_2 Measurements of Interest

The proportion of participants experiencing a treatment emergent SpO_2 measurement of interest (<96%, ≥ 96%), (<92%, ≥92%) through Day 11 and through Day 29 will be summarized.

6.16.2.6. Viral Load Plots

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

The 4th, 5th, 6th, and 7th octile for viral load data adjusted for days from symptom onset at baseline will be plotted across Day 1, Day 5, Day 7, and Day 11. 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.

6.17. 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 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 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 may not be included if a 5% threshold is chosen (5% is the minimum threshold).

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

7. References

Betts A, Keunecke A, van Steeg TJ, et al. Linear pharmacokinetic parameters for monoclonal antibodies are similar within a species and across different pharmacological targets: a comparison between human, cynomolgus monkey and hFcRn Tg32 transgenic mouse using a population-modeling approach. *mAbs*. 2018;10(5):751-764. https://doi.org/10.1080/19420862.2018.1462429

Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*. 2005;61(3):738-748. https://doi.org/10.1111/j.1541-0420.2005.00344.x

Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical Decision Making*. 2013:33(5):607-617. https://doi.org/10.1177/0272989x12458724

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

Gould AL. BMA-Mod: a Bayesian model averaging strategy for determining dose-response relationships in the presence of model uncertainty. *Biom J*. 2019;61(5):1141-1159. https://doi.org/10.1002/bimj.201700211

[OCP] Office of Clinical Pharmacology Division of Pharmacometrics. Request for qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. Available at: https://www.fda.gov/media/99313/download. Published 2015.

8. Appendices

Appendix 1. NEWS2 Scoring Scale

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

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

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

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

Figure APP.1.1. NEWS2 scoring.

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

Abbreviation: NEWS2 = National Early Warning Score 2.

Figure APP.1.2. NEWS2 scoring clinical risk thresholds.

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

Signature Page for VV-CLIN-066190 v1.0

Approval	PPD 15-Aug-2022 16:21:50 GMT+0000

Signature Page for VV-CLIN-066190 v1.0