Statistical Analysis Plan: J2X-MC-PYAJ (version 3)

A Prospective Cohort Study to Evaluate the Real World Effectiveness of Bamlanivimab in Participants with Mild to Moderate COVID-19 at High Risk for Progressing to Severe.

NCT04701658

Approval Date: 13-Aug-2021

Statistical Analysis Plan:

Protocol J2X-MC-PYAJ: A Prospective Cohort Study to Evaluate the Real World Effectiveness of Bamlanivimab in Participants with Mild to Moderate COVID-19 at High Risk for Progressing to Severe

LY3819253 (bamlanivimab)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

J2X-MC-PYAJ
Phase 2

Approval Date: 13-Aug-2021 GMT

Table of Contents

Table of Abbreviations

Term	Definition
AE	adverse event
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CRF	case report form
COVID-19	coronavirus disease 2019
ED	emergency department
ER	emergency room
EDC	electronic data capture
EMR	electronic medical record
EUA	emergency use authorization
FDA	Food and Drug Administration
ICF	informed consent form
IQR	Interquartile range
IgG	immunoglobulin G
IPD	important protocol deviation
ISR	infusion site reaction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MSSO	MedDRA Maintenance and Support Services Organization
NM Health System	New Mexico Health System
PT	Preferred Term
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event

SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	Standardized MedDRA Query
SoA	schedule of activities
SOC	System Organ Class
SpO2	saturation of peripheral oxygen

1. Revision History

The first version of the Statistical Analysis Plan (SAP) for J2X-MC-PYAJ was approved prior to first patient visit.

Overall Rationale for the Revision on Version 2

Due to low enrollment, the minimum sample size required for the primary objective analysis could not be met; therefore, enrollment into the PYAJ study was terminated early, on 31 March 2021, due to infeasibility. Follow-up on patients treated with bamlanivimab enrolled in the study continued for 90 days, per protocol.

Based on the study's inability to enroll sufficient participants, no control group was utilized; therefore, no comparative analyses was conducted. All analyses were descriptive in nature and conducted only on bamlanivimab-treated participants, based on Electronic Data Capture (EDC) and Electronic Medical Record (EMR) data. The revisions in the SAP Version 2 updated analysis population and analysis methods reflect these decisions.

The SAP Version 2 was approved prior to the database lock. The changes incorporated in Version 2 are summarized as follows:

Section No. and Name	Description of Change	Brief Rationale
Table of Abbreviations	• Added and removed abbreviations	Propensity score matching method utilizing control group will not be conducted. Clarification of text.
2. Objectives and Endpoints	• Removed "compared to external controls" from all objectives • Added time periods, Days 60 and 90, to the primary objectives • Replaced death with all-cause death in the primary objectives • Replaced ED with ER	Comparative analyses utilizing the control group will not be conducted. Clarification of text. Changing from COVID-19-related death to all-cause death due to inability to distinguish the cause of death from EMR data. To distinguish with early discontinuation.
3.1. Summary of Study Design	• Removed language regarding matched or external control group • Added screening	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
3.2. Data Collection	• Removed language regarding matched or external control group	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
3.3. Sample Size Determination	• Updated sample size • Changed power to precision estimation • Removed power for subgroup analyses	Alignment with primary objective. Clarification of text.
3.4.1. Selection Criteria	• Removed insurance	Not relevant.

Section No. and Name	Description of Change	Brief Rationale
3.6. Endpoints	• Removed language regarding matched or external control group • Updated endpoints to reflect the objectives	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
3.7. Study Therapies	• Removed language regarding matched or external control group	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
3.8. Variables/Measures	• Removed language regarding matched or external control group • Clarified the definition of the study variables	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
General Considerations	• Removed language regarding matched or external control group	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
Populations Analysis	• Removed study populations related to matched controls • Updated population to include BAM-treated patients only	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
4.4.1. Pre-Matching Identification of Risk Factors as Matching Covariates 4.4.2. Primary Efficacy Outcome Analysis: COVID-19-Related Hospitalization or Death up to Day 29	• Removed as the control group and propensity score methods are not applicable	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
4.4.3. Primary Efficacy Outcome Analysis: COVID-19-Related Hospitalization or all-cause Death up to Days 29, 60, and 90	• Removed all comparative effectiveness analyses • Updated the analyses methods to descriptive	Clarification of text describing methodology.
4.4.4. Sensitivity Analyses for the Primary Objective	• Removed all comparative effectiveness analyses • Updated the analyses methods to descriptive	Clarification of text describing methodology
4.5. Secondary Analyses	• Expanded the safety analyses • Updated text	Clarification of text describing methodology
4.6. Heading of Missing Data or Dropouts	• Removed context related to the control group	Comparative analyses utilizing the control group will not be conducted. Clarification of text.
5. References	• Removed all references related to propensity score methods	Comparative analyses utilizing the control group will not be conducted. Clarification of text.

Abbreviations: BAM = bamlanivimab; ED = emergency department; ER = emergency room; No. = number.

Overall Rationale for the Revision on Version 3

Due to limitations in the availability of some data elements in the EMR, this SAP Version 3 modified variable definitions for prior and concomitant therapy. Other changes included updated analyses for vital signs, removal of hospitalization and healthcare utilization events collected from EDC, and removal of subgroup analyses due to low sample size.

This SAP Version 3 supersedes the statistical plans described in the SAP V2. It will be approved prior to the final database lock.

The changes incorporated in Version 3 are summarized as follows:

Section No. and Name	Description of Change	Brief Rationale
Entire SAP	• Corrected study alias name J2W-MC-PYAJ to J2X-MC-PYAJ	Typo
Entire SAP	• Replaced "by Days 29, 60, and 90" to "up to Days 29, 60, and 90"	Language changed to avoid confusion
Entire SAP	• Defined acronyms at first presentation throughout the document	To clarify in-text acronyms for ease of reading
3.2. Data collection	• Reworded the description of data collection	Clarification
3.5. Endpoints	• Updated the follow-up days on Figure 3.2	Language changed to avoid confusion
3.7. Variables/Measures	• Changed height unit from m to cm • Added data source "from EMR" to age variable • Added the following additional COVID-19 symptoms: o chills o loss of sense of taste o loss of sense of smell o fatigue • Specified the time frame "during 1 year prior to the infusion" for preexisting conditions and medical history • Changed variable "prior treatments of special interest within the 30 days" to "Treatments of special interest prescribed within 30 days prior to infusion" • Specified "other investigational treatments" to include ivermectin, COVID-19 vaccine, and oxygen • Changed variable "Concomitant medications" to "Prior or concomitant therapy 90 days before and 90 days after infusion" o Removed "other investigational treatments" • Added time frame "during 10 days prior infusion" for Procedures of special interest • Removed "ongoing hospital medical care" from Procedures of special interest	Data format in EMR Clarification According to the FDA COVID guidance (September, 2020) Clarification Due to incomplete medication days of supply data, prior treatments cannot be well-defined. Changed to treatment prescribed. Included definition of "other investigational treatments" Due to incomplete medication days of supply data, concomitant medication cannot be well-defined. Study team decision due to concomitant medication can't be well-defined. Clarification Not captured in EMR

	• Removed "other respiratory support" from Respiratory support • Removed Hospitalization and healthcare utilization events	Not captured in EMR Purposed for EDC quality checking, no plan for analysis.
4.5. Secondary analyses	• Changed treatment-emergent adverse events (TEAEs) to AEs • Removed Hospitalization and healthcare utilization events collected from EDC • Added the explanation of how to report vital signs	No plan for TEAE Purposed for EDC quality checking, no plan for analysis. Clarification
4.7. Other Analyses	• Removed previously planned subgroup analysis	Due to a small sample size

2. Objectives and Endpoints

Table 2.1 shows the primary and secondary objectives and endpoints of the study.

Table 2.1 Protocol-Defined Objectives and Their Endpoints

Objectives	Endpoints
Primary	
• To determine the proportion of patients with COVID-19-related hospitalization or all-cause death up to Days 29, 60, and 90 among bamlanivimab-treated participants	• Proportion (percentage) of participants who experience COVID-19-related hospitalization (defined as ≥24 hours of acute care) or all-cause death up to Days 29, 60, and 90
Secondary	
• To determine the proportion of patients with COVID-19-related hospitalization up to 29, 60, and 90 days among bamlanivimab-treated participants	• Proportion (percentage) of participants who experience COVID-19-related hospitalization, defined as ≥24 hours of acute care, up to Days 29, 60, and 90
• To determine the proportion of patients with a COVID-19-related ER visit up to Days 29, 60, and 90 among bamlanivimab-treated participants	• Proportion (percentage) of participants who experience ER visits for COVID-19-related causes up to Days 29, 60, and 90
• To describe the safety of bamlanivimab-treated participants up to Days 29, 60, and 90	• Incidence (counts and percentage) of AEs or SAEs up to Days 29, 60, and 90

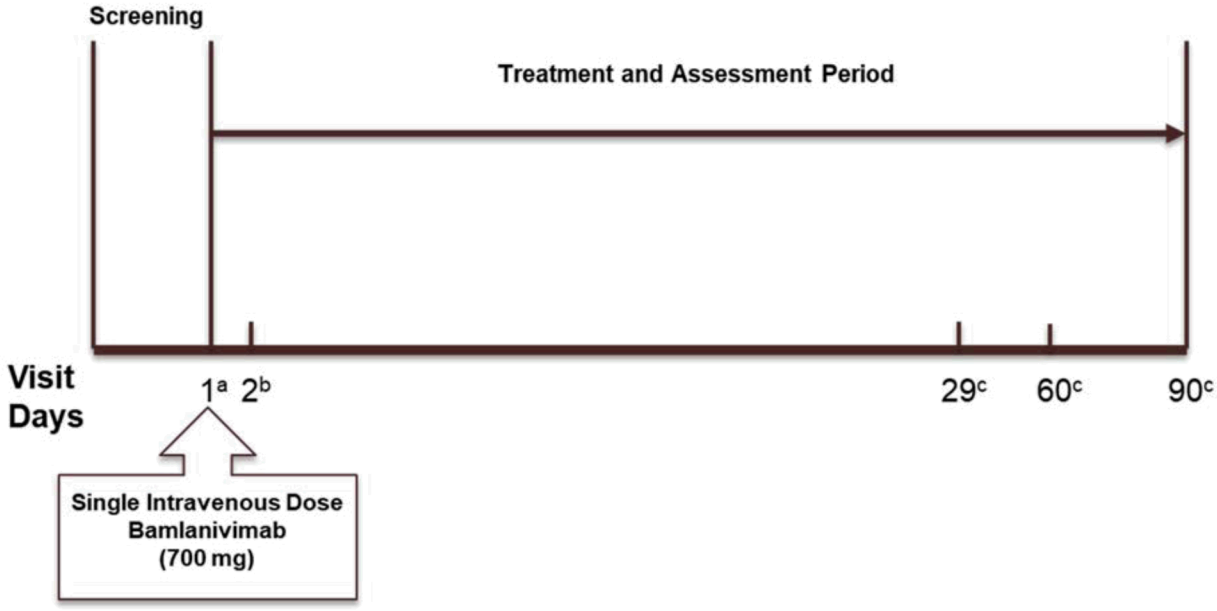
Abbreviation: AE = adverse event; COVID-19 = coronavirus disease 2019; ER = emergency room; SAE = serious adverse event.

3. Research Design

3.1. Summary of Study Design

This study is being conducted in the same population as in the emergency use authorization (EUA) (FDA 2020).

Study J2X-MC-PYAJ is an open-label, prospective, single-arm observational study in participants with mild to moderate COVID-19 (see Section 3.3.1 for criteria). Study participants who received a one-time IV infusion of bamlanivimab (LY3819253) within 10 days of symptom onset and following the first positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test sample collection will then be followed for 90 days to assess any additional medical care needed or if hospitalization was required (Figure 3.1).



Abbreviation: EMR = electronic medical record.

a Screening and Day 1 procedures may occur on the same day.

b Telephone call 24 hours post-infusion.

c EMR review and phone call.

Figure 3.1 Study J2X-MC-PYAJ study design.

Screening

Interested participants or their legally authorized representative will sign the appropriate informed consent and adolescent assent document(s), as appropriate, prior to completion of any procedures.

The investigator will confirm a positive reverse transcription-polymerase chain reaction (RT-PCR) test or antigen testing confirmation for COVID-19 (if antigen test is accompanied by symptoms suggestive of SARS-CoV-2 infection) and complete baseline procedures to confirm eligibility per inclusion and exclusion criteria and review criteria for high risk under the EUA.

Treatment and Assessment Period

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

- participants receive study intervention, and
- complete all safety monitoring and post-infusion data collection.

Treated Population Visit Types

The visit types for the Treatment Population table in Section 4.1 of the protocol describes the visit types for the treatment population for this study.

Guidelines if a Participant is Hospitalized

If a participant is hospitalized, procedures and assessments will continue per the Schedule of Activities (SoA) (Study PYAJ Protocol Section 1.3).

The Description of Discharge from Hospital Scenarios table in Section 4.1 of the protocol describes discharge from hospital scenarios if an outpatient is subsequently hospitalized.

Post-treatment

Post-treatment assessments will be conducted at Days 2, 29, 60, and 90 to assess study endpoints.

3.2. Data Collection

Data for bamlanivimab-treated patients will be captured at the infusion visit (Day 1), at 24 hours post-infusion (Day 2), and at subsequent follow-up periods (Days 29, 60, and 90). Case report form (CRF) data documented within the EDC system will be captured on-site on Day 1 and via telephone call on Days 2, 29, 60, and 90. The EMR records will be extracted during 1 year prior to and 90 days post the infusion date.

Sample Size Determination

Due to early termination, the study enrolled 109, rather than the anticipated 500-3000, bamlanivimab-treated patients. Given that the revised primary objective is to determine the proportion of patients with COVID-19-related hospitalization or all-cause death up to 29 days among bamlanivimab-treated participants and without the use of a comparison group, the observed sample size was 109 participants. This achieved sample size of 109 participants will allow for estimating the proportion with a precision of ±4.4% ($=1.96*\sqrt{(p(1-p)/n)}$) under the assumption of normal approximation of a binomial distribution at a 2-sided significance level of 0.05 and 6% of the true rates of COVID-19-related hospitalization or all-cause death.

3.3. Study Population

3.3.1. Selection Criteria

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Due to the criticality of participant health, verbal interview of the potential participant, or their legal representative or family member, may be the source for disease characteristics and medical history, unless otherwise specified within the eligibility criteria.

Inclusion Criteria:

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Are ≥12 years of age at the time of screening

Disease Characteristics

2. Are currently not hospitalized
3. Have one or more mild or moderate COVID-19 symptoms (FDA 2020)
    i. Fever
    ii. Cough
    iii. Sore throat
    iv. Malaise
    v. Headache
    vi. Muscle pain
    vii. Gastrointestinal symptoms, or
    viii. Shortness of breath with exertion.
4. Must have first positive SARS-CoV-2 viral infection determination and as soon as possible within 10 days of symptom onset
5. Are males or non-breastfeeding females Reproductive and Contraceptive agreements and guidance is provided in the protocol Section 10.3, Appendix 3. Contraceptive use by males or females should be consistent with local regulations for those participating in clinical studies

Study Procedures

6. Understand and agree to comply with planned study procedures

Informed Consent

7. The participant or legally authorized representative gives signed informed consent and/or assent as described in the protocol Section 10.1.3, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in the protocol

High risk as defined per EUA fact sheet (FDA 2020)

8. For example, participants who meet at least 1 of the following criteria:
    - Have a body mass index (BMI) ≥35
    - Have chronic kidney disease
    - Have diabetes
    - Have immunosuppressive disease
    - Are currently receiving immunosuppressive treatment
    - Are ≥65 years of age
    - Are ≥55 years of age AND have
        - cardiovascular disease, OR
        - hypertension, OR
        - chronic obstructive pulmonary disease or other chronic respiratory disease.
    - Are 12–17 years of age AND have

- BMI ≥85th percentile for their age and gender based on Centers for Disease Control and Prevention (CDC) growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
- sickle cell disease, OR
- congenital or acquired heart disease, OR
- neurodevelopmental disorders, for example, cerebral palsy, OR
- a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
- asthma, reactive airway or other chronic respiratory disease that requires daily medication for controls.

3.3.2. Exclusion Criteria:

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. More specifically, participants are excluded from the study if any of the following criteria apply:

Medical Conditions

9. Participants who:
   a) are hospitalized due to COVID-19,
   b) require oxygen therapy due to COVID-19, OR
   c) require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.
10. Have SpO2 ≤90% on room air or PaO2/FiO2 <300, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA 2020)
11. Have body weight <40kg
12. Require mechanical ventilation or anticipated impending need for mechanical ventilation
13. Have known allergies to any of the components used in the formulation of the interventions
14. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
15. Have any comorbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
16. Have any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in this study

Other Exclusions

17. Have a history of a positive SARS-CoV-2 serology test
18. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study

19. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
20. Have received treatment with a SARS-CoV-2-specific monoclonal antibody, remdesivir, or other treatment for COVID-19
21. Have received convalescent COVID-19 plasma treatment
22. Have participated in a previous SARS-CoV-2 vaccine study
23. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
24. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
25. Are breast-feeding
26. Are investigator site personnel directly affiliated with this study

3.4. Patient Group

There is 1 study population: participants treated with bamlanivimab.

3.5. Endpoints

The study endpoints are defined as at 29, 60, and 90 days of the date of the bamlanivimab infusion.

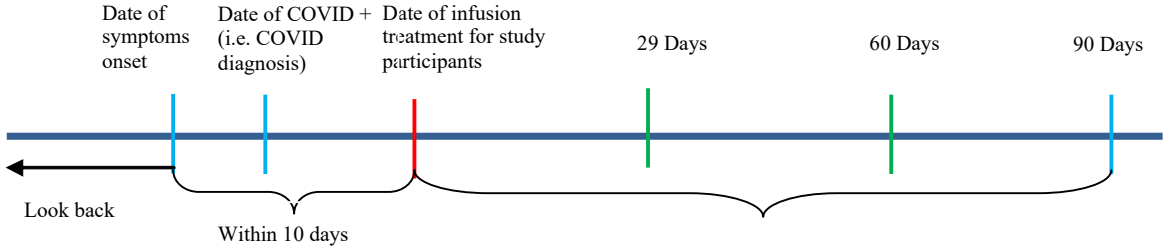


Figure 3.2. Illustration of the timeline for study participants.

The following endpoints are defined based on the EDC and EMR data.

- Primary endpoint:
  - COVID-19-related hospitalization (defined as ≥24 hours of acute care for COVID-19) or all-cause death up to 29, 60, and 90 days
- Secondary endpoints:
  - COVID-19-related hospitalization, defined as ≥24 hours of acute care, up to 29, 60, and 90 days
  - COVID-19-related emergency department (ED) visits up to 29, 60, and 90 days
  - Adverse Events (AEs) or Severe Adverse Events (SAEs) up to 2 hours, 24 hours, and 29, 60, and 90 days

The period of follow-up for ascertainment of these endpoints will be 29, 60, and 90 days following the infusion date. The COVID-19-related hospitalization or all-cause death will be

defined as binary, and secondarily time to event variable will also be included. For time-to-event endpoints, days to the first COVID-19-related hospitalization or death will be calculated from the infusion date. For patients who do not experience a particular endpoint up to 29, 60, and 90 days following the infusion date, a censoring date will be defined as the earliest of

- 29, 60, and 90 days following the infusion date, or
- the early discontinuation date (study participants).

The AEs or SAEs will be collected from the CRF. The proportion of patients with an SAE or AE will be reported.

3.6. Study Therapies

Bamlanivimab (LY3819253) is a neutralizing IgG1 monoclonal antibody to the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially preventing and treating COVID-19.

3.7. Variables/Measures

The following variables will be defined based on the EDC/EMR data.

Table 3.1 Variable Definitions/Data Source

Variables	Definition	Data Source
Demographics		
Age at index date, year	Age: whole numbers calculated from bamlanivimab index date Age group: Age ≥65; Age 55 to 64; Age 18 to 54; and Age 12 to 17	From EMR
Sex	Female and male	From EMR
Race	American Indian / Alaskan Native Asian Black / African American Native Hawaiian / Pacific Islander White Multiple	
Ethnicity	Hispanic, non-Hispanic	
Weight, kg	Continuous variable	
Height, cm	Continuous variable	
BMI	Calculated as BMI = kg/m^2 where kg is a person's weight in kilograms and m^2 is their height in meters squared. Continuous and categorical ≤25; 25 to <30; and ≥30	
Tobacco use	current use, former, and never	
Vital signs	• body temperature • pulse rate • systolic blood pressure • diastolic blood pressure • respiratory rate • SpO2	From EMR

Variables	Definition	Data Source
	• supplemental oxygen flow rate • FiO2 and method of delivery, if applicable	
COVID-19 symptoms	Total of 8-binary indicator variables will be created for the below symptoms: • fever • cough • sore throat • malaise • chills • loss of sense of taste • loss of sense of smell • fatigue. • headache • muscle pain • gastrointestinal symptoms • shortness of breath with exertion The date of COVID-19 symptom onset is defined as the earliest start date of symptoms suggestive of SARS-CoV-2 infection; calculated by difference of bamlanivimab index date and reported symptom date	From EMR
Days since COVID-19 symptom onset.	Calculated as the difference index date and COVID-19 symptom onset date. Category: ≤8 days and >8 days	
Type of COVID-19 diagnosis test	RT-PCR, antigen testing COVID-19 diagnosis date	
Preexisting conditions and medical history during 1 year prior to the infusion	Binary indicator variables will be created for the below: • chronic kidney disease • diabetes (type I, type II) • immunosuppressive disease • currently receiving immunosuppressive treatment • cardiovascular disease • hypertension • chronic obstructive pulmonary disease or other chronic respiratory disease • sickle cell disease • congenital or acquired heart disease • neurodevelopmental disorders • medical-related technological dependence; for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19) • asthma, reactive airway or other chronic respiratory disease that requires daily medication for controls	From EMR

Variables	Definition	Data Source
Treatments of special interest prescribed within 30 days prior to infusion (exclusive infusion date)	Dates of: • NSAIDs • antivirals • antibiotics • anti-malarials • corticosteroids • immunomodulators • other investigational treatments (including ivermectin, COVID-19 vaccine, and oxygen)	From EMR
Prior or concomitant therapy 90 days before and 90 days after infusion	Dates of: • NSAIDs • antivirals • antibiotics • anti-malarials • corticosteroids • immunomodulators	From EMR
Procedures of special interest during 10 days prior infusion	Dates of: • supplemental oxygen • non-invasive ventilation • high flow oxygen device • mechanical ventilation • Extracorporeal membrane oxygenation (ECMO) • additional organ support	From EMR
Respiratory support	Dates of: • high flow nasal cannula • noninvasive positive pressure ventilation	From EMR
Mortality	• date • cause of death	From EMR
Pregnancy	Date of confirmed pregnancy	From EMR

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; EMR = electronic medical record; FiO2 = fraction of inspired oxygen in the air; NSAID = nonsteroidal anti-inflammatory drug; RT-PCR = reverse transcription-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = saturation of peripheral oxygen.

4. Statistical Analyses

4.1. General Considerations

All analyses will be conducted on bamlanivimab-treated study participants.

Descriptive analysis will be conducted without imputation of missing values. Categorical variables will be summarized using frequencies and proportions. Continuous variables will be summarized using mean with standard deviations, and medians with interquartile range.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

All statistical analyses will be performed using SAS software Version 9.4 (or a higher version).

4.2. Participant Dispositions

The number and percentage of study participants who complete the study or discontinue early will be tabulated up to 29, 60, and 90 days follow-up. Reasons for discontinuation will be summarized.

4.3. Populations for Analyses

The analysis population includes all patients who meet inclusion criteria and receive bamlanivimab in a single IV infusion of 700 mg or less.

4.4. Primary Analyses and Methodology

To address the primary study objective, this section describes the primary analysis determining the rates of COVID-19-related hospitalization or death among bamlanivimab-treated patients.

Primary Efficacy Outcome Analysis: COVID-19-Related Hospitalization or all-cause Death up to Days 29, 60, and 90

The primary analysis will determine the number and proportions of the bamlanivimab-treated patients with a COVID-19-related hospitalization or all-cause death up to Days 29, 60, and 90 (binary outcome).

Ninety-five-percent confidence intervals (CIs) for hospitalization or all-cause death proportion at Days 29, 60, and 90 will be provided. The 95% CIs will be constructed using the asymptotic method without continuity correction (that is, normal approximation to the binomial distribution).

Sensitivity Analyses for the Primary Objective

In addition to the above primary analysis, the following analyses maybe performed as sensitivity analyses.

Time to Event

Time to the first COVID-19-related hospitalization or all-cause death at Days 29, 60, and 90 will be calculated as the duration from the infusion date to the first date of admission to COVID-19-related hospitalization or death date (the duration = the first date of admission to COVID-19-related hospitalization or death date plus - infusion date +1). For patients who do not experience a COVID-19-related hospitalization or death up to Day 29 (60, 90) following the infusion date, a

censoring date is defined as the earliest of 29 (60, 90) days following the infusion date, or the early discontinuation date (such as due to lost to follow-up or drop out). For those who are not admitted due to COVID-19 or have not died up to Day 29 (60, 90), the outcome will be treated as a censored response after Day 29 (60, 90). Cumulative incidence of COVID-19-related hospitalization or all-cause death at Days 29, 60, 90 will be estimated based on Kaplan-Meier estimates. Kaplan-Meier curves will also be plotted. The number of patients who experienced COVID-19-related hospitalization or die from any cause, cumulative incidence of each endpoint, 95% CI of the cumulative incidence, and number of patients at risk over time will be reported at Days 29, 60, and 90.

4.5. Secondary Analyses

To support the secondary study objectives, analyses will include:

- determination of the proportions of patients with COVID-19-related hospitalizations up to Days 29, 60, and 90
- COVID-19-related ER visits up to Days 29, 60, and 90
- Description of AEs and SAEs up to 2 hours, 24 hours, Days 29, 60, and 90.

Descriptive analyses for these secondary objectives will follow the same statistical methodology as used for the primary analysis.

COVID-19-related ED visits, AEs, and SAEs defined in Section 3.5 will be summarized by numbers and percentage up to 2 hours, 24 hours, and 29, 60, and 90 days after infusion. A listing of AE data for patients at any time during the study will be provided, including age, gender, race, the description of AE, start date, stop date, time from infusion (in days), and severity.

Exposure to Therapy

Exposure to therapy will be listed, including timing of infusion, planned dose, total dose administered, treatment interrupted, and reason for interruption. Exposure to therapy will be represented as the total number of complete and incomplete infusions and will be summarized using descriptive statistics.

Adverse Events

Although all AEs after signing the ICF are recorded by the site in the CRF/EDC, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study intervention. However, if a SAE occurs after signing the ICF, but prior to receiving study intervention, it will be reported within the SAE reporting timeframe if it is considered reasonably possibly related to study procedures.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will include the number of participants with at least 1 AE. When reporting by System Organ Class (SOC) and Preferred Term (PT), the reports will present the SOC in alphabetical order; PTs within the SOCs will be presented in order of 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.

The number and percentage of participants who experienced an AE, SAE, AE related to study drug, died due to an AE, discontinued from the study treatment, or discontinued from the study due to an AE will be summarized by during infusion and after infusion for up to 2 hours, 24 hours, 29 days, 60 days, and 90 days. The summary method for each event type is described in Table 4.1.

Table 4.1 Types of Adverse Events to be Summarized

Event Type	Summary Method
SAE	SAEs will be summarized for study participants by SOC and PT. These reports will also include the total number of SAE for each SOC and PT.
AE Resulting in Death	If there are any AEs 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 PT.
AE Leading to Study Drug Discontinuation	AEs for which the action taken with medication as 'Drug Withdrawal' will be identified as AEs that lead to study drug discontinuation. The AEs that lead to study drug discontinuation will be summarized by SOC and PT for the safety population. A by-patient listing of the AEs that lead to study drug discontinuation will also be provided.
Treatment-Related AE	Every AE will be assessed by the investigator for its relationship to the study treatment.
AE 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 AEs that share the same SOC or PT. A table of AEs by maximal severity will be prepared by SOC and PT.
AE (Not Including Serious)	The most common, nonserious AEs will be summarized. All PTs that occur in at least 1% of the safety population participants, when not counting the serious AEs, will be tabulated by SOC and PT. These reports will also present the total number of AEs for each SOC and PT.

Abbreviations: AE = adverse event; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class.

Infusion Site Reactions

Infusion site reactions are AEs localized to the immediate site of the administration of a drug and will be defined using terms from the MedDRA High-Level Term, Infusion Site Reactions. All ISRs will be listed.

The number and percentage of patients with AEs related to infusion sites, SAEs related to infusion sites, and AEs related to infusion sites resulting in study drug discontinuation will be summarized using MedDRA PT. Events will be ordered by decreasing frequency.

The number and percentage of patients with AEs related to infusion sites by maximum severity will be summarized using MedDRA PT.

Hypersensitivity, Anaphylactic, and Infusion-Related Reactions

Hypersensitivity reactions is used as an overarching term to describe events that are systemic or localized reactions that likely have an allergic/hypersensitivity etiology. At all visits in Phase 3 clinical studies, patients will be evaluated by the investigator for signs and symptoms suggestive of hypersensitivity. Investigators will complete a CRF designed to record additional information about AEs suggestive of a hypersensitivity reaction.

Two main analyses are performed respectively assessing (a) potential immediate hypersensitivity, including anaphylaxis and IRRs, and (b) potential nonimmediate hypersensitivity.

Time Period A, of potential immediate hypersensitivity, includes all AEs occurring on the day of study drug administration.

Time Period B, of potential nonimmediate hypersensitivity, includes all AEs occurring strictly after the day of study drug administration.

Analyses for both time periods are based on the following Standard MedDRA Queries (SMQs):

- Anaphylactic reaction SMQ (20000021; narrow and broad)
- Hypersensitivity SMQ (20000214; narrow and broad), and
- Angioedema SMQ (20000024; narrow and broad).

Additionally, for the Anaphylactic reaction SMQ in Time Period A, the algorithmic query (per the MedDRA Maintenance and Support Services Organization [MSSO] SMQ guide) will be performed. An algorithmic case must include either

- a narrow term from the SMQ (Category A of the SMQ), or
- multiple terms from the SMQ comprising terms from at least 2 of the following categories from the SMQ

    - Category B - (Upper Airway/Respiratory)
    - Category C - (Angioedema/Urticaria/Pruritus/Flush), or
    - Category D - (Cardiovascular/Hypotension).

Where algorithm is mentioned below, this applies only to Time Period A.

The number and percentage of patients reported with an AE for the following will be analyzed for each of the 2 time periods:

- any narrow or algorithmic term from any 1 of the 3 SMQs indicated above (that is, combined search across narrow and algorithmic portions of all 3 SMQs)
- any narrow term within each SMQ, separately (that is, narrow SMQ search), and
- any term within each SMQ, separately (that is, broad SMQ search).

Within queries, individual PTs that satisfied the queries will be summarized.

For Time Period A only, the number and percentage of each PT that is not in any of the 3 SMQs (that is, other events occurring on the day of study drug administration) will be summarized overall and by individual PT. Only PTs that occur in at least 3 patients receiving bamlanivimab will be displayed in this portion of the table.

The PTs will be arranged in the summary in decreasing order of frequency for patients in the total bamlanivimab treatment group. Note that an individual patient may contribute multiple events. Also, a single event may satisfy multiple SMQs, in which case the event contributes to every applicable SMQ.

The analyses above are the starting point for medical interpretation of any apparent differences between treatment groups. For notable events, case review will be applied to make the final determination of whether an event is most accurately described as a potential hypersensitivity reaction to a drug or another event that is not clearly associated with drug administration. This judgment will be on the basis of totality of information available, including the content of the follow-up CRF collected for potential hypersensitivity events.

Vital Signs and Other Physical Findings

The measurements analyzed for vital signs and physical characteristics include systolic blood pressure (BP), diastolic BP, pulse, peripheral oxygen saturation, respiratory rate, and temperature, if data warrant.

Given different total volumes of solution for administration of 700mg bamlanivimab (200ml, 100ml, and other volume which will be entered in the CRF by site), the infusion duration will differ, such as about 1 hour for the total amount of 200 ml, and about 30 minutes for the total amount of 100 ml. For this reason, vital signs will be summarized at the following timepoints: baseline, half infusion, end of infusion, 30 minutes post-infusion, and 1 hour post-infusion, rather than using the recommended timing (immediately before the infusion, every 15 minutes during the infusion, and every 30 minutes for at least 1 hour after the infusion). Baseline is defined as the last non-missing value before patient's bamlanivimab infusion.

Vital signs data will be summarized by box plots for observed values, along with changes from baseline by timepoints.

Box plots for observed values by timepoints will include participants with a non-missing value at the timepoint. Values outside 1.5 interquartile range (IQR) below 25% and above 75% will be shown as outliers. Descriptive summary statistics will be included in a table below the box plot.

Box plots for change from baseline values to each post baseline timepoints will be presented similarly to those for observed values by timepoints described above. They will include participants with a non-missing value at the timepoint, and values outside 1.5 IQR below 25% and above 75% will be shown as outliers. Descriptive summary statistics will be included in a table below the box plot.

All vital signs and other physical findings for individual participants will be listed.

Protocol Violations

Protocol violations 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.

The number and percentage of participants having IPDs will be summarized within each category and subcategory of deviations. A by-patient listing of IPDs will be provided.

4.6. Handling of Missing Data or Dropouts

Due to low study enrollment, all objectives are descriptive in nature. Summary statistics will be based on nonmissing data.

4.7. Other Analyses

The total number of bamlanivimab-treated participants is 109. No subgroup analyses will be conducted.

4.8. Interim Analyses

Not applicable.

4.9. Changes to Protocol-Planned Analyses

Since enrollment was determined to be infeasible, and the total number of bamlanivimab-treated participants is 109, analyses using a control group and propensity score matching are not feasible. The study is underpowered for the comparative analyses that were originally planned and described in the protocol and Version 1 of the SAP, and any results from such comparative analyses would be uninterpretable and lack scientific rigor. For this reason, the decision was made to change the protocol-planned comparative analyses to descriptive noncomparative analyses.

5. References

[FDA] United States Food and Drug Administration. COVID-19: developing biological products for treatment or prevention: guidance for industry. Published May 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid19-developing-drugs-and-biological-products-treatment-or-prevention.

[FDA] Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment: Guidance for Industry. Issued September 2020. https://www.fda.gov/media/142143/download.

[FDA] United States Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab. Revised December 2020. Accessed January 19, 2021. https://www.fda.gov/media/143603/download.

Leo Document ID = 7b5f99bf-f3d5-492f-b738-42248c5c617d

Approver: PPD

Approval Date & Time: 13-Aug-2021 14:53:23 GMT

Signature meaning: Approved