Protocol J2X-MC-B003

A Cohort Study to Evaluate the Real-World Utilization and Effectiveness of Bebtelovimab Compared to Paxlovid among Patients with Mild-to-Moderate COVID-19 Who Are at High Risk for Progressing to Severe Illness

Protocol and Statistical Analysis Plan

LY3853113 (bebtelovimab)

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Protocol Electronically Signed and Approved by Lilly on date provided below.

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2. List of Abbreviations and Definitions

List of Abbreviations

Term	Definition
BEB	bebtelovimab
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CEM	coarsened exact matching
CI	confidence interval
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CPT	Current Procedural Terminology
CSV	comma-separated values
ED	emergency department
eGFR	estimated glomerular filtration rate
EHR	electronic health record
EUA	emergency use authorization
HCO	health care organization
HCPCS	Healthcare Common Procedure Coding System
HRU	healthcare resource utilization
ICD-9/10-CM	International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification
ICD-10-CM	International Classification of Disease, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Disease, Tenth Revision, Procedure Coding System
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
ICU	intensive care unit
IDN	integrated delivery network
ITT	intention-to-treat

Term	Definition
LOINC	Logical Observation Identifiers Names and Codes
NDC	National Drug Code
NI	noninferiority
OR	odds ratio
PASS	postauthorization safety study
PAX	Paxlovid™
PS	propensity score
RD	risk difference
RWD	real-world data
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
UCL	upper confidence limit

List of Definitions

Term	Definition
TriNetX Dataworks USA Network	A federated network of 50 US-based HCOs that provide access to their EHR data for secondary /observational research. Referred to as the "EHR database"
TriNetX Linked Network	A subset of HCOs from the TriNetX Dataworks USA Network that allow their EHR data to be linked to data from outside their institution. The Linked Network includes EHR data linked to a closed claims medical and pharmacy database
Index period	16 February 2022 to 31 August 2022
RxNorm	RxNorm is a medication standard that provides names for clinical drugs and links its names to many of the drug vocabularies commonly used in pharmacy management and drug interaction software. RxNorm serves as the central vocabulary for all medications in the TriNetX Network

3. Responsible Parties

This is not an EU PASS study, and therefore, this section is not applicable.

4. Abstract

Title, date, and responsible individual

Title: A Cohort Study to Evaluate the Real-World Utilization and Effectiveness of Bebtelovimab Compared to Paxlovid among Patients with Mild-to-Moderate COVID-19 Who Are at High Risk for Progressing to Severe Illness

Dates:

Milestone	Planned Date
First data extraction	15-Feb-2023
Last data extraction	15-Feb-2023
Final report of study results submission	31-Jul-2023

Rationale and background

On 11 February 2022, the US FDA issued an EUA for BEB, an antibody that demonstrated neutralization against the Omicron variant of COVID-19. BEB is used for the treatment of mild-to-moderate COVID-19 in adults and children (aged 12 years and older weighing at least 88 pounds [40 kg]) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom other COVID-19 treatment options approved or authorized by the FDA are not available or clinically appropriate.

Recognizing the limitations of the available clinical data, conditions of the letter of authorization require Eli Lilly and Company (Lilly) to collect additional information on BEB outcomes. As such, we propose an active control, NI study to assess the effectiveness of BEB compared with oral nirmatrelvir and ritonavir (PAX) in adults and adolescents aged 12 years and older who were at high risk for progressing to severe COVID-19 illness.

On 30 November 2022, during protocol development, the US FDA suspended the BEB EUA due to the high level of circulating Omicron subvariants BQ.1 and BQ.1.1, variants not expected to be neutralized by BEB (FDA 2022a). This study will continue to address research questions regarding the effectiveness of BEB prior to the suspension of the EUA.

Research question and objectives

The primary objective is to estimate the 30-day RD of the composite outcome of all-cause hospitalization or all-cause death for patients who received BEB compared to patients who received PAX. The primary analysis will use NI hypothesis testing with an *a priori* specified NI margin. The secondary objective is to estimate the 30-day RD of all-cause hospitalizations, all-cause deaths, and all-cause ED visits.

To evaluate the consistency of the treatment effect, additional subgroup analyses will be conducted for patients

- aged 65 years and older and aged less than 65 years

- with evidence of COVID-19 vaccination
- who had a pre-index ED visit, and
- who were immunocompromised.

Sensitivity analyses to assess the impact of unmeasured confounding and to mitigate potential channeling bias based on disease severity will also be conducted.

Study design

An observational, cohort study design will be used to describe and compare the effectiveness of BEB to PAX in adults and adolescents with mild-to-moderate COVID-19.

Study cohorts

The study cohorts will include patients who received BEB or PAX during the index period (that is, 16 February 2022 to 31 August 2022). The index date is the date of the first BEB or first PAX record during the index period. If a patient was exposed to both BEB and PAX during the index period, they will be included in the cohort (BEB or PAX) based on the first date of BEB or PAX exposure. However, patients who were exposed to both BEB and PAX on the same date will be excluded. Therefore, patients will be included in only 1 cohort for this study.

Both cohorts will be restricted to include patients who meet all of the following inclusion/exclusion criteria:

1. BEB or PAX exposure during index period
2. age 12 years and older as of the index date
3. at least 1 healthcare encounter within 6 to 36 months pre-index
4. no inpatient admission within 30 days pre-index (inclusive of index date)
5. no hospice care within 30 days pre-index (inclusive of index date)
6. no treatment indicated or used for COVID-19 within 90 days pre-index (inclusive of index date)
    a. note that this exclusion criterion does not pertain to BEB or PAX exposure on the index date), and
7. no supplemental or chronic oxygen therapy within 30 days pre-index (inclusive of index date).

Study variables

The analyses will be conducted in 2 phases. For the Phase I analyses, study variables will be ascertained from EHR data within the TriNetX Dataworks USA Network. For the Phase II or supplemental analyses, study variables will be ascertained from EHR data linked to health insurance claims and mortality data within the TriNetX Linked Network.

BEB exposure data will be ascertained from facility-based infusion centers and outpatient administrations. Oral PAX exposure data will be ascertained from facility-based and outpatient medication records. Outcome data will be classified using facility-based and outpatient records. Baseline characteristics will be ascertained from all available inpatient and outpatient records

prior to and including the index date. The baseline characteristics include the following categories:

- demographics
- clinical parameters
- comorbidities
- pharmacotherapy exposure, and
- HRU.

Data sources

EHR data from the TriNetX Dataworks USA Network will be used as the primary data source. These data include de-identified, longitudinal outpatient and inpatient data from the HCOs across the US. TriNetX Dataworks USA Network data are sourced from a global federated health research network with frequent updates of anonymized EHRs. Currently, the standardized EHR fields are available for approximately 86 million patients from 54 US-based HCOs. Network members include academic medical centers, IDNs, specialty hospitals, and large specialty physician practices. For Phase II (supplementary) analyses, EHR data will be linked with mortality data and "closed" health insurance claims data from the TriNetX Linked Network.

Study size

From 16 February 2022 to 31 August 2022, a total of 14,347 and 40,369 patients received BEB and PAX, respectively. After enforcing the proposed inclusion/exclusion criteria, it is estimated that more than 8000 BEB and more than 20,000 PAX exposed patients will be available for matching.

A total of 1390 patients in each group are needed to establish that BEB is not inferior to PAX using a 1.795% NI margin with 90% power. Based on the feasibility estimates, the sample sizes for BEB and PAX should provide sufficient power to test the NI null hypothesis.

Data analysis

For patients included in both study cohorts, descriptive statistics will be used to describe baseline characteristics. Differences between baseline characteristics will be calculated using standardized differences before and after PS matching.

An ITT approach will be used to derive the cumulative incidence (risk) and RD and 95% CI of 30-day all-cause hospitalization or all-cause death (primary analysis composite outcome). For comparing the outcomes between the 2 cohorts, confounding control will be achieved using CEM on highly selected and *a priori* defined baseline variables in conjunction with PS matching on a broader set of baseline variables. For the primary analysis only, the NI null hypothesis for this objective will be tested using the 1-sided Type I error of 0.025 by setting the RD_{UCL} 95%CI of the BEB versus PAX to be less than the prespecified NI margin of 1.795%.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned Date
First data extraction	15-Feb-2023
Last data extraction	15-Feb-2023
Final report of study results submission	31-Jul-2023

7. Rationale and Background

SARS-CoV-2 and its resulting illness COVID-19 is associated with over 90 million cases of COVID-19 and over 1 million deaths in the US (CDC 2022b). Common symptoms of mild COVID-19 disease include fever, myalgia, headache, difficulty breathing, weakness, gastrointestinal symptoms, and loss of smell or tastes (Parasher 2021). Progression to more severe disease may lead to hospitalization, non-invasive and invasive ventilation, and death (WHO working group 2020; Parasher 2021). Patients with COVID-19 suffering from chronic diseases and those with multiple comorbidities are more likely to experience severe disease and progress rapidly (Emami et al. 2020; Hodge et al. 2020; Choi et al. 2021; CDC 2022a).

In December 2020, COVID-19 vaccinations became available in the US. The successful distribution and utilization of COVID-19 vaccines resulted in less severe clinical disease, lower hospitalization rates, and reduced mortality (Bernal et al. 2021; Monto 2021; Nguyen et al. 2021; Wagner et al. 2021; Andrews et al. 2022; Khairat et al. 2022). Nonetheless, important questions remain regarding waning immunity, re-infection rates, and the clinical impact of new variants (Pei et al. 2021).

In December 2021, two oral antiviral treatments received EUAs for the treatment of mild-to-moderate COVID-19 in certain high risk patients. However, these treatments have limitations including numerous drug-drug interactions for PAX (FDA 2021b) and age and pregnancy restrictions and possibly decreased efficacy for molnupiravir (FDA 2021a). PAX was subsequently recommended as first-line therapy for the treatment of patients at high risk of severe disease. Remdesivir is also listed as first-line therapy, but it requires an infusion 3 days in a row. Additionally, PAX was available free of charge to patients while remdesivir was available for purchase through normal commercial channels (NIH 2022). With the emergence of the Omicron variant and reduced viral susceptibility, other available monoclonal antibodies in the US were restricted in January 2022 (ASPR 2022). Later, in April 2022, the only other monoclonal antibody available for treatment, other than BEB, was restricted from use due to the Omicron subvariant BA.2 prevalence in the US.

On 11 February 2022, the US FDA issued an EUA for BEB, an antibody that demonstrates neutralization against the Omicron variant of COVID-19 (FDA 2022b). BEB is used for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19 illness, including hospitalization or death, and for whom other COVID-19 treatment options approved or authorized by the FDA are not available or clinically appropriate. BEB, administered as a single intravenous injection over at least 30 seconds in an appropriate clinical setting, should be administered as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset.

Data supporting the EUA for treatment of mild-to-moderate COVID-19 are primarily based on analyses from the Phase 2 portion of the BLAZE-4 trial (NCT04634409), which was conducted before the emergence of the Omicron variant. Based on the totality of scientific evidence available, including the available Phase 2 and pharmacokinetic data, along with the nonclinical

viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that BEB may reduce the risk of progression to hospitalization or death (Iketani et al. 2022).

Cohort studies using EHRs in the US and a double-blind, Phase 2 to 3 randomized controlled trial found that BEB and PAX, respectively, were associated with decreased rates of hospitalizations for high-risk patients within 28 or 30 days after drug initiation. A 2022 study, which included high-risk patients who had a positive SARS-CoV-2 test from 30 March 2022 through 28 May 2022, found the 28-day incidence of hospitalization or death was 3.1% versus 5.5% (conditional OR=0.53; 95% CI: 0.32 to 0.86) in 930 BEB treated versus 930 PS matched non-treated patients, respectively (McCreary et al. 2022).

Similarly, a study using the Mayo Clinic's integrated healthcare delivery network comprising of patients in Minnesota, Iowa, Wisconsin, Florida, and Arizona who were treated with BEB or PAX from 20 March 2022 through 14 June 2022 found that 1.4% of BEB treated patients (N=2833), and 1.2% of PAX treated patients (N=774) progressed to a severe disease outcome (Razonable et al. 2022). These rates were found not to be significantly different from each other. The study also found that 0.5% of patients treated with BEB (N=14) and 0.3% of patients treated with PAX (N=2) were admitted to the ICU.

A randomized controlled trial conducted between 16 July 2021 and 9 December 2021, consisting of 2246 patients with a confirmed SARS-CoV-2 diagnosis from 343 worldwide sites, found that patients treated with PAX had a lower rate of hospitalization at the 28-day benchmark compared with the placebo group. In the modified ITT analysis, which had a population of 774 patients, 0.77% of patients in the PAX group (N=389) compared with 7.01% of patients in the placebo group (N=385) had a COVID-19 related hospitalization (Hammond et al. 2022).

Recognizing limitations of the available clinical data, conditions of the letter of authorization require Lilly to collect additional information on the effectiveness of BEB. This NI study to evaluate the effectiveness of BEB relative to the effectiveness of PAX is proposed to meet the conditions in the letter of authorization for BEB for emergency use.

On 30 November 2022, during protocol development, the US FDA suspended the BEB EUA due to the high level of circulating Omicron subvariants BQ.1 and BQ.1.1 that are not expected to be neutralized by BEB (FDA 2022a). This study will continue to address research questions regarding the effectiveness of BEB prior to the suspension of the EUA.

8. Research Questions and Objectives

8.1. Study Objectives

Primary objective

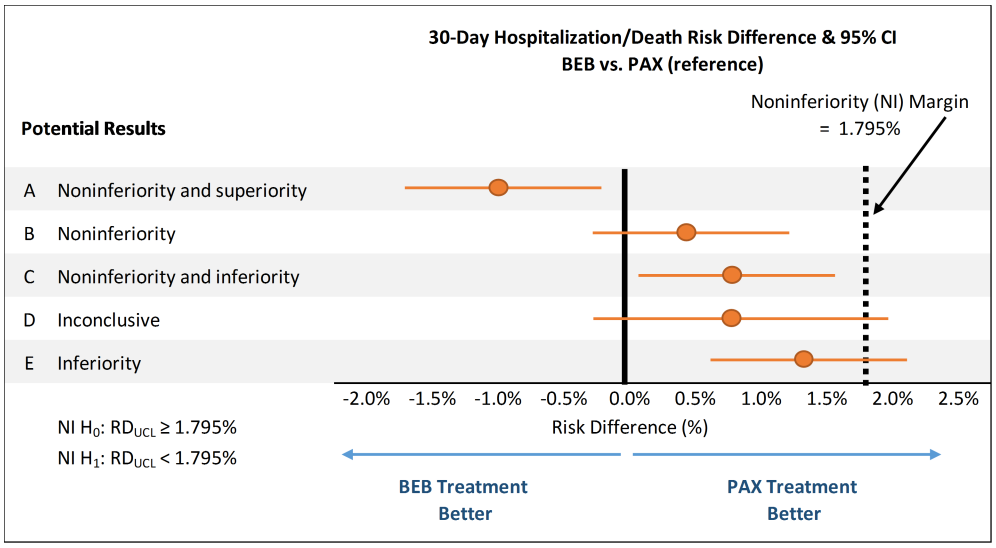
The primary objective is to estimate the 30-day RD and 95% CI of the composite outcome, all-cause hospitalization or all-cause death, for patients who received BEB compared with patients who received PAX. The cumulative incidence and RD and the corresponding 95% CIs will be reported.

The NI null hypothesis for this objective will be tested using the one-sided Type I error of 0.025 by setting the RD_{UCL} 95% CI of the BEB versus PAXto be less than the *a priori* specified NI margin of 1.795%. The null hypothesis is the risk of 30-day all-cause hospitalization or all-cause death is higher for patients treated with BEB compared with patients treated with PAX, by at least 1.795%. We reject the null hypothesis and establish NI, if the RD_{UCL} excludes 1.795%.

The NI null (H_0) and alternative (H_1) hypotheses are

- NI H_0: $RD_{UCL} \geq 1.795\%$, and
- NI H_1: $RD_{UCL} < 1.795\%$.

Figure.8.1 shows the 5 potential results (A, B, C, D, and E) that will be used to test the null hypothesis (Mauri and D'Agostino 2017). If potential results A, B, or C are observed, it will be established that BEB treatment is not inferior to PAX treatment. If potential results D or E are observed, NI will not be established.



Abbreviations: BEB = bebtelovimab; CI = confidence interval; H_0 = null hypothesis, H_1 = alternative hypothesis; PAX = Paxlovid; NI = noninferiority; RD = risk difference; UCL = upper confidence limit.
Note: The hypothetical BEB versus PAX RD are presented as percentages with two-sided 95% CIs to facilitate interpretation (RD null value = 0.0%).

Figure.8.1. Noninferiority assessment.

Secondary objectives

The secondary objective is to estimate the 30-day RD of all-cause hospitalization, all-cause death, and all-cause ED visits for patients who received BEB compared with patients who received PAX.

The cumulative incidence, RD, and 95% CI will be reported; however, hypothesis testing will not be conducted for the secondary objectives.

9. Research Methods

9.1. Study Design

The study objectives will be assessed using a cohort study design. A cohort design is appropriate to complement clinical trials to

- evaluate multiple study outcomes
- determine the cumulative incidence (that is, the risk) and RD of each outcome, and
- increase the precision of outcome estimation.

9.2. Setting

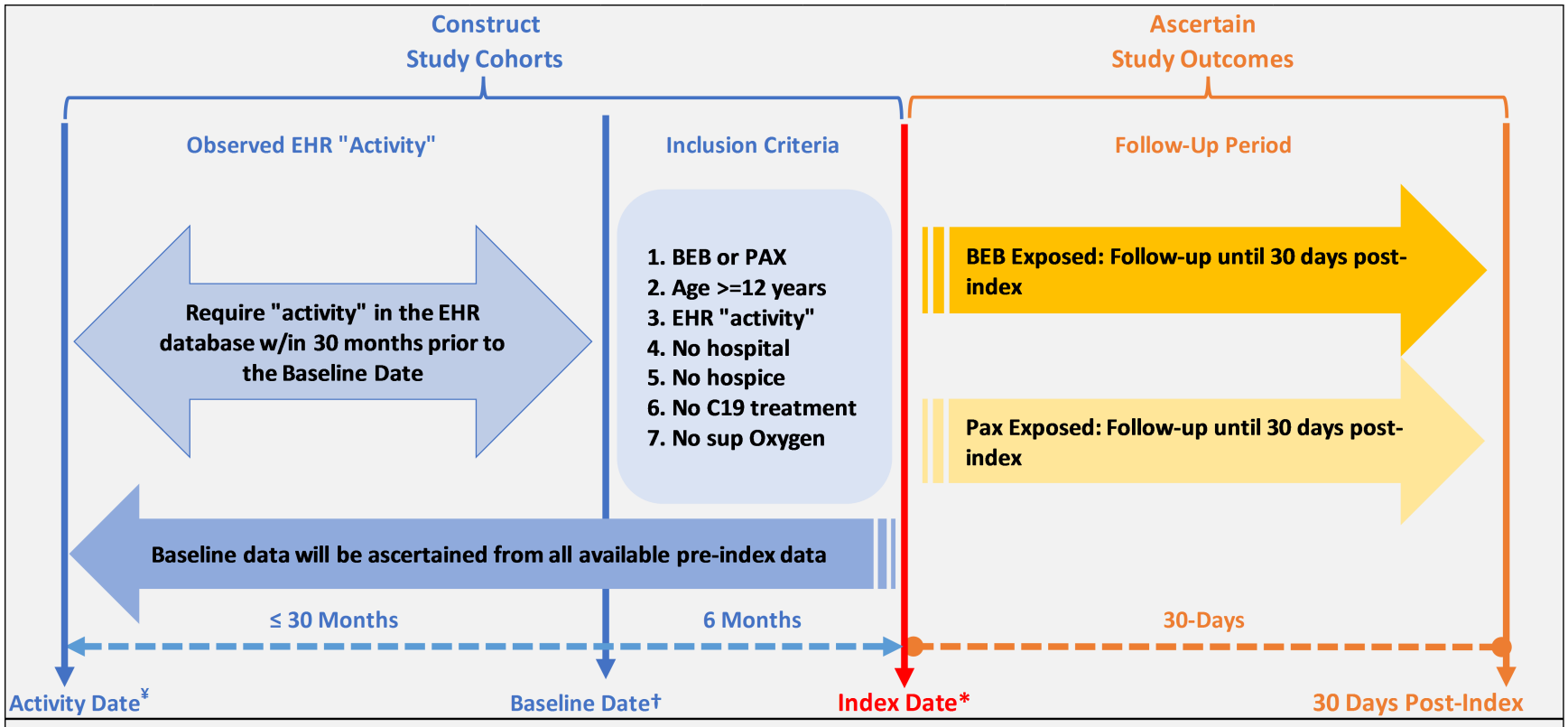
9.2.1. Study Cohort Development

The study cohorts will include patients who received BEB or PAX during the index period (that is, 16 February 2022 to 31 August 2022). The index date is the date of the first BEB or first PAX record during the index period. If a patient was exposed to both BEB and PAX during the index period, they will be included in the cohort (BEB or PAX) based on the first date of BEB or PAX exposure. However, patients who were exposed to both BEB and PAX on the same date will be excluded. Therefore, patients will be included in only 1 cohort for this study.

Both cohorts will be restricted to include patients who meet all the following inclusion/exclusion criteria:

1. BEB or PAX exposure during index period
2. age 12 years and older as of the index date
3. at least 1 healthcare encounter within 6 to 36 months pre-index
    a. Qualifying healthcare encounters include any of the following: office visit, inpatient admission, ED visit, diagnosis or procedure code, clinical measurement (e.g., blood pressure measurement), laboratory or diagnostic test, or medication prescribing record.
4. no inpatient admission within 30 days pre-index (inclusive of index date)
5. no hospice care within 30 days pre-index (inclusive of index date)
6. no treatment indicated or used for COVID-19 within 90 days pre-index (inclusive of index date)
    a. excluding BEB/PAX on the index date, and
7. no supplemental or chronic oxygen therapy within 30 days pre-index (inclusive of index date).

Figure.9.1 provides a schematic representation of the study cohort development and study time periods.



Abbreviations: BEB = bebtelovimab; PAX = Paxlovid; COVID-19 = coronavirus disease 2019; C19 treatment = convalescent plasma, monoclonal antibody therapy, antiviral; EHR = electronic health record; w/in = within.

** The Index date is the date of the first record for BEB or Pax during the index period (02/16/2022-08/31/2022)*

¥ The Activity Date is the date corresponding to 36 months prior to the Index Date

† The Baseline Date is the date corresponding to 6-months prior to the Index Date

Figure.9.1. Schematic representation of the study cohort development and study time periods.

9.3. Variables

9.3.1. Study Variable Identification

The codes used to classify each study variable will be ascertained from the EHR data within the TriNetX Dataworks USA Network (initial analyses). For the supplemental analysis, the EHR data will be augmented with health insurance claims codes (for example, NDC) from the TriNetX Linked Network.

Unless otherwise specified, each study variable will be classified by the presence of 1 code recorded in any setting (for example, inpatient or outpatient). The specific codes to classify each variable will be included in a separate code list document. For each variable type, the code systems include the following:

- Medical diagnoses will be classified using
  - ICD-9/10-CM
- COVID-19 symptoms will be classified using
  - ICD-10-CM
  - LOINC
- Pharmacotherapy will be classified using
  - RxNorm
  - HCPCS
  - CPT
  - NDC
- Healthcare procedures will be classified using
  - ICD-10-CM
  - CPT
  - HCPCS
  - ICD-10-PCS
- Laboratory data will be classified using
  - LOINC
- Healthcare encounters will be classified using
  - CPT
  - HCPCS
  - ICD-10-CM

9.3.2. Variables to Classify the Study Cohorts

BEB and PAX classification

BEB exposure data will be ascertained from facility-based infusion centers and outpatient administrations. BEB exposure will be classified as a binary indicator variable (yes/no) during the index period by at least 1 HCPCS or RxNorm code. The first BEB administration date will be used to classify the BEB index date.

Oral PAX (combination of nirmatrelvir and ritonavir) will be ascertained from facility-based and outpatient medication records. PAX exposure will be classified as a binary indicator variable (yes/no) during the index period by at least 1 RxNorm code. The first PAX date will be assigned as the PAX index date.

Age

Patient age will be classified as of the index date. Age will be classified as a continuous variable (in years), a binary variable (for example, age ≥65 years), and a categorical variable (for example, 12 to <40, 40 to <50, 50 to <65, ≥65). The age categories may be revised after examining the empirical distribution.

Baseline activity in the EHR network

Patients in the study cohorts will be required to have at least 1 healthcare encounter in the EHR database between 6 and 36 months prior to the index date. This requirement is intended to increase the likelihood of ascertaining important study variables by ensuring all patients have a history of receiving care with the contributing HCO network.

Inpatient admission

To restrict the study cohorts to patients with mild-to-moderate COVID-19 disease, patients who had an inpatient admission within 30 days prior to index date will be excluded from the study cohorts (inclusive of the index date). Inpatient admissions will be classified using facility-based EHR data.

Hospice care

Patients with evidence of hospice care within 30 days prior to index date will be excluded from the study cohorts (inclusive of the index date). Hospice care will be classified using facility-based and outpatient EHR data.

Treatments indicated or used for COVID-19

Patients who were exposed to inpatient or outpatient therapy indicated or used for the treatment of COVID-19 within 90 days prior to the index date (inclusive of the index date) will be excluded from both study cohorts. Table.9.1 provides the specific exclusionary treatments.

Convalescent plasma, monoclonal antibody, or antiviral therapy will be classified using outpatient prescribing records and/or facility-based administrations. Of note, this does not include exposure to BEB or PAX on the index date.

Table.9.1. Treatments Indicated or Used for COVID-19

Convalescent plasma
COVID-19 convalescent plasma
Monoclonal antibody therapy
Bamlanivimab
Bamlanivimab/etesevimab
Bebtelovimab
Casirivimab/imdevimab
Sotrovimab
Antiviral therapy
Chloroquine or hydroxychloroquine[a]
Ivermectin[a]
Molnupiravir
Nirmatrelvir/ritonavir
Remdesivir

Abbreviation: COVID-19 = coronavirus disease 2019.

[a] Not approved by the FDA but known to be used for the treatment of COVID-19.

Oxygen support

Patients who utilize oxygen support (that is, invasive/non-invasive ventilation or extracorporeal membrane oxygenation/extracorporeal life support) within 30 days prior to the index date (inclusive of index date) will be excluded. Oxygen support will be classified using outpatient and facility-based EHR data.

9.3.3. Variables to Classify the Study Outcomes – Initial Analyses Using EHR Data Only

Outcomes will be ascertained within 30 days following the index date (that is, the follow-up period). The index date (Day 0) is not included in the follow-up period. All study outcomes will be classified using outpatient and facility-based EHR data within the TriNetX Dataworks USA Network. Outpatient records will be used to augment facility-based records to ascertain deaths which occurred outside the hospital.

The primary outcome is the composite of all-cause hospitalization or all-cause mortality. The primary outcome will be classified by the first evidence of an inpatient confinement or death

during follow-up. The secondary outcomes are all-cause hospitalization, all-cause mortality, and all-cause ED visit.

All-cause hospitalization

All-cause hospitalization will be classified by the first inpatient confinement, including ICU admissions but not 24-hour observations or ED visits. The outcome date will be the date of the first inpatient confinement recorded in the EHR. Subsequent hospitalizations will not be ascertained or analyzed.

All-cause hospitalization includes all inpatient admissions regardless of the admitting or discharge diagnosis. The rationale for studying all-cause hospitalization, as opposed to COVID-19 related hospitalization, is to include events that may otherwise be excluded due to symptom-based coding practices. That is, patients who were hospitalized due to COVID-19 illness but where the primary diagnosis was recorded as something other than COVID-19 (for example, shortness of breath, chronic obstructive pulmonary disease or pneumonia) would require the study investigators to impose subjective criteria to classify a COVID-19 related hospitalization. Using the broader outcome definition of all-cause hospitalization will capture worsening COVID-19 illness without excluding events based on healthcare provider coding practices.

All-cause mortality

All-cause mortality will be classified from in-hospital death, physician-recorded death, or a change in the patients' vital status (death) during follow-up. To protect patient privacy, the month and year of death, for the month following the true death date, are included in TriNetX Dataworks USA EHR data. For example, if the true date of death was 30 April 2022, the month and year of death, as observed in the EHR data, will be May 2022.

To account for this death date characteristic, the ascertainment of all-cause mortality will extend into the month after the follow-up period end date. For example, if the index date for a hypothetical patient was 18 April 2022, the first and last date of the follow-up period would be 19 April 2022 and 18 May 2022, respectively. In this scenario, we would ascertain deaths recorded in May and June 2022. However, the date of death will be assigned to the date of the last post-index EHR record during the follow-up period, that is, 19 April 2022 to 18 May 2022 in this example. If the last post-index EHR record occurs after the end of the follow-up period, for example, after 18 May 2022, the death will not be counted as an outcome event. If there are zero post-index EHR records prior to a recorded death, the death date will be assigned to the first day of follow-up, that is, index date plus 1 day or 19 April 2022 in this example.

ED visit

ED visits (including observation encounters or less than 24-hour stays) not resulting in an inpatient confinement on the same day will be classified by 1 encounter code from facility-based EHRs during follow-up. The first date an ED visit is recorded will define the outcome date. Only the first ED visit during follow-up will be ascertained and analyzed.

9.3.4. Variables to Classify the Study Outcomes – Supplementary Analyses Using EHR Data Linked to Health Insurance Claims and Mortality Data

For supplementary analyses using data from the TriNetX Linked Network, the study outcomes will be the same as those described for the Phase I analyses. The TriNetX Linked Network includes longitudinal, de-identified, patient-level data for a subset of patients whose EHRs are linked to closed medical and pharmacy health insurance claims and to external mortality data. The concept of closed claims means that all healthcare interactions that are paid by the health insurance provider are available, regardless of the site of care.

Participating HCOs within the TriNetX Dataworks USA Network permit the linkage of EHR data to closed health insurance claims data and to external mortality data using de-identified Datavant tokens. Datavant's death index is comprised of mortality data obtained from the Social Security Death Index and from obituary feed data.

The linked population for this study will include a subset of patients from the primary study cohorts who have health records in both the TriNetX EHR database and the closed health insurance claims or mortality databases. The linked population will be used to ascertain events that occur outside the HCO network.

All de-identified patient data in the TriNetX Linked Network are harmonized to standard terminologies. Clinical facts from the EHR and claims data are defined by

- ICD-10-CM diagnosis codes
- CPT, HCPCS, and ICD-10-PCS procedure codes
- NDC, RxNorm Drug, RxNorm Ingredient, CPT, HCPCS, and ICD-10-PCS medication codes, and
- LOINCs for laboratory test results.

The outcomes for the supplementary analyses, using the linked population, are those listed and described in Section 9.3.3. The outcomes will be classified using the same methodology as described for the initial analyses; however, the coding systems will be augmented with codes from health insurance claims data (for example, place of service codes to classify inpatient confinements, ED visits, and discharge status to classify in-hospital death).

9.3.5. Variables to Classify Baseline Covariates

Baseline covariates will be ascertained from ambulatory and inpatient EHRs within the TriNetX Dataworks USA Network. Unless otherwise specified, each baseline covariate will be classified by 1 code using all available data prior to and including the index date. If more than 1 baseline value is available (for example, BMI and BP), the value recorded on the index date or closest to the index date will be ascertained.

Demographics

- Age will be classified as a continuous variable (in years), a binary variable (for example, ≥65 [yes/no]), and a categorical variable (for example, 12 to <40, 40 to <50, 50 to <65, ≥65). The age categories may be revised after examining the observed distribution.
- Sex will be classified as a binary variable (male/female) as reported in the EHR.
- Race will be classified as a categorical variable (for example, Black, Caucasian, Other, Unknown/Missing). Race categories may be revised after examining the distribution of available data.

Clinical parameters

Clinical parameters will be classified from EHR data during *a priori* specified ascertainment windows in close temporality prior to BEB and PAX initiation. This approach provides baseline data with greater clinical relevance regarding patient health status immediately prior to or at the time of BEB and PAX initiation.

However, with this approach, it is expected that a large percentage (for example, more than 50%) of patients will not have recorded clinical data during the ascertainment window as listed here, and longer ascertainment windows would likely yield lower levels of missingness. The rationale for ascertaining and including these variables, given the high degree of missingness, is to better describe the study cohorts despite the inherent limitations of absent data.

- BP will be ascertained within 7 days prior to the index date using the last available pre-index value and classified as a categorical variable (for example, normotensive [systolic BP ≤120 mm Hg and diastolic BP ≤80 mm Hg], Stage 1 [systolic BP 130 to 139 mm Hg or diastolic BP 80 to 89 mm Hg], Stage 2 [systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg], missing)
- Oxygen saturation will be ascertained within 7 days prior to the index date using the last available pre-index value and classified as a continuous and categorical variable (for example, <85%, 85 to <95%, ≥95%, missing)
- BMI will be ascertained using the last available value prior to the index date as reported in the EHR or calculated using the formula:
    - $\text{BMI} = \text{Weight in Kg}/\text{Height in m}^2$
        - Classified as a categorical variable
            - Underweight: BMI <18.5 kg/m^2
            - Normal: 18.5 ≤BMI<25.0 kg/m^2
            - Overweight: 25.0 ≤BMI<30.0 kg/m^2
            - Obese: BMI ≥30.0 kg/m^2
            - Missing

Smoking status

Smoking status will be classified as reported in the EHR as current, past, or unknown. The last available value prior to the index date and as reported in the EHR will be used.

Laboratory data

Serum creatinine, used to calculate the eGFR, will be ascertained using all available pre-index data. However, it is expected that serum creatinine will be absent for a large percentage (for example, more than 50%) of cohort members.

The rationale for ascertaining and including eGFR, given the high degree of absent data, is to better describe the study cohorts and to augment the classification of CKD. eGFR will be calculated using the Mayo Clinical Quadratic formula and classified as a continuous and categorical variable (for example, eGFR ≥90, 60 to 89, 30 to 59, 15 to 29, <15 mL/min/1.73 m², missing).

Comorbidities

Baseline comorbidities will include conditions associated with high risk of severe COVID-19 illness and hospitalization as defined by the CDC (Kompaniyets et al. 2021; CDC 2022c). Additionally, guided by the recent COVID-19 publication by McCreary et al. (2022), we will include comorbidities to classify immunocompromised status.

Each baseline comorbidity will be classified using all available pre-index data as a binary variable (yes/no) by at least 1 inpatient or outpatient diagnosis code. In addition to diagnosis codes, the classification of CKD and obesity will be augmented by eGFR (that is, eGFR <60 mL/min/1.73 m²) and BMI (that is, BMI >30 kg/m^2). Patients who do not have a code or laboratory/clinical value for a given comorbidity will be classified as not having the comorbidity.

Diagnosis codes to classify each comorbidity will be ascertained from the Agency for Healthcare Research and Quality Clinical Classifications Index using the lowest level clinical classifications index grouping for each comorbidity.

Table.9.2 presents baseline comorbidities. Table.9.3 presents additional baseline comorbidities to classify immunocompromised status.

Table.9.2. Baseline Comorbidities

Baseline comorbidities	
Pulmonary	Disabilities
Alpha 1 antitrypsin deficiency	Attention Disorder (ADHD)
Asthma	Cerebral Palsy
Bronchopulmonary dysplasia	Congenital Malformations (Birth Defects)
COPD and bronchiectasis	Intellectual and Developmental Disabilities
Cystic fibrosis	Learning Disabilities
Interstitial lung disease	Limitations with self-care
Pulmonary embolism	Spinal Cord Injuries
Pulmonary hypertension	
Endocrine	Infectious disease
Diabetes Type 1	Hepatitis B
Diabetes Type 2	Hepatitis C

Baseline comorbidities	
Diabetes Type 1 or 2 w/complications	Tuberculosis
Obesity	
Renal	Neurocognitive
Chronic kidney disease	Dementia
End stage renal disease	
Hepatic	Mental health
Alcoholic liver disease	Anxiety and fear-related disorders
Non-alcoholic fatty liver disease	Mood disorders, including depression
Autoimmune hepatitis	Schizophrenia spectrum disorders
Cirrhosis	Substance use disorders
Circulatory	Blood disorder
Cardiomyopathy or myocarditis	Aplastic anemia
Cerebrovascular disease	Sickle cell disease
Coronary artery disease	Thalassemia
Heart failure	
Hypertension	Pregnancy

Abbreviations: ADHD = attention deficit hyperactivity disorder; COPD = chronic obstructive pulmonary disease.

Table.9.3. Baseline Comorbidities to Classify Immunocompromised Status

Baseline comorbidities to classify immunocompromised status	
Aortic arch syndrome [Takayasu]	Mast cell activation disorder
Autoimmune hepatitis	Mast cell activation syndrome & related disorders
Autoimmune lymphoproliferative syndrome	Microscopic polyangiitis
Behcets disease	Multifocal fibrosclerosis
Chronic thyroiditis	Multisystem inflammatory syndrome
CR (E) ST syndrome	Necrotizing vasculopathies
Cryoglobulinemia	Overlap syndromes
Cytokine release syndrome	Personal history of antineoplastic chemotherapy
Dermatomyositis	Personal history of immunosuppression therapy
Dermatopolymyositis	Personal history of irradiation
Diffuse (eosinophilic) fasciitis	Personal history of monoclonal drug therapy
Disorders involving immune mechanism	Personal history of systemic steroid therapy
Giant cell arteritis	Polyarteritis nodosa & related conditions
Giant cell arteritis with polymyalgia rheumatica	Polyclonal hypergammaglobulinemia
Graft versus host disease	Polymyalgia rheumatica
HSCT-TMA	Polymyositis
Hereditary alpha tryptasemia	Relapsing panniculitis [Weber-Christian]
Human immunodeficiency virus	Rheumatoid arthritis
Hypergammaglobulinemia, unspecified	Sarcoidosis
Hypermobility syndrome	Sjogren syndrome

Baseline comorbidities to classify immunocompromised status	
Hypersensitivity angiitis	Systemic involvement of connective tissue
Immune reconstitution syndrome	Systemic lupus erythematosus
Immunodeficiency (primary and secondary)	Systemic sclerosis
Inflammatory bowel disease	Transplant – solid organ or hematopoietic
Juvenile dermatomyositis	Thrombotic microangiopathy
Lethal midline granuloma	Wegener's granulomatosis
Malignancy – hematologic	
Malignancy - solid organ (except skin)	

Abbreviations: HSCT-TMA = Hematopoietic stem cell transplant thrombotic microangiopathy.

COVID-19 diagnosis (past and present)

A present COVID-19 diagnosis will be ascertained within 7 days pre-index and classified as a binary variable. A past COVID-19 diagnosis will be ascertained anytime in the baseline period, except within 7 days pre-index.

COVID-19 symptoms

The COVID-19 related symptoms listed in Table.9.4 will be ascertained within 7 days pre-index and classified as binary variables.

Table.9.4. Baseline Symptoms

Baseline symptoms
Anosmia and parosmia
Cough
Diarrhea
Fatigue
Fever or chills
Headache
Muscle or body aches/myalgia
Nausea or vomiting
Shortness of breath or difficulty breathing/dyspnea
Sore throat/pharyngitis

Pharmacotherapy

Baseline pharmacotherapy will be used to describe the study cohorts and evaluated for inclusion in the PS generating model.

Pharmacotherapy utilization, described as binary variables, will be classified as present and past. Unless otherwise specified, present use will be classified within 6-months pre-index (that is, index date to 6-months pre-index, inclusive of both dates). Past use will be classified any time prior to 6-months pre-index.

Table.9.5 presents the specific baseline comorbidities.

Notes regarding specific medications:

- COVID-19 vaccines:
  - Classified as
    - present use: within 9 months pre-index
    - past use: greater than 9 months pre-index
  - Based on feasibility from the EHR data ascertained in September 2022, at least 1 past COVID-19 vaccination was documented for approximately 25% of patients exposed to BEB/PAX. Approximately 12% of patients have documentation of a present COVID-19 vaccination.
- Antiemetics (used to augment the classification of nausea and vomiting)
  - Classified as
    - present use: within 7 days pre-index
    - past use: greater than 7 days pre-index
- Corticosteroids (inhaled, oral, or systemic)
  - Classified as
    - present use: within 7 days pre-index
    - past use: greater than 7 days pre-index
- Antivirals
  - Classified as
    - present use: within 6 months pre-index
      - Note: Patients will be excluded who received antivirals listed in Table.9.1 within 90 days pre-index
    - past use: greater than 6 months pre-index
- SARS-CoV-2–neutralizing monoclonal antibodies
  - Classified as
    - present use: within 6 months pre-index
      - Note: Patients will be excluded who received SARS-CoV-2–neutralizing monoclonal antibodies listed in Table.9.1 within 90 days pre-index
    - past use: greater than 6 months pre-index

Table.9.5. Baseline Pharmacotherapy

Medication Class	Medication Sub-class	Medication
COVID-19 vaccine		See code list for details
Anticoagulant	Novel anticoagulant	Rivaroxaban, dabigatran, apixaban, edoxaban
	Anticoagulant	Warfarin
Antihypertensive		Angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, MRA, loop diuretic, thiazide diuretic, beta blocker
Lipid-lowering agent	Statin	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin calcium, simvastatin
	Cholesterol absorption inhibitor	Ezetimibe
	Bile Acid Sequestrant	Cholestyramine, colestipol, colesevelam
	PCSK9 inhibitor	Alirocumab and evolocumab
	Adenosine triphosphate-citrate lyase inhibitor	Bempedoic acid
	Fibrate	Gemfibrozil, fenofibrate, clofibrate
Bronchodilator	Short-acting beta2-agonist	Albuterol, levalbuterol, albuterol and ipratropium bromide
	Long-acting beta2-agonist	Salmeterol, arformoterol, formoterol, olodaterol, vilanterol
	Anticholinergic	Ipratropium bromide, tiotropium bromide
	Theophylline	Theophylline
Leukotriene modifier		Montelukast, zafirlukast, and zileuton
Antiemetic		Metoclopramide, ondansetron, prochlorperazine, promethazine
Antidiabetic agent	Alpha-glucosidase inhibitor	Acarbose, miglitol
	Amylin analog	Pramlintide
	Dipeptidyl peptidase 4 inhibitor	Alogliptan, linagliptin, saxagliptin, sitagliptin
	Incretin mimetic	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide
	Insulin	
	Meglitinide	Nateglinide, repaglinide
	Non-sulfonylurea	Metformin
	SGLT-2 inhibitor	Canagliflozin, dapagliflozin, empagliflozin

Medication Class	Medication Sub-class	Medication
	Sulfonylurea	Chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide
	Thiazolidinedione	Rosiglitazone, pioglitazone
Immune modulatory agent	B-cell depleting therapy	Belimumab, ocrelizumab, rituximab, ofatumumab
	CAR-T therapy	Axicabtagene ciloleucel, brexucabtagene autoleucel, ciltacabtegene autoleucel, idecabtagene vicleucel, tisagenlecleucel
	Cell death protein 1 therapy (PD-1 and PDL-1)	Cemiplimab, dostarlimab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab
	Corticosteroid (inhaled, oral, or systemic)	Beclomethasone, budesonide, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, fluticasone, mometasone
	Immunosuppressant	Cyclosporine, everolimus, sirolimus, tacrolimus
	TNF inhibitor	Adalimumab, etanercept, golimumab, infliximab
	Other immune modulatory agent	Abatacept, anakinra, tocilizumab, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine, cyclophosphamide
Antiviral		Chloroquine, hydroxychloroquine sulfate, ivermectin, molnupiravir, nirmatrelvir and ritonavir, ritonavir, remdesivir
SARS-CoV-2–neutralizing monoclonal antibodies		Tixagevimab and cilgavimab, bamlanivimab and etesevimab, casirivimab and imdevimab, sotrovimab

Abbreviations: CAR-T = chimeric antigen receptor-modified T cell; COVID-19 = coronavirus disease 2019; MRA = mineralocorticoid receptor antagonist; PCSK9 = proprotein convertase subtilisin/kexin Type 9; PD-1 = programmed cell death 1; PDL-1 = programmed cell death ligand 1; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGLT-2 = sodium-glucose co-transporter-2; TNF = tumor necrosis factor.

Healthcare resource utilization

Baseline HRU variables will be classified by 1 code from facility and ambulatory encounter records within 7 days pre-index and within 1 year pre-index. HRU will be described as continuous (for example, number of office visits), binary (for example, inpatient admission [yes/no]), and categorical variables. The categories will be empirically derived from the observed distribution of the continuous variables.

The HRU variables include the following:

- outpatient office encounter (including telehealth and virtual encounters)
- inpatient admission (including ICU admissions)
    - Classified within 1 year pre-index excluding the 30 days before the index date. Note: Patients will be excluded who had an inpatient admission within 30 days pre-index (inclusive of the index date).
- ED visit, and
- observation encounter (that is, less than 24-hour stay).

HCO type

HCO type will be classified as a categorical variable based on the facility where the BEB/PAX record occurred on the index date.

The categories include the following:

- academic medical center
- IDN
- specialty hospital
- large specialty physician practice, and
- other

9.4. Follow-Up and Censoring (Primary and Sensitivity Analysis Methodology)

Follow-up begins on the day after index date (that is, index date plus 1 day) and continues until 30-days post-index. Using an ITT approach, the exposure status (that is, BEB or PAX) classified on the index date will be carried forward for the entire 30-day follow-up period. With this approach, all patients in the study cohorts will be included in the analysis set, regardless of post-index use of convalescent plasma, monoclonal antibody, or antiviral therapy.

We will describe the proportion of patients who received post-index convalescent plasma, monoclonal antibody, or antiviral treatment indicated, authorized, or used to treat or prevent COVID-19 (excluding BEB/PAX on the index date). Table.9.1 lists the specific treatments.

9.5. Data Sources

9.5.1. TriNetX Dataworks USA Network (Initial Data Source)

This observational cohort study will use the EHR data from the TriNetX Dataworks USA Network as the primary data source. This de-identified, longitudinal data source includes outpatient and inpatient EHRs from participating HCOs across the US. These patient-level data are sourced from a global federated health research network (Dataworks - USA) with real-time updates, typically every 2 to 4 weeks. Currently, the standardized EHR fields are available for approximately 86 million patients from 54 US-based HCOs. Network members include academic medical centers, IDNs, specialty hospitals, and large specialty physician practices.

EHR data from the TriNetX Dataworks USA Network are generated from routine healthcare encounters within an open network. Patients may receive all or a proportion of their care through this network. Healthcare encounters which occur outside the contributing HCO network will not be observed. To mitigate the potential for missing data, eligibility requirements have been incorporated to restrict the study population to only patients who previously received care within the contributing HCO network.

All patient data in the TriNetX Dataworks USA Network are harmonized to standard terminologies. Clinical facts from the EHR are defined by

- ICD-9/10-CM diagnosis codes
- CPT, HCPCS, and ICD-10-PCS procedure codes
- RxNorm medication codes
- VA drug classification system, ICD-10-PCS medication codes, and
- LOINCs for laboratory test results.

This EHR data source is rich in longitudinal data and includes

- laboratory test results (including serum creatinine to classify eGFR)
- pharmacotherapy data (to classify BEB and PAX exposure)
- inpatient admission, in-hospital and physician-recorded death, and ED encounter data (to classify the study outcomes), and
- detailed data on patient demographics, medical history, pharmacotherapy, and healthcare utilization (to classify baseline patient characteristics).

9.5.2. TriNetX Linked Network (Supplemental Data Source)

For supplemental analyses, the source population and study cohorts will be developed from the TriNetX Linked Network. The TriNetX Linked Network includes patients from the TriNetX Dataworks USA Network EHR database who also have linked closed health insurance claims data and linked mortality data.

The linked study population will include a subset of patients in the primary study cohorts who have health records in both the TriNetX Dataworks USA Network EHR database and in the linked claims or mortality databases. Patients included in the linked study population will be used to ascertain study outcomes and covariate data that were documented outside the EHR database. For example, the linked study population will enable the ascertainment of

hospitalizations and deaths that occur outside the site-specific care setting of the HCOs contributing EHR data to the TriNetX Dataworks USA Network.

Participating HCOs within the TriNetX Dataworks USA Network permit the linkage of EHR data to closed health insurance claims data, including medical and pharmacy claims, and mortality data using de-identified tokens from Datavant. Datavant's death index is comprised of data from the Social Security Death Index and obituary feed data. The HCOs that contribute data to the TriNetX Linked Network are de-identified as are the individual patient records. Approximately 10% of all patients in the TriNetX Dataworks USA Network are included in the TriNetX Linked Network.

All patient-level, longitudinal data in the TriNetX Linked Network are harmonized to standard terminologies. Clinical records from the EHR and claims data are defined by

- ICD-9/10-CM diagnosis codes
- CPT, HCPCS, and ICD-10-PCS procedure codes
- NDC, RxNorm, CPT, HCPCS, and ICD-10-PCS medication codes, and
- CPT and LOINCs for laboratory test results.

9.6. Study Size

9.6.1. Feasibility Assessment

From 16 February 2022 to 31 August 2022, a total of 14,347 and 40,369 patients received BEB and PAX, respectively. After enforcing the proposed inclusion/exclusion criteria, it is estimated that 8794 patients receiving BEB and 24,744 patients receiving PAX will be available for matching (Table.9.6).

Table.9.6. Feasibility Assessment

Feasibility Assessment - Estimated (Data From 16 Feb 2022 to 31 Aug 2022)				
0	Included in source population	86,489,783		
		BEB	**PAX**	**Retained[a]**
1	Exposure to BEB or PAX during index period	14,347	40,369	n/a
2	Age ≥12 years at index date	14,275	40,167	0.995
3	≥1 healthcare encounter within 6-36 months pre-index	9993	28,117	0.700
4	No inpatient admission within 30 days pre-index	9693	27,273	0.970
5	No hospice care within 30 days pre-index	9644	27,137	0.995
6	No treatment for COVID-19	9066	25,509	0.940
7	No supplemental or chronic oxygen therapy	8794	24,744	0.970

Feasibility Assessment - Estimated (Data From 16 Feb 2022 to 31 Aug 2022)				
	Estimated sample size based on I/E criteria	**8794**	**24,744**	
n/a	COVID-19 vaccination anytime pre-index	2198	6186	0.250
n/a	COVID-19 vaccination within 9 months pre-index	1099	3093	0.500

Abbreviations: BEB = bebtelovimab; COVID-19 = coronavirus disease 2019; I/E criteria = inclusion/exclusion criteria; n/a = not applicable; PAX = Paxlovid.

a "Retained" refers to the estimated proportion of patients to be retained after enforcing each inclusion or exclusion criterion.

9.6.2. Noninferiority Margin

For the NI study design of BEB versus PAX, the fixed margin method, also referred to as the 95% to 95% method, will be used to define the NI margin for the RD (FDA 2016):

- The first 95% refers to the CI of the estimated effect of the control based on the historical studies demonstrating the effect.
- The second 95% refers to the CI used to test the null hypothesis in the NI study with the first 95% lower CI defined as the margin (M1).

In this study, a fraction (50%) of M1 is used to provide reasonable assurance that BEB preserves a clinically sufficient fraction of the PAX treatment effect.

Based on this consideration, the NI margin was calculated using the available historical data from the PAX Phase 2 to 3 double-blind, randomized, controlled trial (Hammond et al. 2022). In this trial, symptomatic, unvaccinated, non-hospitalized adults at high risk of progression for COVID-19 were assigned in a 1:1 ratio to receive either PAX or placebo every 12 hours for 5 days to assess COVID-19–related hospitalization or death from any cause through Day 28. The study showed a reduction in COVID-19–related hospitalization or death of 6.32% (95% CI: -9.04% to -3.59%) for PAX compared to placebo.

The lower 95% CI (3.59%) is used in our NI study as the M1 and 50% of M1 (1.795%) is used as the NI margin (M2) for this BEB versus PAX NI study. This M2 of absolute 1.795% increase in hospitalization or death must be excluded by the one-sided 95% CI for the hospitalization/mortality RDs between BEB and PAX in the NI study to establish the NI of BEB compared with PAX.

9.6.3. Sample Size and Power

The primary objective is to estimate the 30-day RD and 95% CI of the composite outcome of all-cause hospitalization or all-cause death for patients who received BEB compared with patients who received PAX.

For the NI test of the primary objective, N=1065 for each arm will provide 80% power and N=1390 for each arm will provide 90% power, assuming a hospitalization rate of 1.4% for BEB and 1.2% for PAX (Razonable et al. 2022) with the NI margin of 1.795%.

9.7. Data Management

The TriNetX Dataworks USA Network platform natively supports the ingestion of EHR data, such as

- demographics
- diagnosis history
- medications administered and prescribed
- procedures
- laboratory results, and
- vital signs from a variety of external sources (for example, i2b2, Observational Health Data Sciences and Informatics, Epic).

A combination of purpose-built products and toolkits have been developed by the TriNetX Engineering and Technical Services teams for reuse across the federated network.

Before being accessible through the network platform, the data are first staged within the TriNetX clinical data warehouse. Once the data reside within the clinical data warehouse, the EHR data are mapped to a common data model, direct patient identifiers are removed, and data quality measures are run to assess the cleanliness, consistency, correctness, and completeness of the data. After this evaluation process is completed, the data are ingested into optimized data marts designed to support the capabilities and performance of the network platform. As TriNetX Dataworks USA is a federated network, all the technology and data reside either on a TriNetX appliance, at the HCO, or within a cloud-based hosting infrastructure.

The source population and study cohorts required for this study will be defined using terminologies in the TriNetX Dataworks USA Network platform. A download of de-identified, patient-level data will be extracted through a secure process and saved as set of CSV files. The CSV files will be combined into an analytic dataset based on synthetic patient identifiers and transformed in the Stata data files. The files will be stored on a shared drive to be accessed by the lead scientist and analyst. All analyses will be performed using Stata Version 16.1 (StataCorp LLC; College Station, Texas USA).

10. Statistical Analysis Plan

10.1. Analysis Overview

The following steps will be followed sequentially:

1. Construct BEB and PAX study cohorts (unmatched):
    a. describe patients included and excluded, and
    b. describe baseline characteristics and standardized differences for unmatched cohorts.
2. Construct matched cohorts using CEM in conjunction with PS matching:
    a. evaluate PS distributions before and after matching, and
    b. describe baseline characteristics and standardized differences for matched cohorts.
3. Describe proportion of patients in the matched cohorts who initiated post-index convalescent plasma, monoclonal antibody, or antiviral therapy for the treatment of COVID-19.
4. Execute analysis for the primary objective:
    a. unmatched and matched cohorts.
5. Execute analyses for the secondary objectives:
    a. unmatched and matched cohorts.
6. Execute subgroup analyses:
    a. matched cohorts.
7. Execute sensitivity analyses:
    a. matched cohorts.
8. Repeat Steps 1 and 2 using data from the TriNetX Linked Network (supplementary analysis).
9. Execute analyses for the primary and secondary objectives using data from the TriNetX Linked Network (Steps 3 to 7).

10.1.1. Method to Control for Confounding

Confounding control will be achieved using CEM on highly selected and *a priori* defined baseline variables in conjunction with PS matching on a broader set of baseline variables.

The rationale for using CEM in conjunction with PS matching is 2-fold. Firstly, it ensures tight control of critical baseline confounders (for example, age 65 years or older, immunocompromised, COVID-19 vaccine exposure, and pre-index ED visit). Secondly, it permits sensitivity or restricted analyses on the CEM variables without breaking the matched pairs used for the primary analyses. For example, if age 65 years or older (yes/no) and immunocompromised status (yes/no) are included as CEM variables, these covariates will be consistent for patients in each matched pair. Sensitivity analyses could then be restricted to patients age 65 years or older or immunocompromised patients without re-matching.

The 4 binary CEM variables include:

- age >65

- immunocompromised
- ED visit within 7 days pre-index (inclusive of the index date), and
- COVID-19 vaccination within 9 months pre-index.

The method of PS matching within each exact matching category (n=16 CEM categories) is the primary approach. However, should there be insufficient patients taking BEB or PAX available in each exact matching category, we may consider dropping CEM variables. The *a priori* specified threshold for dropping a CEM variable is less than 85% matching rate (using 1:1 matching) within any CEM category.

In summary, the predicted probability of exposure (that is, BEB versus PAX) will be generated from a multi-variable logistic regression model conditioned on baseline covariates. The CEM procedure will then be implemented to create unique groupings or risk-sets based on the observed combination of CEM variables. Each CEM risk-set will include at least 1 BEB exposed patient and potentially many PAX exposed patients. Within each CEM risk-set, the match selected for each BEB exposed patient will be the PAX exposed patient with the nearest PS values. Nearest neighbor matching without replacement with a caliper of 0.01 on the PS will be used to ensure the estimated probability of exposure does not differ by more than 1.0% between each patient in each matched pair. Each BEB exposed patient will be matched to 1 PAX exposed patient (1:1 matching).

Using methodology to generate a high-dimensional PS, all baseline covariates presented in the baseline covariate section (Section 9.3.5 and Table.9.2, Table.9.3, Table.9.4, and Table.9.5) and 2-way interaction terms will be evaluated for inclusion in the PS generating model, as permitted given model degrees of freedom. High-dimensional PS methodology uses a data-driven approach to covariate selection that prioritizes covariates according to the amount of confounding each covariate accounts for after adjusting for demographic covariates (Schneeweiss et al. 2009). To avoid model assumption violations, continuous baseline variables will be categorized into quintiles or dichotomized, if a clinically relevant threshold exits.

Baseline covariates will not be included in the PS generating model if any cell count of the 2x2 table is less than 10 or if the variable has missing values for more than 5% of cohort members. When a given baseline variable (for example, BMI, age, sex) has missingness more than 0% and less than or equal to 5%, the variable value will be imputed to the most prevalent value of the observed variable distribution. The rationale for imputing missing baseline covariate values, where missingness is more than 0% and less than or equal to 5%, is to retain the analytic set sample size while introducing only a minor degree of misclassification bias, which is likely to be non-differential. A sensitivity analysis will be conducted using multiple imputation of baseline covariates where the missingness pattern is more than 0% and less than or equal to 30% (Granger et al. 2019).

The following PS generating model will be used to predict exposure status given baseline covariates:

- **logistic regression model to generate the PS:**

$$\text{logit}\{\Pr(A_i = 1)\} = \alpha_0 + \alpha_1 Z_i$$

where, A = exposure status; Z = baseline covariates.

Based on this model, the predicted probability of BEB exposure (versus PAX exposure) given baseline covariates (that is, the PS) will be generated. Matching on the PS, in conjunction with CEM matching, will then be used to account for baseline confounding.

10.2. Analysis

10.2.1. Describe Baseline Characteristics

Analysis: Describe baseline characteristics

Analysis type: Descriptive

Analysis sets:

- BEB and PAX unmatched cohorts
- BEB and PAX matched cohorts

Methodology:

Baseline variables will be ascertained using all available EHR data on or before the index date, unless otherwise specified. If data are not available on the index date, the last pre-index value will be used. For continuous variables (e.g., eGFR), if data are not available during the baseline period, the variable value will be set to missing. Binary and categorical variables will be described as the frequency and percentage of patients. Continuous variables will be described by the

- mean
- standard deviation
- median
- 25th and 75th percentiles, and
- minimum and maximum.

Standardized differences (BEB versus PAX) will be calculated before matching and after matching. Standardized differences describe the balance of a given variable between 2 groups (cohorts). Absolute standardized differences ≥0.1 and <0.1 depict poor balance and acceptable balance, respectively.

Additionally, we will describe the PS distributions before and after matching.

10.2.2. Primary and Secondary Analyses

Outcomes

- Primary (composite outcome)
  - All-cause hospitalization or all-cause mortality
- Secondary
  - All-cause hospitalization

- All-cause death
- All-cause ED visit

Analysis type: Descriptive and comparative

Analysis sets:

- BEB and PAX unmatched cohorts
- BEB and PAX matched cohorts

Exposure contrast: BEB versus PAX (reference category)

Measures of effect

- Cumulative incidence and 95% CI
  - Clopper-Pearson 95% CI (exact binomial)
- RD and 95% CI

Hypothesis testing (primary analysis only)

- Hypothesis testing will be conducted for the primary outcome for patients included in the matched cohorts.
- The NI null hypothesis for this objective will be tested using the 1-sided Type I error of 0.025 by setting the RD_{UCL} 95% CI of the BEB versus PAX to be less than the prespecified NI margin of 1.795%. The null hypothesis is *the risk of 30-day all-cause hospitalization or all-cause death is higher for patients treated with BEB compared to patients treated with PAX – by at least 1.795%.* We reject the null hypothesis, and establish NI, if the RD_{UCL} excludes 1.795%.
- The NI null (H_0) and alternative (H_1) hypotheses are:
  - NI H_0: $RD_{UCL} \geq 1.795\%$; NI H_1: $RD_{UCL} < 1.795\%$
- Figure.8.1 shows the 5 potential results (A, B, C, D and E) that will be used to test the null hypothesis (Mauri and D'Agostino 2017). If potential results A, B, or C are observed, it will be established that BEB treatment is not inferior to PAX treatment. If potential results D or E are observed, NI will not be established.
  Note: The hypothetical BEB versus PAX RDs are presented as percentages with 2-sided 95% CIs to facilitate interpretation (RD null value = 0.0%).

Table shell: see Table.10.1.

Table.10.1. Table Shell for Primary and Secondary Analyses for Unmatched and Matched Cohorts

Outcome	Sample Size	Exposure	Analysis	Number of Patients with Event	Cumulative Incidence (CI)			Risk Difference (RD, PAX = reference)		
					CI	95% LCL	95% UCL	RD	95% LCL	95% UCL
Unmatched cohorts										
Primary analysis										
Hospitalization or death	N	BEB	Unmatched	n						
	N	PAX		n						
Secondary analyses										
Hospitalization	N	BEB	Unmatched	n						
	N	PAX		n						
ED visit	N	BEB	Unmatched	n						
	N	PAX		n						
Death	N	BEB	Unmatched	n						
	N	PAX		n						
Matched cohorts										
Primary analysis										
Hospitalization or death	N	BEB	Matched (1:1)	n						
		PAX		n						
Secondary analyses										
Hospitalization	N	BEB	Matched (1:1)	n						
		PAX		n						
ED visit	N	BEB	Matched (1:1)	n						
		PAX		n						

Outcome	Sample Size	Exposure	Analysis	Number of Patients with Event	Cumulative Incidence (CI)			Risk Difference (RD, PAX = reference)		
					CI	95% LCL	95% UCL	RD	95% LCL	95% UCL
Death	N	BEB	Matched (1:1)	n						
		PAX		n						

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; CI = cumulative incidence; ED = emergency department; N = number of patients in the cohort; n = number of patients with the event; PAX = Paxlovid; RD = risk difference.

Note: For the RD analyses, PAX is the reference category.

10.2.3. Subgroup Analyses

Among patients included in the matched pairs, the same primary and secondary analyses will be conducted for the subgroups presented here. The subgroup analyses will be conducted for

1) all matched pairs
2) matched pairs with the condition present (for example, age 65 years or older), and
3) matched pairs with the condition absent (for example, age less than 65 years).

Table.10.2 reports the results for all subgroup analyses.

- Age 65 years or older (yes/no)
    - Analyses will be conducted for matched pairs stratified by age at least 65 years and age less than 65 years. The rationale for this analysis is to evaluate the consistency of the treatment effect for older and younger patients who were exposed to BEB or PAX for the treatment of COVID-19.
- COVID-19 vaccine status (yes/undetermined)
    - Analyses will be conducted for matched pairs stratified by COVID-19 vaccine status. That is where COVID-19 vaccination status was documented in the prior 9 months and where vaccine status was undetermined. The rationale for this analysis is to evaluate the treatment effect within the subgroup of patients where there is the lowest likelihood of vaccine status misclassification.
- Pre-index ED visit (yes/no)
    - Analyses will be conducted for matched pairs who had and did not have an ED visit within 7 days before initiating BEB or PAX. As we will match on baseline ED visit status (that is, within 7 days pre-index), we have eliminated potential channeling bias by ED visit status, which may be a marker of COVID-19 disease severity. The rationale for this sensitivity analysis is to evaluate the consistency of the treatment effect for patients who had more severe disease (that is, patients who had a pre-index ED visit) and for patients who had less severe disease (that is, patients who did not have a pre-index ED visit).
- Immunocompromised (yes/no)
    - Analyses will be conducted for matched pairs stratified by baseline immunocompromised status (McCreary et al. 2022). This analysis will evaluate the consistency of the treatment effect for patients who were moderately to severely immunocompromised and for patients who were not immunocompromised.
    - Table.10.3 includes the algorithm, defined by McCreary et al. (2022) to classify immunocompromised status.

Table.10.2. Primary and Secondary Analyses for Each Subgroup (Matched Cohorts Only)

Outcome	Number of Matched Pairs	Exposure	Matched Pairs Analyzed	Number of Pts with Event	Cumulative Incidence (CI)			Risk Difference (RD, PAX = reference)		
					CI	95% LCL	95% UCL	RD	95% LCL	95% UCL
Primary analysis										
Hospitalization or death	N	BEB	All	n						
		PAX		n						
Hospitalization or death	N	BEB	With condition present	n						
		PAX		n						
Hospitalization or death	N	BEB	With condition absent	n						
		PAX		n						
Secondary analyses										
Hospitalization	N	BEB	All	n						
		PAX		n						
Hospitalization	N	BEB	With condition present	n						
		PAX		n						
Hospitalization	N	BEB	With condition absent	n						
		PAX		n						
ED Visit	N	BEB	All	n						
		PAX		n						
ED Visit	N	BEB	With condition present	n						
		PAX		n						
ED Visit	N	BEB	With condition absent	n						
		PAX		n						
Death	N	BEB	All	n						
		PAX		n						
Death	N	BEB	With condition present	n						
		PAX		n						
Death	N	BEB	With condition absent	n						
		PAX		n						

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; CI = cumulative incidence; ED = emergency department; N = number of patients in the cohort; n = number of patients with the event; PAX=Paxlovid; RD = risk difference.

Note: For the RD analyses, PAX is the reference category.

Table.10.3. Baseline Immunocompromised Classification

Baseline immunocompromised classification - by at least 1 condition listed in this table
Procedures
Radiation oncology procedure
Organ or stem cell transplant
Comorbidities
Cancer diagnosis for example, heme malignancies, leukemia, lymphoma, myeloma, breast cancer, bone cancer, solid organ cancers, Myelodysplastic syndromes, myeloproliferative disorders, chronic lymphocytic leukemia, acute myeloid leukemia, diffuse large B-cell lymphoma, follicular lymphoma.
Diagnosis of graft versus host disease
Systemic lupus erythematosus
Rheumatoid arthritis
Inflammatory bowel disease
HIV
Other conditions indicative of immune compromised see Table.9.4
Pharmacotherapy
Any CAR-T therapy
Actively being on biologics
Cell death protein 1 (PD-1) therapy
B-cell depleting therapy medications

Abbreviations: CAR-T = chimeric antigen receptor-modified T cell; HIV = human immunodeficiency virus.
Citation: from Appendix B of McCreary et al. 2022

10.2.4. Sensitivity Analyses

Among patients included in the matched cohorts, the same primary and secondary analyses will be conducted for the sensitivity analyses described here.

Sensitivity analysis to mitigate potential channeling bias (Table.10.4)

In this analysis, the index date will be imputed or "lagged" to the primary index date plus 1 day. The rationale for this sensitivity analysis is to mitigate potential channeling bias that may occur if the observed treatment with 1 agent (BEB or PAX) is differentially utilized based on the likelihood of experiencing an early outcome event (for example, hospitalization). By systematically lagging the index date 1 day forward in time for all study cohort members, we thereby exclude patients who had an event very early during follow-up and mitigate bias related to disease severity at the time of BEB or PAX treatment.

Sensitivity analysis to assess the impact of unmeasured confounding (Table.10.5)

Using E-value methodology proposed by VanderWeele and Ding (VanderWeele and Ding 2017; VanderWeele et al. 2019), we will perform sensitivity analyses to assess the potential impact of unmeasured confounding on the observed treatment effect (that is, the RD) for the primary and secondary analyses. The E-value is defined as the minimum strength of association an unmeasured confounder would need to have with both the exposure (that is, BEB or PAX) and the outcome, conditional on the measured baseline covariates, to explain the exposure-outcome association. With this approach, the investigator does not select a baseline confounder or specify the confounding association *a priori*. Rather, the E-value depicts the strength of association between a hypothetical confounder and the exposure and outcome required to expunge or explain the observed treatment effect. The investigator (and readers) may then assess if a confounder association of that magnitude is plausible. The E-value was originally developed on the risk-ratio scale; however, modifications of this approach have been developed to estimate the E-value on the RD scale (Linden et al. 2020).

Sensitivity analysis to assess the impact of missing baseline covariate data (Table.10.6)

To assess the potential impact of missing baseline covariate data, we will use multiple imputation for select baseline covariates (for example, BMI, age, sex) where the missingness pattern is more than 0% and less than or equal to 30% (Granger et al. 2019). The rationale for this sensitivity analysis is to further mitigate potential confounding for important baseline covariates which may be omitted from the PS generating model using the primary approach (that is, because they have missingness more than 5%). Note: The primary approach is to systematically impute to the most prevalent value of the observed variable distribution when a given baseline variable (for example, BMI, age, sex) has missingness more than 0% and less than or equal to 5%.

Table.10.4. Sensitivity Analysis to Mitigate Potential Channeling Bias

Outcome	Number of Matched Pairs	Exposure	Analysis	Number of Patients with Event	Cumulative Incidence (CI)			Risk Difference (RD, PAX = reference)		
					CI	95% LCL	95% UCL	RD	95% LCL	95% UCL
Primary analysis										
Hospitalization or death	N	BEB	Primary	n						
		PAX		n						
Hospitalization or death	N	BEB	Lagged index date	n						
		PAX		n						
Secondary analyses										
Hospitalization	N	BEB	Primary	n						
		PAX		n						
Hospitalization	N	BEB	Lagged index date	n						
		PAX		n						
ED Visit	N	BEB	Primary	n						
		PAX		n						
ED Visit	N	BEB	Lagged index date	n						
		PAX		n						
Death	N	BEB	Primary	n						
		PAX		n						
Death	N	BEB	Lagged index date	n						
		PAX		n						

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; CI = cumulative incidence; ED = emergency department; N = number of patients in the cohort; n = number of patients with the event; PAX=Paxlovid; RD = risk difference.

Note: For the RD analyses, PAX is the reference category.

Table.10.5. Sensitivity Analysis to Assess the Impact of Unmeasured Confounding

Outcome	Number of Matched Pairs	Exposure	Analysis	Number of Patients with Event	Cumulative Incidence (CI)			Risk Difference (RD, PAX = reference)			Bias Analysis E-value (EV)		
					CI	95% LCL	95% UCL	RD	95% LCL	95% UCL	EV	95% LCL	95% UCL
Primary analysis													
Hospitalization or death	N	BEB	Primary	N									
		PAX		N									
Secondary analyses													
Hospitalization	N	BEB	Primary	N									
		PAX		N									
ED Visit	N	BEB	Primary	N									
		PAX		N									
Death	N	BEB	Primary	N									
		PAX		N									

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; CI = cumulative incidence; ED = emergency department; EV = E-value; N = number of patients in the cohort; n = number of patients with the event; PAX = Paxlovid; RD = risk difference.

Note: For the RD analyses, PAX is the reference category.

Table.10.6. Sensitivity Analysis to Assess the Impact of Missing Baseline Covariate Data

Outcome	Number of Matched Pairs	Exposure	Imputation Approach	Number of Patients with Event	Cumulative Incidence (CI)			Risk Difference (RD, PAX = reference)		
					CI	95% LCL	95% UCL	RD	95% LCL	95% UCL
Primary analysis										
Hospitalization or death	N	BEB	Primary	n						
		PAX		n						
Hospitalization or death	N	BEB	Multiple imputation	n						
		PAX		n						
Secondary analyses										
Hospitalization	N	BEB	Primary	n						
		PAX		n						
Hospitalization	N	BEB	Multiple imputation	n						
		PAX		n						
ED Visit	N	BEB	Primary	n						
		PAX		n						
ED Visit	N	BEB	Multiple imputation	n						
		PAX		n						
Death	N	BEB	Primary	n						
		PAX		n						
Death	N	BEB	Multiple imputation	n						
		PAX		n						

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; CI = cumulative incidence; ED = emergency department N = number of patients in the cohort; n = number of patients with the event; PAX = Paxlovid; RD = risk difference.

Note: For the RD analyses, PAX is the reference category.

10.3. Quality Control

All data gathering and analyses will be overseen by 2 analysts experienced in the field of retrospective, observational research using EHR data. Programming for this project will be conducted by a primary analyst and code review by a separate analyst, the validation analyst. For all data processing steps, the validation analyst will review the program code along with input/output datasets and results tables/figures. For each analysis step, code review will be employed to reduce the potential risk of programming errors.

10.4. Limitations of the Research Methods

10.4.1. Overview

We acknowledge the proposed NI study to evaluate the effectiveness of BEB versus PAX using RWD has limitations. However, no single study could address these research questions without limitations. For example, conducting a randomized, controlled clinical trial would be limited in the choice of control group. Furthermore, randomizing high-risk patients to placebo would be potentially unethical due to available treatments. Additionally, active controls, such as oral antivirals or monoclonal antibodies could be less effective at new circulating variants during the trial. Lastly, oral antivirals, such as PAX are easily attainable while BEB requires intravenous injection with 1-hour post-administration monitoring period, which could lead to a disparity in access and availability to patients.

Given these limitations and ethical considerations, an interventional study may not include a control group and would, therefore, need to rely on external data to assess the effectiveness of BEB, a design that also has limitations. Patient enrollment is also a challenge for interventional trials when treatments are available outside the trial setting and mostly free of charge to patients. The ethical and logistical challenges of a traditional, interventional trial are key considerations to weigh in study design selection. As such, we consider the proposed RWD study the best approach for these specific circumstances. In addition, the use of RWD is the most appropriate design for rapidly generating data to inform public health.

10.4.2. Methods to Mitigate Bias

EHR data from the TriNetX Dataworks USA Network are generated from routine healthcare encounters within an “open” healthcare structure. Patients may receive all or a proportion of their care from healthcare providers within the HCO network. However, healthcare encounters which occur outside the HCO network will not be observed. Most contributing HCOs are large academic medical centers and IDNs with multiple affiliated sites of care. Using EHR data from large health systems, in some cases, spanning large geographic areas increases the likelihood of ascertaining data needed to classify and characterize the study cohorts and to ascertain covariate and outcome data. To further mitigate the potential for missing data, eligibility requirements have been incorporated to restrict the study cohorts to include only patients who regularly received care within the TriNetX HCO Network. In addition to improving the ascertainment of baseline data to characterize the study cohort, this also increases the probability that study cohort members will receive follow-up care at these institutions. Therefore, leading to an increased likelihood of outcome ascertainment.

The active comparator study design increases confidence that comparisons are being made between more similar patient populations requiring treatment for COVID-19. This approach reduces the opportunity for channeling bias that may occur when using an untreated comparator. Although channeling bias can be mitigated in an untreated comparator design, using an active comparator design provides increased sample size by eliminating the need to require a laboratory confirmed COVID-19 infection in both groups. It also simplifies design elements that are needed to account for the lack of a medication index date when an untreated comparator is used.

Regarding missing data, healthcare encounters that occur outside the HCO network will not be captured. This may result in incomplete healthcare profiles and potentially missing exposure, confounder, or outcome data. Strategies to mitigate missing data and other sources of information bias have been incorporated into the study design and study methodology. These include the following:

- including only patients who regularly received care with the contributing HCOs
- using medication records to classify the study cohorts
- conducting subgroup analyses for patients with documented evidence of COVID-19 vaccine exposure, and
- conducting sensitivity analyses, using multiple imputation, to account for missing baseline covariate data.

To mitigate potential confounding bias (for example, by COVID-19 illness severity), the study cohorts will be restricted to patients who were not hospitalized prior to receiving BEB or PAX. Additional confounding control will be achieved using CEM on highly selected and *a priori* defined baseline variables in conjunction with PS matching on a broader set of baseline covariates. A lagged index date sensitivity analysis will be conducted to exclude patients who had an event very early during follow-up to mitigate potential bias related to disease severity at time of treatment. A sensitivity analysis using multiple imputation of missing baseline covariate data will be conducted to further mitigate potential confounding bias. Finally, a quantitative bias sensitivity analysis will be conducted to estimate the minimum strength of association that an unmeasured confounder would need to have to explain the observed treatment effect.

10.4.3. Methods to Evaluate Effect Modification

To evaluate the consistency of the treatment effect for specific subgroups of patients compared to the treatment effect for the overall study population (that is, effect modification), the primary and secondary analyses will be stratified by matched pairs who:

- were of age 65 years or older (yes/no)
- were immunocompromised (yes/no); and
- had a pre-index ED visit (yes/no).

Additionally, we will conduct stratified analyses for matched pairs where COVID-19 vaccine status is documented and where vaccine status is undetermined (that is, no documented record of COVID-19 vaccination). The rationale for these analyses is to evaluate the treatment effect within the subgroup of patients where there is the lowest likelihood of vaccine status

misclassification (that is, patients with documented evidence of COVID-19 vaccination in the EHR).

10.4.4. Data Source

The TriNetX Dataworks USA Network has been used in over 50 epidemiologic studies of COVID-19 (citations listed in Section 14.1). This database contains EHRs for approximately 86 million patients from 54 HCOs in the US. The EHR data are mapped to a common data model, direct patient identifiers are removed, and data quality measures are run to assess the cleanliness, consistency, correctness, and completeness of the data.

The ability to observe monoclonal antibody and antiviral administrations in the TriNetX Dataworks USA Network is a major advantage of this data source. That is, the ability to classify BEB and PAX exposure in EHR data provides a substantial advantage compared to using solely health insurance claims data, where insurance claims for BEB and other products made available under EUA are likely missing. A limitation of the data source, like most retrospective, population-based data sources, is missingness of COVID-19 vaccine exposure data.

10.4.5. Generalizability

Generalizability is the ability to apply the results of a study to other populations. Patients included in the TriNetX Dataworks USA Network have shown to be broadly representative of patients who receive medical care in the US. Therefore, findings from the primary and secondary analyses should be broadly generalizable to non-hospitalized patients in the US with a COVID-19 infection who were treated with monoclonal antibody or antiviral therapy. The results may also be generalizable to patients in other countries that have similar healthcare structures, healthcare utilization patterns, and patient populations with similar age and racial distributions.

10.4.6. Statistical Error

NI testing for the primary (composite) outcome will be conducted. Feasibility estimates provided in Table.9.6 show sample sizes of patients who potentially meet the study inclusion/exclusion criteria and would be eligible for matching (that is, 8794 patients receiving BEB; 24,744 patients receiving PAX).

These sample sizes are sufficient to test the null hypothesis with an NI margin of 1.795%, where N=1065 for each arm provides 80% power and N=1390 for each arm provides 90% power, assuming hospitalization/death incidence of 1.4% for BEB and 1.2% for PAX (Razonable et al. 2022). However, if the observed incidence of hospitalization/death is substantially lower than published estimates, the power to establish NI, using the *a priori* established NI margin (that is, 1.795%), may be limited.

10.4.7. Bias

Bias is systematic error resulting from incorrect estimation of the exposure and outcome association. Potential forms of bias include confounding, selection bias and information bias. Bias may be independent of exposure status (non-differential bias) or associated with the exposure under investigation (differential bias).

10.4.7.1. Confounding

A confounding variable is a variable that is associated with the outcome of interest and independently associated with the exposure. A confounder can create a spurious association when one does not exist, or mask one when in fact an association exists. For this study, confounding is particularly relevant, as it relates to the association between COVID-19 treatment selection (that is, BEB or PAX) and independently with the study outcomes (that is, hospitalization, death, and ED visit) with:

- COVID-19 disease severity
- the presence of high-risk comorbidities (for example, immunocompromised status)
- advanced age, and
- COVID-19 vaccine exposure status.

Methods have been incorporated in the study design (for example, active comparator, non-hospitalized patients) and analysis (for example, CEM and PS matching, lagged index date sensitivity analysis) to mitigate confounding and to estimate a valid treatment effect. Additionally, a sensitivity analysis using multiple imputation of missing baseline covariate data will be conducted to further mitigate potential confounding bias. Finally, a quantitative bias sensitivity analysis will be conducted to estimate the minimum strength of association that an unmeasured confounder would need to have to explain the observed treatment effect.

Other sources of potential confounding bias that may impact this study are COVID-19 vaccine exposure status and time-dependent confounding from post-index exposure to monoclonal antibody or antiviral therapy (other than BEB or PAX). The initial feasibility assessment showed only 25% of BEB-treated patients had a COVID-19 vaccination record in the EHR. Whereas, the CDC data show approximately 89% of patients aged 12 years and older have received at least 1 COVID-19 vaccination. These disparate findings indicate a high degree of missingness. Given this, patients classified as ‘unvaccinated’ are more likely ‘undetermined’ than truly unvaccinated. Therefore, we will execute the primary analyses on all patients meeting inclusion/exclusion criteria, agnostic of EHR-defined vaccination status. Under the assumption that the high vaccination rate reported by the CDC applies equally to patients included in the BEB and PAX cohorts, it is unlikely that the results would be confounded by vaccine status; however, misclassification of vaccine status limits a data-driven assessment of imbalances. Therefore, subgroup analyses within vaccinated patients will be conducted, as evidence of COVID-19 vaccination in the EHR is not likely to be misclassified. Characteristics of the vaccine distribution will be examined in efforts to ensure that the treatment groups are as comparable as possible. To assess potential time-dependent confounding, we will describe the proportion of patients who received post-index treatment with monoclonal antibody or antiviral therapy (other than BEB or PAX).

10.4.7.2. Selection Bias

Selection bias occurs when study inclusion (or exclusion) is associated with an extraneous factor (for example, severe COVID-19 illness leading to hospitalization or death) that is not the exposure under investigation. Importantly, this selection factor is associated with the study exposure and independently with the study outcome. In circumstances where a selection factor

excludes patients from cohort entry, the resulting bias cannot be controlled for in the analysis and must be accounted for in the study design or potentially illuminated through sensitivity analyses or descriptive analyses.

To mitigate the potential for selection bias, the study cohorts will systematically include non-hospitalized patients in the TriNetX Dataworks USA Network who were treated with BEB or PAX during the study period.

10.4.7.3. Information Bias

Information bias arises from systematic errors in the way study variables are ascertained, classified, and/or attributed to patients. Information bias is common to all retrospective studies and may include data entry errors, coding specificity challenges, and missing data. Regarding missing data, healthcare encounters that occur outside the HCO network will not be captured. This may result in incomplete healthcare profiles and potentially missing exposure or outcome data. Strategies to mitigate missing data and other sources of information bias have been incorporated into the study design and study methodology. These include the following:

- including only patients who regularly received care with the contributing HCOs
- using outpatient and facility-based records to classify the study cohorts and outcomes, and
- conducting subgroup analyses for patients with evidence of COVID-19 vaccination.

10.4.7.3.1. Misclassification of the Exposure

Misclassification of the exposure can occur when patients are erroneously categorized with regard to exposure status. To minimize the potential for exposure misclassification, we utilized precise medication coding criteria to classify BEB and PAX as the first exposure during the index period. Using health insurance claims in the Linked Network will further mitigate this type of misclassification.

Despite this, the likelihood of exposure misclassification may be greater for patients exposed to PAX (dispensed as an oral medication) than for patients exposed to BEB (administered via infusion). This may occur if patients did not “fill” the PAX prescription or adhere to the prescribing guidelines (for example, they do not take the full dosing regimen). The potential impact of this differential misclassification may result in

1. a greater risk of the study outcomes for patients classified with PAX exposure
2. a larger RD (in favor of BEB) with a narrower CI, and
3. an increased likelihood of rejecting the null hypothesis and establishing the NI of BEB.

While this type of exposure misclassification is both unavoidable and unmeasurable in EHR data, the likelihood of this occurring is mitigated, to some degree, by

- the very nature of the indication (that is, COVID-19 requiring antiviral therapy)
- the severity of the outcome (that is, hospitalization or death), and
- the context of disease acquisition (that is, COVID-19 acquired during a global pandemic with heightened awareness of potential harm).

Another form of measurable exposure misclassification may occur if the exposure status, as classified on the index date, is “contaminated” by post-index antibody or antiviral therapy. To address this form of exposure misclassification, we will describe the use of non-index monoclonal antibody and antiviral treatment during follow-up for patients in both cohorts.

10.4.7.3.2. Misclassification of the Outcome

Misclassification of the outcome is present when patients are erroneously categorized with regard to outcome status. This can be a problem in retrospective studies when outcome data are missing, equivocal, or uninterruptible.

In the present study, hospitalization and ED visits that occur outside the TriNetX HCO Network will not be ascertained. To mitigate this type of outcome misclassification, eligibility requirements have been incorporated, which restrict the study cohorts to include only patients who regularly received care within the TriNetX HCO Network. Additionally, the Phase II analyses, using data from the TriNetX Linked Network, will include complete (or near complete) ascertainment of outcome data from closed insurance claims with linked mortality data.

To protect patient privacy, the date of death in the EHR includes the year and month only. Therefore, a true date of death is not available. As a proxy for the death date, among patients with death recorded in the EHR during follow-up, we propose to classify the last post-index record in the EHR database as the death date.

While this approach has been used in other TriNetX studies, the date of death may be misclassified. This misclassification would likely over-count the number of deaths, as the actual date of death may have occurred after the 30-day follow-up window. To some degree, the supplemental analyses using data from the Linked Network will assess the robustness of the treatment effect and expose outcome misclassification; however, the reduced sample size in the Linked Network will limit the number of events and precision substantially.

10.5. Other Aspects

Not applicable.

11. Protection of Human Subjects

This retrospective, observational database study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

This study presents no more than minimal risk of harm to patients. All study data will be accessed in compliance with data use principles and in accordance with the Health Insurance Portability and Accountability Act and applicable state and federal laws governing the privacy and security of health information and personal data. This retrospective database study is not classified as research involving human subjects (under 45 Code of Federal Regulation 46.101) for the following reasons:

- there will be no interaction with human subjects
- all data will be collected during routine clinical practice prior to accessing the final data cut from the TriNetX Dataworks USA Network EHR database (no additional data will be collected and/or documented beyond the data available from the TriNetX Dataworks USA Network), and
- all study data are de-identified and no patient identifiers were available to the study investigators.

12. Management and Reporting of Adverse Events/Adverse Reactions

12.1. Secondary Data Use Study

This is a non-interventional study based on secondary data use, and therefore, no Individual Case Safety Report reporting is required. This study has no protocol-defined adverse events, so a summary of adverse events cannot be included in the final study report.

12.2. Product Complaints

Lilly collects product complaints on marketed Lilly products such as drugs, drug/device combinations, medical devices, software as medical device (for example, mobile medical applications), and comparator product(s) used in postmarketing medical research studies to ensure the patient safety, monitor quality, and to facilitate process and product improvements.

For Lilly products under evaluation and/or Lilly products not under evaluation but discovered in the course of the study, study personnel are instructed to report product complaints as they would for products in the marketplace.

For non-Lilly products, such as comparator drugs or medical devices, or concomitant drugs or medical devices, study personnel are instructed to report product complaints as they would for products in the marketplace.

13. Plans for Disseminating and Communicating Study Results

Final reports will be submitted to regulatory agencies. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

14. References

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