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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

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PASS Information

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Author	PPD
Signature of principal investigator	Signature on file/see approval date below

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Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

1 Abstract

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

Keywords

COVID-19, bebtelovimab, effectiveness, noninferiority, cohort study

Rationale and background

On 11 February 2022, the United States (US) Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for bebtelovimab (BEB), an antibody used for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who were 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 were not available or clinically appropriate.

Recognizing the limitations of the available clinical data, conditions of the letter of authorization required Eli Lilly and Company (Lilly) to submit a protocol for a clinical trial to collect additional information on BEB effectiveness outcomes. Although the US FDA de-authorized BEB 30 November 2022 due to the high level of circulating BEB-resistant Omicron subvariants BQ.1 and BQ.1.1, this study was conducted to address research questions regarding the effectiveness of BEB prior to de-authorization.

Research question and objectives

The primary objective was to estimate the 30-day risk difference (RD) of the composite outcome of all-cause hospitalization or all-cause death for patients who received BEB compared to patients who received Paxlovid™ (nirmatrelvir / ritonavir; PAX). The primary analysis used noninferiority (NI) hypothesis testing with an *a priori* specified NI margin. The secondary objective was to estimate the 30-day RD of all-cause hospitalizations, all-cause deaths, and all-cause emergency department (ED) visits.

Study design

An observational, cohort study design was used to compare the effectiveness of BEB to PAX in adults and adolescents with mild-to-moderate COVID-19. Confounding control was achieved using coarsened exact matching (CEM) on *a priori* defined baseline variables in conjunction with variables selected for high-dimensional propensity score (HDPS) methods. For the primary analysis only, the NI null hypothesis was tested using the 1-sided Type I error of 0.025 by setting the upper confidence level of the risk difference (RD_{UCL}) 95% confidence interval (CI) for BEB versus PAX to be less than the prespecified NI margin of 1.795%.

Setting

The study cohorts included patients who received BEB or PAX between 16 February 2022 and 31 August 2022. Follow-up began on the day after index date and continued until 30-days post-index using an intention-to-treat (ITT) approach.

Subjects and study size, including dropouts

After applying patient identification criteria, 12,920 BEB-exposed and 70,741 PAX-exposed patients remained in the unmatched cohorts. After conducting HDPS matching, 5,827 BEB-exposed and 5,827 PAX-exposed patients remained in the matched cohorts.

Variables and data sources

Study variables were ascertained from the TriNetX Dataworks USA Network, an electronic health record (EHR) network that includes de-identified, longitudinal outpatient and inpatient data from health care organizations (HCOs) across the US. BEB exposure data were obtained from facility-based infusion centers and outpatient administrations. Oral PAX exposure data were ascertained from facility-based and outpatient medication records. Outcomes data were classified using facility-based and outpatient records. Baseline characteristics, including demographics, clinical parameters, comorbidities, pharmacotherapy exposure, and healthcare resource utilization (HRU), were ascertained from all available inpatient and outpatient records prior to and including the index date.

Results

In the matched cohorts, the median age was 65 (interquartile range [IQR] 50 – 74) and 65 (IQR 50 – 74) years in BEB and PAX, respectively. Patients were primarily female (60.24% in BEB and 60.53% in PAX), White (84.07% in BEB and 84.06% in PAX), and non-Hispanic (77.43% in BEB and 78.05% in PAX). Adequate balance was achieved in all but 3 pre-specified covariates (eGFR, blood pressure, and oxygen saturation). Due to missingness >5%, these variables were not included in the PS generating model. Before matching, baseline differences between BEB and PAX treated patients were observed for demographics (e.g., median age: BEB 66 years; PAX 61years); comorbidities (e.g., immunocompromised status: BEB 50%; PAX 33%); pharmacotherapy utilization (e.g., COVID-19 vaccination status: BEB 18%; PAX 11%); and healthcare utilization (e.g., ED visit within 7 days before treatment: BEB 19%; PAX 8%).

The cumulative incidence of the composite outcome all-cause hospitalization or all-cause death in the matched cohorts was 2.03% (95% confidence interval [CI]: 1.68%, 2.42%) among patients treated with BEB and 1.84% (95% CI: 1.51%, 2.21%) among patients treated with PAX. BEB was noninferior to PAX for composite all-cause hospitalization or all-cause death; the RD was 0.19% (95% CI: -0.31%, 0.69%), with its UCL (0.69%) well within the noninferiority margin of 1.795%.

The cumulative incidence of hospitalization, ED visit, and death, respectively in matched cohorts, was 1.94% (95% CI: 1.60%, 2.33%), 5.08% (95% CI: 4.53%, 5.68%), and 0.10% (95% CI: 0.04%, 0.22%) for patients treated with BEB, and 1.82% (95% CI: 1.49%, 2.20%), 4.58%

(95% CI: 4.06%, 5.15%), and 0.02% (95% CI: 0.00%, 0.10%) for patients treated with PAX. BEB (compared to PAX) was not associated with increased risks of hospitalization (RD 0.12%; 95% CI: -0.37%, 0.61%), ED visit (RD 0.50%; 95% CI: -0.28%, 1.28%), or death (RD 0.086%; 95% CI: -0.003%, 0.175%). There was no evidence of effect modification by subgroups for age ≥ 65 years, immunocompromised status, COVID-19 vaccine, or ED visit within 7 days pre-index. Sensitivity analyses suggest that channeling bias and unmeasured confounding do not pose major threats to the validity of findings.

Discussion

BEB was noninferior for the primary outcome (composite all-cause hospitalization or all-cause death) and had no statistically significant differences in the risk of hospitalization, ED visit, or death compared to PAX based the point estimates and confidence intervals. The treatment effect was consistent among subgroups of interest and results from sensitivity analyses were generally consistent with the primary findings. Overall, findings from this study were consistent with those of prior studies investigating the real-world effectiveness of BEB for COVID-19.

Conclusion

This study of the real-world utilization and effectiveness of BEB compared to PAX found BEB-treated patients (before matching) were older and a higher percentage had comorbidities associated with experiencing severe COVID-19 illness. After matching, to account for channeling bias, BEB- and PAX-treated patients were well balanced on baseline demographics, comorbidities, pharmacotherapy, and healthcare utilization. We observed BEB was not inferior to PAX with respect to 30-day all-cause hospitalization or death based on the *a priori* specified non-inferiority margin (primary composite outcome). Similarly, the risk of hospitalization, ED visit, and death (secondary outcomes) was not different for patients treated with BEB compared to those treated with PAX. Given evidence supporting the effectiveness of BEB, research on newer antibody therapies for emerging COVID-19 variants is warranted. As observed in the present study, real-world data permit the description of potentially important utilization disparities and, after accounting for baseline differences, estimating a valid treatment effect.

Marketing Authorisation Holder

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2 List of Abbreviations

Term	Definition
ACH	anticholinergic
ADL	activities of daily living
ASD	absolute standardized difference
BEB	bebtelovimab
BMI	body mass index
BP	blood pressure
CCSR	Clinical Classifications Software Refined
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
ESRD	end-stage renal disease
EUA	emergency use authorization
FDA	Food and Drug Administration
HCO	health care organization
HCPCS	Healthcare Common Procedure Coding System
HCUP	Healthcare Cost and Utilization Project
HDPS	high-dimensional propensity score
HRU	healthcare resource utilization
ICD-9/10-CM	International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Disease, Tenth Revision, Procedure Coding System
ICU	intensive care unit
IDN	integrated delivery network
IQR	interquartile range
ITT	intention-to-treat
LABA	long-acting beta agonist

LCL	lower confidence limit
LOINC	Logical Observation Identifiers Names and Codes
M1	margin
M2	noninferiority margin
MCQ	Mayo Clinic Quadratic
MICE	multivariate imputation using chained equations
NDC	National Drug Code
NI	noninferiority
OR	odds ratio
PAX	Paxlovid™
PDL	programmed death-ligand
PS	propensity score
RD	risk difference
RR	risk ratio
SABA	short-acting beta agonist
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sCr	serum creatinine
TNFX	tumor necrosis factor inhibitors
UCL	upper confidence limit
UPMC	University of Pittsburgh Medical Center
US	United States
VA	Department of Veterans Affairs

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4 Other Responsible Parties

Not applicable.

5 Milestones

Milestone	Planned date	Actual date	Comments
Start of Data Collection (Primary Analysis)	15 February 2023	23 March 2023	
End of Data Collection (Primary Analysis)	15 February 2023	23 March 2023	
Final report of study results (Primary Analysis)	31 July 2023	See Page 1	
Start of Data Collection (Supplemental Analysis)	5 September 2023	5 September 2023	
End of Data Collection (Supplemental Analysis)	5 September 2023	5 September 2023	
Final report of study results (Supplemental Analysis)	11 December 2023	11 December 2023	

6 Rationale and Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its resulting illness coronavirus disease 2019 (COVID-19) is associated with over 90 million cases of COVID-19 and over 1 million deaths in the United States (US) (CDC 2022b). Common symptoms of mild COVID-19 disease include fever, myalgia, headache, difficulty breathing, weakness, gastrointestinal symptoms, and loss of smell or taste (Parasher 2021). Progression to more severe disease may lead to hospitalization, non-invasive and invasive ventilation, and death (WHO 2020; Parasher 2021). Patients with COVID-19 who also have multiple comorbidities or chronic diseases 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, outcomes among immunocompromised persons and the clinical impact of new variants (Pei et al. 2021).

In December 2021, two oral antiviral treatments, Paxlovid™ (nirmatrelvir / ritonavir) and Lagevrio™ (molnupiravir), received emergency use authorizations (EUAs) for the treatment of mild-to-moderate COVID-19 in certain high-risk patients. PAX was subsequently recommended as first-line therapy for the treatment of patients at high risk of severe disease, and it was made available free of charge. Remdesivir was also listed as first-line therapy but required an infusion 3 consecutive days and was only available for purchase through commercial channels (NIH 2022). Limitations for these antiviral treatments include numerous drug-drug interactions for Paxlovid™ (PAX) (FDA 2021b) and age and pregnancy restrictions and possibly decreased efficacy for molnupiravir (FDA 2021a).

A randomized controlled trial conducted between 16 July 2021 and 9 December 2021, consisting of 2,246 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 intention-to-treat (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). On 25 May 2023 the US Food and Drug Administration approved the oral antiviral Paxlovid™ for the treatment of mild-to-moderate COVID-19 in adults at high risk of severe disease progression (FDA 2023).

Several monoclonal antibody therapies were made available for the treatment of COVID-19. In November 2020, bamlanivimab and REGEN-COV™ (casirivimab/imdevimab) received EUAs for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric patients who were at high risk for progressing to severe COVID-19 and/or hospitalization (ASPR 2023a; ASPR 2023b). Subsequently in February 2021, bamlanivimab in combination with etesevimab received an EUA for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric

patients as well as post-exposure prophylaxis. By January 2022 however, bamlanivimab alone, bamlanivimab/etsevimab, and casirivimab/imdevimab were no longer available in the US due to the increased frequency of viral variants with resistance to these treatments, such as the Omicron variant (ASPR 2022; ASPR 2023a; ASPR 2023b). Sotrovimab, another monoclonal antibody, was issued an EUA in May 2021 for the treatment of mild-to-moderate COVID-19; this EUA was revoked in April 2022 due to increased frequency of the Omicron BA.2 subvariant (FDA 2022c).

On 11 February 2022, the US Food and Drug Administration (FDA) issued an EUA for BEB, an antibody that demonstrated neutralization against the Omicron variant of COVID-19 (FDA 2022b). By April 2022, bebtelovimab (BEB) remained the only monoclonal antibody available for treatment due to the high Omicron subvariant BA.2 prevalence in the US and the de-authorization of sotrovimab. BEB was used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (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 were 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 were not available or clinically appropriate. BEB, administered as a single intravenous injection over at least 30 seconds in an appropriate clinical setting, required administration as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset.

Data that supported the EUA for treatment of mild-to-moderate COVID-19 were 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 was reasonable to believe that BEB may reduce the risk of progression to hospitalization or death (Iketani et al. 2022). Recognizing limitations of the available clinical data, however, the letter of authorization required Lilly to submit a proposed clinical trial protocol to further evaluate the effectiveness of BEB.

In the time since the BEB EUA, studies evaluating the effectiveness of BEB and PAX have been conducted externally. Cohort studies using electronic health records (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 odds ratio [OR]=0.53; 95% confidence interval [CI]: 0.32 to 0.86) in 930 BEB treated versus 930 propensity score (PS) matched non-treated patients, respectively (McCreary et al. 2022).

Similarly, a study using the Mayo Clinic's integrated healthcare delivery network (IDN) 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 intensive care unit (ICU).

On 30 November 2022, during protocol development of the current study, the US FDA de-authorized BEB due to the high level of circulating Omicron subvariants (BQ.1 and BQ.1.1) that were not expected to be effectively neutralized (FDA 2022a). To address research questions regarding the effectiveness of BEB prior to the suspension of the EUA, this noninferiority (NI) study was conducted to evaluate the effectiveness of BEB relative to PAX to address research questions regarding the effectiveness of BEB prior to the de-authorization.

7 Research Question and Objectives

7.1 Study Objectives

Primary objective

The primary objective was to estimate the 30-day risk difference (RD) and 95% CI of a composite outcome of all-cause hospitalization or all-cause death, for patients who received BEB compared with patients who received PAX. The cumulative incidence and RD and corresponding 95% CIs were reported.

This analysis used NI hypothesis testing with an *a priori* specified NI margin. The NI null hypothesis was tested using the one-sided Type I error of 0.025 by setting the upper confidence level of the risk difference (RD_{UCL}) 95% CI for BEB versus PAX to be less than the *a priori* specified NI margin of 1.795%. The null hypothesis was defined as a higher risk of 30-day all-cause hospitalization or all-cause death for patients treated with BEB compared with patients treated with PAX by at least 1.795%. We rejected the null hypothesis and established NI if the RD_{UCL} excluded 1.795%. More detail can be found in Sections 9.7.2 and 9.7.3.

The NI null (H_0) and alternative (H_1) hypotheses were:

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

Secondary objectives

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

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

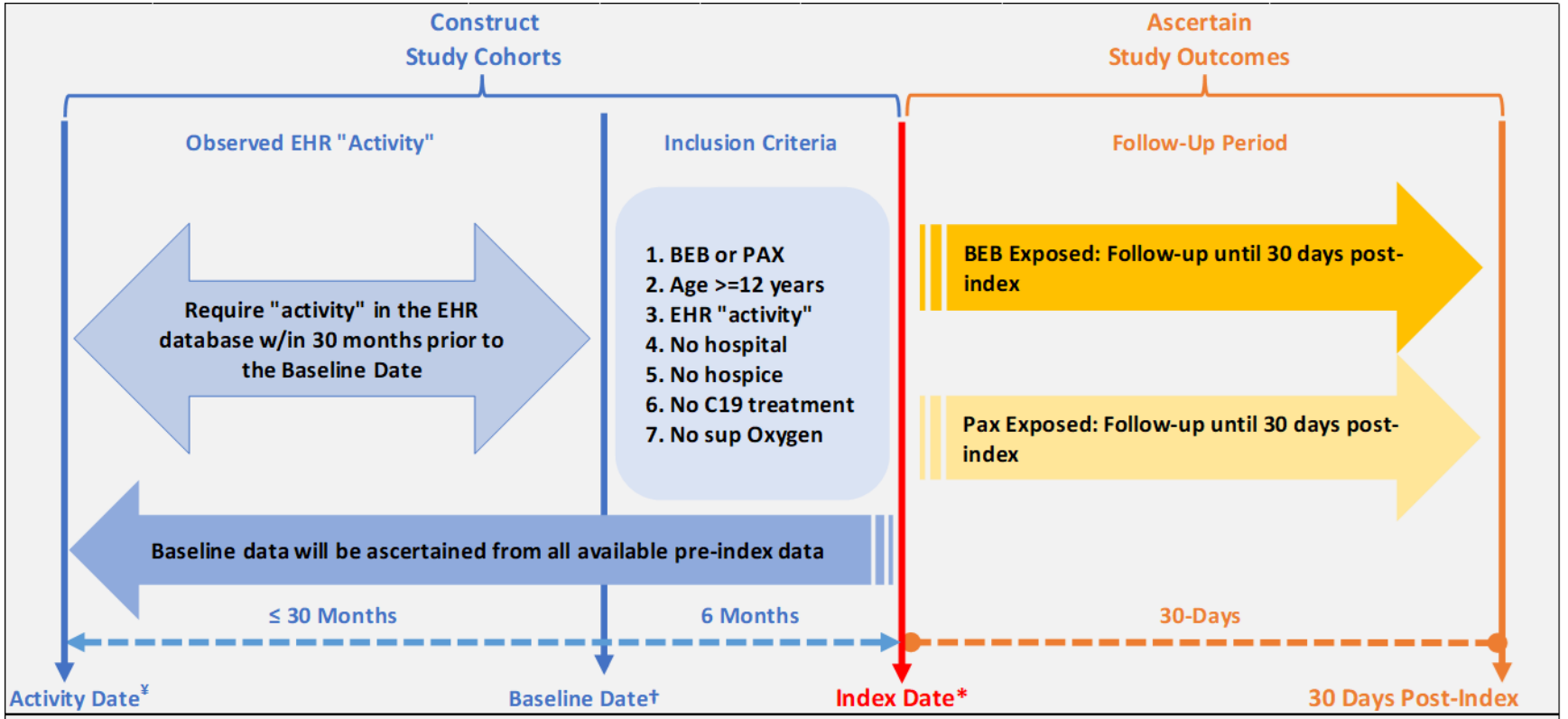
8 Amendments and Updates

Not applicable.

9 Research Methods

9.1 Study Design

An observational, cohort study design was used to describe and compare the effectiveness of BEB to PAX in adults and adolescents with mild-to-moderate COVID-19. A balanced and well confounding controlled cohort study design is appropriate to complement clinical trials to 1) evaluate multiple study outcomes, 2) determine the cumulative incidence (risk) and RD of each outcome, and 3) increase the precision of outcome estimation. The study cohorts were identified from the TriNetX Dataworks USA Network and included patients who received BEB or PAX during the index period (16 February 2022 to 31 August 2022). The index date was the date of the first BEB or first PAX record during the index period. An ITT approach was used to derive the cumulative incidence and RD and 95% CI of 30-day all-cause hospitalization or all-cause death (primary analysis composite outcome), and of all-cause hospitalization, all-cause death, and all-cause ED visit (secondary analysis outcomes). For comparing the outcomes between the 2 cohorts, confounding control was achieved using coarsened exact matching (CEM) on a priori defined baseline variables in conjunction with PS matching on a broader set of baseline variables selected with HDPS methodology. For the primary analysis only, the NI null hypothesis for this objective was tested using the 1-sided Type I error of 0.025 by setting the RD_{UCL} 95% CI for BEB versus PAX to be less than the prespecified NI margin of 1.795%. A schematic representation of the study design is displayed in Figure 9.1.



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-period.

9.2 Setting

9.2.1 Study Cohort Development

The study cohorts were identified from the TriNetX Dataworks USA EHR network, which includes over 92 million patients from 56 health care organizations (HCOs). More detail on TriNetX Dataworks USA can be found in Section 9.5.1. The study cohorts included patients who received BEB or PAX during the index period (16 February 2022 to 31 August 2022). The index date was 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 were 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 were excluded. Therefore, patients were included in only 1 cohort for this study.

9.2.2 Follow-Up and Censoring (Primary and Sensitivity Analysis Methodology)

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

We described 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.

9.3 Subjects

Both cohorts were restricted to include patients who met 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 included any of the following: office visit, inpatient admission, ED visit, diagnosis or procedure code, clinical measurement (e.g., blood pressure [BP] 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).

9.4 Variables

9.4.1 Study Variable Identification

The codes used to classify each study variable were ascertained from the EHR data within the TriNetX Dataworks USA Network. For the supplemental analysis, the EHR data was augmented with health insurance claims codes (for example, National Drug Code [NDC]) from the TriNetX Linked Network. Unless otherwise specified, each study variable was classified by the presence of 1 code recorded in any setting (for example, inpatient or outpatient). The specific codes to classify each variable are included in a separate code list document. For each variable type, the code systems included the following:

- Medical diagnoses were classified using:
  - International Classification of Disease, Ninth Revision/International Classification of Disease, Tenth Revision, Clinical Modification (ICD-9/10-CM);
- COVID-19 symptoms were classified using:
  - ICD-10-CM;
  - Logical Observation Identifiers Names and Codes (LOINC);
- Pharmacotherapy was classified using:
  - RxNorm;
  - Healthcare Common Procedure Coding System (HCPCS);
  - Current Procedural Terminology (CPT);
  - NDC;
- Healthcare procedures were classified using:
  - ICD-10-CM;
  - CPT;
  - HCPCS;
  - International Classification of Disease, Tenth Revision, Procedure Coding System (ICD-10-PCS);
- Laboratory data was classified using:
  - LOINC;
- Healthcare encounters were classified using:
  - CPT;
  - HCPCS; and
  - ICD-10-CM

9.4.2 Variables to Classify the Study Cohorts

BEB and PAX classification

BEB exposure data was ascertained from facility-based infusion centers and outpatient administrations. BEB exposure was 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 was used to classify the BEB index date.

Oral PAX (combination of nirmatrelvir and ritonavir) was ascertained from facility-based and outpatient medication records. PAX exposure was classified as a binary indicator variable

(yes/no) during the index period by at least 1 RxNorm code. The first PAX date was assigned as the PAX index date.

Age

Patient age was classified as of the index date. Age was classified as a continuous variable (in years), a binary variable (age ≥65 years), and a categorical variable (12-29 years, 30-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, and ≥85 years).

Baseline activity in the EHR network

Patients in the study cohorts were required to have at least 1 healthcare encounter in the EHR database between 6 and 36 months prior to the index date. This requirement was intended to increase the likelihood of ascertaining important study variables by ensuring all patients had 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 were excluded from the study cohorts (inclusive of the index date). Inpatient admissions were classified using facility-based EHR data.

Hospice care

Patients with evidence of hospice care within 30 days prior to index date were excluded from the study cohorts (inclusive of the index date). Hospice care was 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) were excluded from both study cohorts. Table 9.1 provides the specific exclusionary treatments.

Convalescent plasma, monoclonal antibody, or antiviral therapy was classified using outpatient prescribing records and/or facility-based administrations. Of note, this did 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 or authorized for use by the FDA but known to be used for the treatment of COVID-19.

Oxygen support

Patients who utilized 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) were excluded. Oxygen support was classified using outpatient and facility-based EHR data.

9.4.3 Variables to Classify the Study Outcomes

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

The primary outcome was the composite of all-cause hospitalization or all-cause mortality. The primary outcome was classified by the first evidence of an inpatient confinement or death during follow-up. The secondary outcomes were all-cause hospitalization, all-cause mortality, and all-cause ED visit.

All-cause hospitalization

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

All-cause hospitalization included all inpatient admissions regardless of the admitting or discharge diagnosis. The rationale for studying all-cause hospitalization, as opposed to COVID-

19 related hospitalization, was to include events that may have otherwise been 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 have required the study investigators to impose subjective criteria to classify a COVID-19-related hospitalization. Using the broader outcome definition of all-cause hospitalization captures worsening COVID-19 illness without excluding events based on healthcare provider coding practices.

All-cause mortality

All-cause mortality was 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, were 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, would have been May 2022.

To account for this death date characteristic, the ascertainment of all-cause mortality extended 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 have been 19 April 2022 and 18 May 2022, respectively. In this scenario, we ascertained deaths recorded in May and June 2022. However, the date of death was 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 occurred after the end of the follow-up period, for example, after 18 May 2022, the death was not counted as an outcome event. If there were zero post-index EHR records prior to a recorded death, the death date was 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 were classified by 1 encounter code from facility-based EHRs during follow-up. The first date an ED visit was recorded defined the outcome date. Only the first ED visit during follow-up was ascertained and analyzed.

9.4.4 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 are the same as described in the primary analysis. 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 includes a subset of patients from the primary analysis cohorts who have health records in both the TriNetX EHR database and the closed health insurance claims or mortality databases. The linked population is 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 9.4.3. The outcomes are classified using the same methodology as described for the primary analysis; however, the coding systems are 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).

9.4.5 Variables to Classify Baseline Covariates

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

Demographics

- Age was classified as a continuous variable (in years), a binary variable (≥65 years [yes/no]), and a categorical variable (12-29 years, 30-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, and ≥85 years).
- Sex was classified as a binary variable (male/female) as reported in the EHR.
- Race was classified as a categorical variable (White, Black, Other, Unknown).

Clinical parameters

Clinical parameters were classified from EHR data during *a priori* specified ascertainment windows in close temporality prior to BEB and PAX initiation. This approach provided 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 was expected that a large percentage (for example, more than 50%) of patients would not have recorded clinical data during the ascertainment window as listed here, and longer ascertainment windows would likely have yielded lower levels of missingness. The rationale for ascertaining and including these variables, given the high degree of missingness, was to better describe the study cohorts despite the inherent limitations of absent data.

- BP was 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 was 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 was ascertained using the last available value prior to the index date as reported in the EHR or calculated using the formula:
    - BMI = Weight in Kg/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 was 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 was used.

Laboratory data

Serum creatinine (sCr), used to calculate the estimated glomerular filtration rate (eGFR), was ascertained using all available pre-index data. However, it was expected that serum creatinine would 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, was to better describe the study cohorts and to augment the classification of chronic kidney disease (CKD). eGFR was calculated using the Mayo Clinic Quadratic (MCQ) 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 m^2, missing).

Comorbidities

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

Each baseline comorbidity was 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 was augmented by eGFR (that is, eGFR <60 mL/min/1.73 m²) and BMI (that is, BMI >30 kg/ m²). Patients who did not have a code or laboratory/clinical value for a given comorbidity were classified as not having the comorbidity.

Diagnosis codes to classify each comorbidity were 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
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
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 was ascertained within 7 days pre-index and classified as a binary variable. A past COVID-19 diagnosis was 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 were 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 was used to describe the study cohorts and evaluated for inclusion in the PS generating model.

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

Table 9.5 presents the specific baseline pharmacotherapies.

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 were 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 were excluded who received SARS-CoV-2–neutralizing monoclonal antibodies listed in Table 9.1 within 90 days pre-index; and
    - 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

Medication class	Medication Sub-class	Medication
	SGLT-2 inhibitor	Canagliflozin, dapagliflozin, empagliflozin
	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 healthcare resource utilization (HRU) variables were classified by 1 code from facility and ambulatory encounter records within 7 days pre-index and within 1 year pre-index. HRU was described as continuous (for example, number of office visits), binary (for example, inpatient admission [yes/no]), and categorical variables. The categories were empirically derived from the observed distribution of the continuous variables.

The HRU variables included 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 were 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).

9.5 Data Sources

9.5.1 TriNetX Dataworks USA Network

This observational cohort study used 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 with real-time updates, typically every 2 to 4 weeks. Currently, the standardized EHR fields are available for approximately 92 million patients from 56 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 occurred outside the contributing HCO network were not observed. To mitigate the potential for missing data, eligibility requirements were 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,
- Department of Veterans Affairs (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 were 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 includes 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 were used to ascertain study outcomes and covariate data that were documented outside the EHR database. For example, the linked study population enables 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,
- National Drug Codes (NDC), RxNorm, CPT, HCPCS, and ICD-10-PCS medication codes, and
- CPT and LOINCs for laboratory test results.

9.6 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).

9.6.1 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 was particularly relevant, as it related to the association between COVID-19 treatment selection (that is, BEB or PAX) and independently with the study outcomes (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 were 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 was conducted to further mitigate potential confounding bias. Finally, a quantitative bias sensitivity analysis was 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 have impacted this study were 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 showed approximately 89% of patients aged 12 years and older received at least 1 COVID-19 vaccination. These disparate findings indicated a high degree of missingness. Given this, patients classified as ‘unvaccinated’ were more likely ‘undetermined’ than truly unvaccinated. Therefore, we executed 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 applied equally to patients included in the BEB and PAX cohorts, it was unlikely that the results were confounded by vaccine status; however, misclassification of vaccine status limited a data-driven assessment of imbalances. Therefore, subgroup analyses within vaccinated patients were conducted, as evidence of COVID-19 vaccination in the EHR was not likely to be misclassified. Characteristics of the vaccine distribution were examined in efforts to ensure that the treatment groups were as comparable as possible. To assess potential time-dependent confounding, we described the proportion of patients who received post-index treatment with monoclonal antibody or antiviral therapy (other than BEB or PAX).

9.6.2 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 systematically included non-hospitalized patients in the TriNetX Dataworks USA Network who were treated with BEB or PAX during the study period.

9.6.3 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 occurred outside the HCO network were not captured. This may have resulted in incomplete healthcare profiles and potentially missing exposure or outcome data. Strategies to mitigate missing data and other sources of information bias were incorporated into the study design and study methodology. These included 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.

9.6.3.1 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 TriNetX Linked Network further mitigates this type of misclassification.

Despite this, the likelihood of exposure misclassification may have been greater for patients exposed to PAX (dispensed as an oral medication) than for patients exposed to BEB (administered via infusion). This may have occurred if patients did not fill the PAX prescription or adhere to the prescribing guidelines (for example, they did not take the full dosing regimen). The potential impact of this differential misclassification may have resulted 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 was both unavoidable and unmeasurable in EHR data, the likelihood of this occurring was mitigated, to some degree, by:

- the very nature of the indication (that is, COVID-19),
- the severity of the outcome (that is, hospitalization or death),
- the availability of treatment (the costs of the medications were paid by the US government),
- the relatively short course of PAX treatment (5 days), 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 have occurred if the exposure status, as classified on the index date, was "contaminated" by post-index antibody or antiviral therapy. To address this form of exposure misclassification, we described the use of non-index monoclonal antibody and antiviral treatment during follow-up for patients in both cohorts.

9.6.3.2 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 observational studies when outcome data are missing, equivocal, or uninterruptible.

In the present study, hospitalization and ED visits that occurred outside the TriNetX HCO Network were not ascertained. To mitigate this type of outcome misclassification, eligibility requirements were incorporated, which restricted the study cohorts to include only patients who regularly received care within the TriNetX HCO Network. Additionally, the supplemental analyses, using data from the TriNetX Linked Network, included 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 was not available. As a proxy for the death date, among patients with death recorded in the EHR during follow-up, we classified 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 have likely over-counted 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 TriNetX Linked Network assessed the robustness of the treatment effect and elucidate outcome misclassification; however, the reduced sample size in the TriNetX Linked Network limited the number of events and precision substantially.

9.7 Study Size

9.7.1 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 was estimated that 8,794 patients receiving BEB and 24,744 patients receiving PAX would 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	9,993	28,117	0.700
4	No inpatient admission within 30 days pre-index	9,693	27,273	0.970
5	No hospice care within 30 days pre-index	9,644	27,137	0.995
6	No treatment for COVID-19	9,066	25,509	0.940
7	No supplemental or chronic oxygen therapy	8,794	24,744	0.970

Abbreviations: BEB = bebtelovimab; COVID-19 = coronavirus disease 2019; PAX = Paxlovid

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

9.7.2 Noninferiority Margin

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

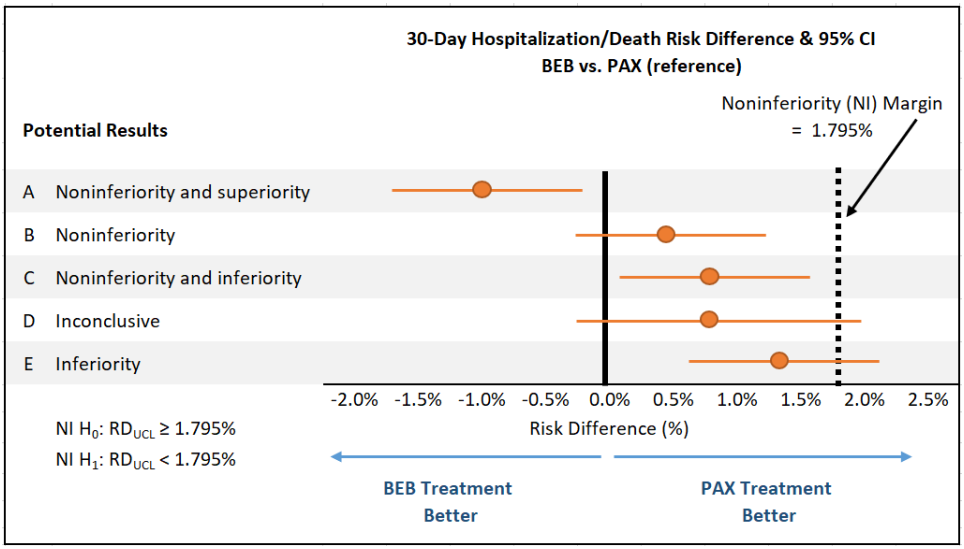
- the first 95% refers to the CI of the estimated effect of the control based on the historical studies demonstrating the effect; and
- the second 95% refers to the CI used to test the null hypothesis in the NI study with the first 95% lower CI defined as the margin (M1).

In this study, a fraction (50%) of M1 was used to provide reasonable assurance that BEB preserved 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%) was used in our NI study as the M1 and 50% of M1 (1.795%) was 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.

Figure 9.2 shows the 5 potential results (A, B, C, D, and E) that were used to test the null hypothesis (Mauri and D'Agostino 2017). If potential results A, B, or C were observed, it would be established that BEB treatment is not inferior to PAX treatment. If potential results D or E were observed, NI would 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 9.2. Noninferiority assessment.

9.7.3 Sample Size and Power

The primary objective was 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=1,065 for each arm would provide 80% power and N=1,390 for each arm would 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%.

9.8 Data Transformation

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

9.9 Statistical Methods

9.9.1 Main Summary Measures

For baseline characteristics, binary and categorial variables were described and summarized using frequencies and percentages, while continuous variables were described and summarized using mean, standard deviation, median, interquartile range (IQR), and minimum and maximum. For primary and secondary outcomes, cumulative incidences with 95% confidence intervals and risk differences with 95% confidence intervals were estimated. More detail can be found in Sections 9.9.2.3 and 9.9.2.4.

9.9.2 Main Statistical Methods

9.9.2.1 Analysis Overview

The following steps were followed sequentially:

1. Construct BEB and PAX study cohorts (unmatched):
    a. describe patients included and excluded, and
    b. describe baseline characteristics and absolute standardized differences (ASD) 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 ASD 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 (supplemental analyses).
9. Execute supplemental analyses for the primary and secondary objectives using data from the TriNetX Linked Network (Steps 3-7).

9.9.2.2 Method to Control for Confounding

Confounding control was 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 was 2-fold. Firstly, it ensured 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 permitted 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) were included as CEM variables, these covariates would be consistent for patients in each matched pair. Sensitivity analyses could then be restricted to patients aged 65 years or older or immunocompromised patients without re-matching.

The 4 binary CEM variables included:

- age $\geq$ 65,
- immunocompromised,

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

In summary, the predicted probability of exposure (that is, BEB versus PAX) was generated from a multi-variable logistic regression model conditioned on baseline covariates. The CEM procedure was then implemented to create unique groupings or risk-sets based on the observed combination of CEM variables. Each CEM risk-set included 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 was the PAX exposed patient with the nearest PS value. Nearest neighbor matching without replacement with a caliper of 0.01 on the PS was used to ensure the estimated probability of exposure did not differ by more than 1.0% between each patient in each matched pair. Each BEB exposed patient was 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 9.4.5 and Table 9.2, Table 9.3, Table 9.4, and Table 9.5) and 2-way interaction terms were 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 were categorized into quintiles or dichotomized, if a clinically relevant threshold existed.

The following PS generating model was 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) was generated. Matching on the PS, in conjunction with CEM matching, was then used to account for baseline confounding.

9.9.2.3 Describe Baseline Characteristics

Analysis: Describe baseline characteristics

Analysis type: Descriptive

Analysis sets:

- BEB and PAX unmatched cohorts, and
- BEB and PAX matched cohorts.

Methodology:

Baseline variables were ascertained using all available EHR data on or before the index date, unless otherwise specified. If data was available on the index date, the last pre-index value was

used. For continuous variables (e.g., eGFR), if data was not available during the baseline period, the variable value was set to missing. Binary and categorical variables were described as the frequency and percentage of patients. Continuous variables were described by the:

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

ASDs (BEB versus PAX) were calculated before matching and after matching. This measure describes the balance of a given variable between 2 groups (cohorts). ASD ≥0.1 and <0.1 depict poor balance and acceptable balance, respectively.

Additionally, PS distributions were described before and after matching.

9.9.2.4 Primary and Secondary Analyses

Outcomes

- Primary (composite outcome):
  - All-cause hospitalization or all-cause mortality;
- Secondary:
  - All-cause hospitalization,
  - All-cause death, and
  - All-cause ED visit.

Analysis type: Descriptive and comparative

Analysis sets:

- BEB and PAX unmatched cohorts, and
- 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); and
- RD and 95% CI.

Hypothesis testing (primary analysis only)

Hypothesis testing was conducted for the primary outcome for patients included in the matched cohorts. The null hypothesis was *the risk of 30-day all-cause hospitalization or all-cause death was higher for patients treated with BEB compared to patients treated with PAX – by at least 1.795%.* We rejected the null hypothesis, and established NI, if the RD_{UCL} excluded 1.795%. More detail on hypothesis testing can be found in Sections 9.7.2 and 9.7.3.

9.9.3 Missing Values

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

9.9.4 Subgroup Analyses

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

The following subgroup analyses were conducted:

- Age 65 years or older (yes/no):
    - Analyses were conducted for matched pairs stratified by age at least 65 years and age less than 65 years. The rationale for this analysis was 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 were 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 was 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 were conducted for matched pairs who had and did not have an ED visit within 7 days before initiating BEB or PAX. As we matched on baseline ED visit status (that is, within 7 days pre-index), we eliminated potential channeling bias by ED visit status, which may be a marker of COVID-19 disease severity. The rationale for this sensitivity analysis was 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 were conducted for matched pairs stratified by baseline immunocompromised status (McCreary et al. 2022). This analysis evaluated the

consistency of the treatment effect for patients who were moderately to severely immunocompromised and for patients who were not immunocompromised.

- Table 9.7 includes the algorithm defined by McCreary et al. to classify immunocompromised status.

Table 9.7. Baseline Immunocompromised Classification

Baseline immunocompromised classification - by at least one condition listed below
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

9.9.5 Sensitivity Analyses

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

Sensitivity analysis to mitigate potential channeling bias

In this analysis, the index date was imputed or "lagged" to the primary index date plus 1 day. The rationale for this sensitivity analysis was to mitigate potential channeling bias that may occur if the observed treatment with 1 agent (BEB or PAX) was 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 excluded patients who had an event very early during follow-up and mitigated bias related to disease severity at the time of BEB or PAX treatment.

Sensitivity analysis to assess the impact of unmeasured confounding

Using E-value methodology proposed by VanderWeele and Ding (VanderWeele and Ding 2017; VanderWeele et al. 2019), we performed 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 was 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 (RR) 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

To assess the potential impact of missing baseline covariate data, we used multiple imputation for select baseline covariates (for example, BMI, age, sex) in which the missingness pattern was more than 0% and less than or equal to 30% (Granger et al. 2019). The rationale for this sensitivity analysis was 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 was 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%.

9.9.6 Amendments to the Statistical Analysis Plan

Variables to classify baseline covariates

HCO Type: HCO type, classified as a categorical variable based on the facility of which the index BEB or PAX record occurred, was stated as a variable to be obtained in the original protocol. However, information on HCO type is not available in TriNetX Dataworks USA. Thus, the variable was not included in the present study.

Methods to control for confounding

Matching Rate Threshold for CEM Variables: An *a priori* threshold for dropping a CEM variable based on the matching rate (less than 85% matching rate within any CEM category) was specified in the original protocol to account for a situation in which there was insufficient sample available in each exact matching category. Though this threshold was met in the present study, CEM variables were not dropped due to the adequate overall sample size and covariate balance in the matched cohorts.

Accounting for calendar time

After protocol approval, additional consideration was given to calendar date of SARS-CoV-2 infection diagnosis as changes in the composition of the circulating SARS-CoV-2 variants may influence study results. Monitoring of COVID-19 variants over time showed bebtelovimab-resistant variant prevalence was low over the study period; however, the potential for differences in disease severity and subsequently study outcomes between variants warranted inclusion of time in the analysis.

Two approaches considered for accounting for calendar time in the propensity score were: 1) including month of the index date in the propensity score model, or 2) including the index date as a CEM variable using time-period bins. Evaluation of circulating variants identified three relevant time-period bins:

- BA.1/BA.1.1: 01 February 2022 through 26 March 2022,
- BA.2/BA.2.12.1: 27 March 2022 through 26 June 2022, and
- BA.4/BA.5: 27 June 2022 through the end of August 2022.

Approach 1, including a categorical variable for month of index date in the propensity score calculations, was selected because it resulted in a higher matching rate than including time-period of the index date as a CEM variable. In the CEM variable approach, the number of CEM categories would have been increased from 16 to 48, limiting the matched cohort sizes.

Consideration of calendar time also promoted consideration of data source. Prior to considering calendar time, the study cohort was developed using the TriNetX Dataworks USA Network (Cohort extracted 30 January 2023). Some healthcare organizations in this network provide data that are "date-shifted" to help protect patient privacy, in which dates associated with encounters in the health record are shifted a specified amount of time. The amount of time that records are shifted is unknown and may differ from patient to patient. During protocol development, the TriNetX study team considered the rate of misclassification due to date-shifting as a minor risk and, therefore, did not initially exclude date shifted patient data. However, upon creating month-specific categorical variables, the TriNetX team investigated the impact that data-shifted data could have on the study population and determined the extent of potential of misclassification required correction. As a result, the final study cohorts were created excluding date-shifted data, resulting in the final unmatched cohort size of 73,479 patients, extracted on 23 March 2023.

Immunocompromised CEM variable

In addition to medication and procedure codes, the immunocompromised status CEM variable was pre-specified to include ICD-10 diagnosis codes used by McCreary et al. (2022). However, a discrepancy was identified after analyses were completed. In addition to codes used by McCreary et al., the immunocompromised status CEM variable included ICD-10 diagnosis codes derived from categories in the Healthcare Cost and Utilization Project (HCUP) Clinical Classifications Software Refined (CCSR), i.e., codes not used by McCreary et al. The HCUP CCSR-derived codes were pre-specified for a separate immunocompromised status variable included in the propensity score but not for the CEM variable. The inclusion of these codes in the CEM variable was accidental. This discrepancy resulted in a minimal difference in the

prevalence of immunocompromised status based on the CEM variable (0.14% difference in the overall cohort when comparing the McCreary et al. and HCUP CCSR-derived codes to McCreary et al. codes only). Thus, the codes used for the immunocompromised status CEM variable were not changed.

9.10 Quality Control

In addition to quality control of the protocol and statistical analysis plan via study team review, all data gathering and analyses that were conducted after protocol and statistical analysis plan approval were overseen by 2 analysts experienced in the field of observational research using EHR data. Programming for this project was conducted by a primary analyst and code review by a separate validation analyst. For all data processing steps, the validation analyst reviewed the program code for protocol consistency, along with input/output datasets and results tables/figures. For each analysis step, code review was employed to reduce the potential risk of programming errors.

10 Results

10.1 Participants

Before applying patient qualification criteria, 12,920 BEB-exposed and 70,741 PAX-exposed patients were identified. After applying patient qualification criteria, 10,431 BEB-exposed and 63,048 PAX-exposed patients remained in the unmatched cohorts (Table 10.1). After conducting high-dimensional propensity score (HDPS) matching, 55.9% of BEB-exposed patients were retained, resulting in 5,827 BEB-exposed and 5,827 PAX-exposed patients in the matched cohorts.

Table 10.1. Patient Disposition

Patient Identification Criteria – Inclusion/Exclusion		BEB				PAX			
		N	N Excluded	% Excluded	% Retained	N	N Excluded	% Excluded	% Retained
1	Exposure to BEB or PAX during index period	12,920				70,741			
2	Age ≥ 12 years at index date	12,919	1	0.0%	100.0%	70,739	2	0.0%	100.0%
3	≥ 1 healthcare encounter within 6-36 months pre-index	11,522	1,397	10.8%	89.2%	64,926	5,813	8.2%	91.8%
4	No inpatient admission within 30 days pre-index	11,062	460	4.0%	96.0%	64,025	901	1.4%	98.6%
5	No hospice care within 30 days pre-index	11,053	9	0.1%	99.9%	64,006	19	0.0%	100.0%
6	No exposure to monoclonal antibody or antiviral within 90 days pre-index	10,609	444	4.0%	96.0%	63,315	691	1.1%	98.9%
7	No supplemental or chronic oxygen therapy within 30 days pre-index	10,431	178	1.7%	98.3%	63,048	267	0.4%	99.6%
	Total in unmatched cohorts	**10,431**				**63,048**			
8	HDPS Matching (1:1) using a caliper of 0.01 & common support	5,827	4,604	44.1%	55.9%	5,827	57,221	90.8%	9.2%
	Total in matched cohorts	**5,827**				**5,827**			

* "Retained" refers to the estimated proportion of patients to be retained after enforcing each inclusion or exclusion criterion or matching
Abbreviations: BEB = Bebtelovimab; PAX = Paxlovid; HDPS = high dimensional propensity score

10.2 Descriptive Data

10.2.1 CEM Matching Rate and Propensity Score Distribution

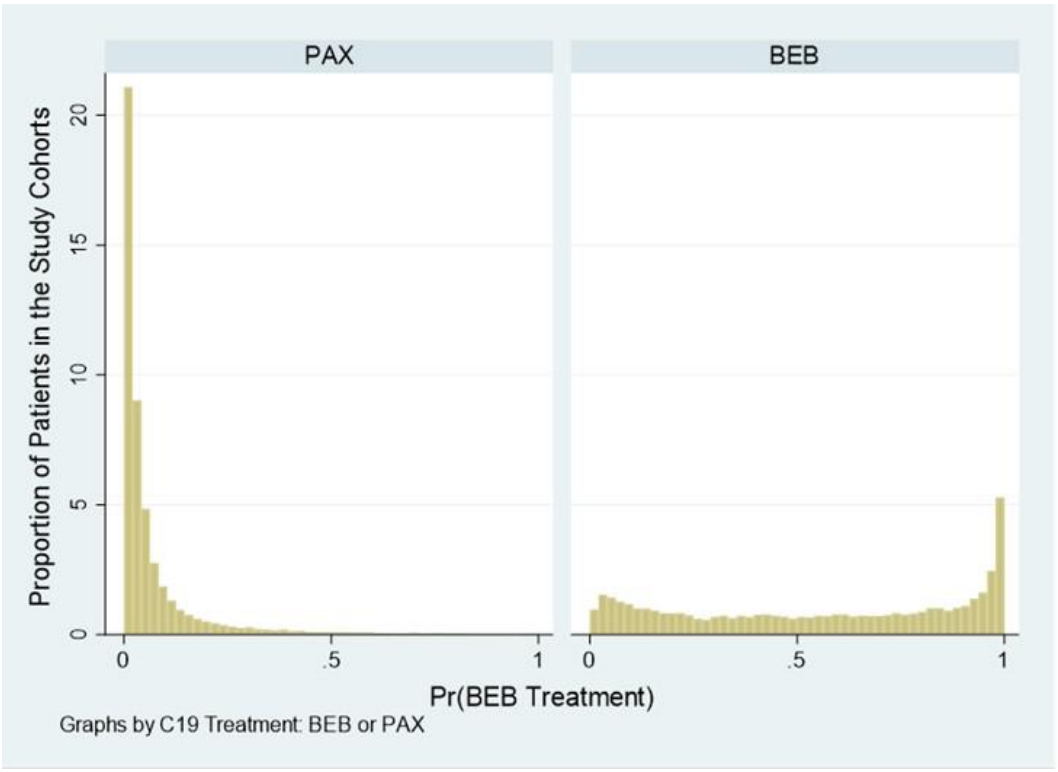
Table 10.2 presents patient distribution within CEM categories. The variables included in the CEM process resulted in 16 categories. The proportion of patients in each category within the BEB and PAX cohorts is more similar after matching. Figure 10.1 displays the PS distribution in the unmatched and matched cohorts. The propensity score represents the predicted probability of receiving BEB (vs. PAX) based on baseline covariate information. The different shapes of the distributions presented in part A of Figure 10.1 indicate that the BEB and PAX were prescribed to different patient populations. PAX treated patients represented a more clearly defined but skewed distributed patient population and were less likely to receive BEB as indicated by the right-skewed distribution. BEB patients were not as clearly defined, as indicated by the relatively uniform distribution. Only a small proportion of BEB patients were unlikely to receive PAX. The overlap of the PS distribution between BEB- and PAX-exposed patients notably improved after HDPS matching.

Table 10.2. Distribution of Patients within CEM Categories for Unmatched and Matched Cohorts

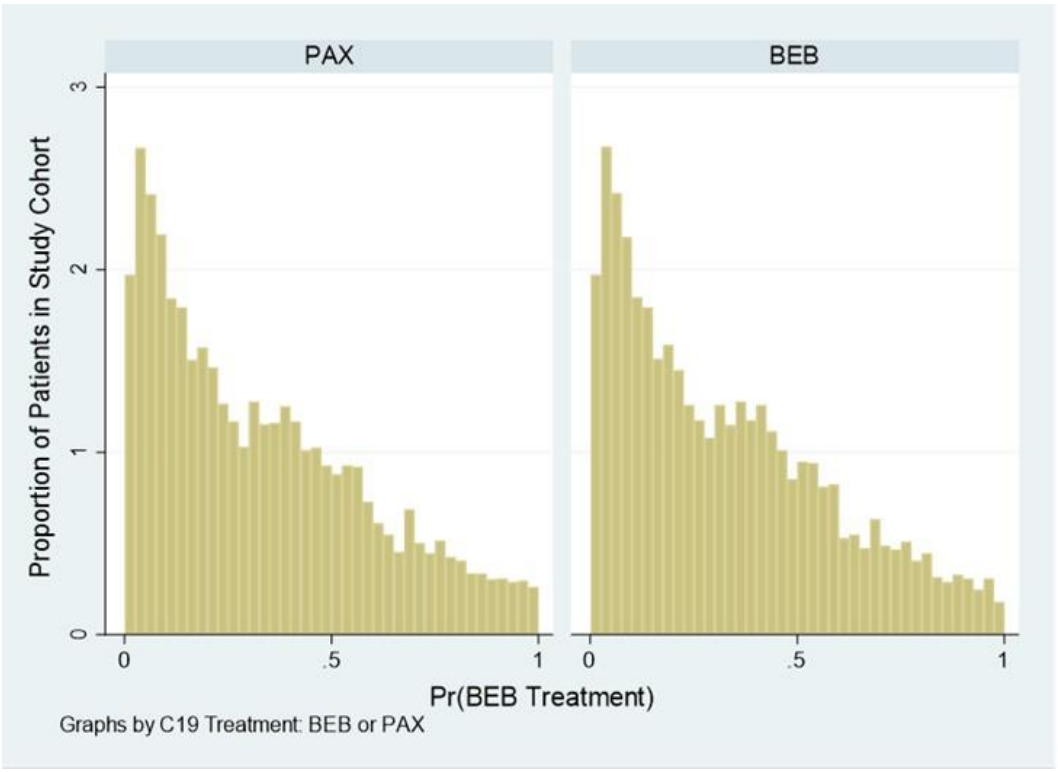
CEM Category	CEM Categories				PAX		BEB		Total	
	Immunocompromised Status	Age ≥ 65	COVID-19 Vaccination within 9 Months Pre-index	ED Visit within 7 Days Pre-index	Frequency	%	Frequency	%	Frequency	%
Unmatched cohorts										
1	No	No	No	No	22,135	35.11%	1,739	16.67%	23,874	32.49%
2	No	No	No	Yes	2,429	3.85%	377	3.61%	2,806	3.82%
3	No	No	Yes	No	2,432	3.86%	333	3.19%	2,765	3.76%
4	No	No	Yes	Yes	115	0.18%	38	0.36%	153	0.21%
5	No	Yes	No	No	12,241	19.42%	1,798	17.24%	14,039	19.11%
6	No	Yes	No	Yes	1,165	1.85%	484	4.64%	1,649	2.24%
7	No	Yes	Yes	No	1,749	2.77%	407	3.90%	2,156	2.93%
8	No	Yes	Yes	Yes	125	0.20%	68	0.65%	193	0.26%
9	Yes	No	No	No	8,364	13.27%	1,532	14.69%	9,896	13.47%
10	Yes	No	No	Yes	573	0.91%	407	3.90%	980	1.33%
11	Yes	No	Yes	No	1,071	1.70%	416	3.99%	1,487	2.02%
12	Yes	No	Yes	Yes	62	0.10%	60	0.58%	122	0.17%
13	Yes	Yes	No	No	8,609	13.65%	1,785	17.11%	10,394	14.15%
14	Yes	Yes	No	Yes	558	0.89%	397	3.81%	955	1.30%
15	Yes	Yes	Yes	No	1,317	2.09%	483	4.63%	1,800	2.45%
16	Yes	Yes	Yes	Yes	103	0.16%	107	1.03%	210	0.29%
Total					63,048	100.00%	10,431	100.00%	73,479	100.00%
Matched cohorts										
1	No	No	No	No	1,112	19.08%	1,112	19.08%	2,224	19.08%
2	No	No	No	Yes	247	4.24%	247	4.24%	494	4.24%
3	No	No	Yes	No	200	3.43%	200	3.43%	400	3.43%
4	No	No	Yes	Yes	14	0.24%	14	0.24%	28	0.24%
5	No	Yes	No	No	933	16.01%	933	16.01%	1,866	16.01%
6	No	Yes	No	Yes	273	4.69%	273	4.69%	546	4.69%

CEM Category	CEM Categories				PAX		BEB		Total	
	Immunocompromised Status	Age ≥ 65	COVID-19 Vaccination within 9 Months Pre-index	ED Visit within 7 Days Pre-index	Frequency	%	Frequency	%	Frequency	%
7	No	Yes	Yes	No	230	3.95%	230	3.95%	460	3.95%
8	No	Yes	Yes	Yes	27	0.46%	27	0.46%	54	0.46%
9	Yes	No	No	No	847	14.54%	847	14.54%	1,694	14.54%
10	Yes	No	No	Yes	191	3.28%	191	3.28%	382	3.28%
11	Yes	No	Yes	No	218	3.74%	218	3.74%	436	3.74%
12	Yes	No	Yes	Yes	19	0.33%	19	0.33%	38	0.33%
13	Yes	Yes	No	No	1,000	17.16%	1,000	17.16%	2,000	17.16%
14	Yes	Yes	No	Yes	211	3.62%	211	3.62%	422	3.62%
15	Yes	Yes	Yes	No	265	4.55%	265	4.55%	530	4.55%
16	Yes	Yes	Yes	Yes	40	0.69%	40	0.69%	80	0.69%
Total					5,827	100.00%	5,827	100.00%	11,654	100.00%

Abbreviations: BEB = bebtelovimab; CEM = coarsened exact matching; COVID-19 = coronavirus disease 2019; ED = early discontinuation; PAX = paxlovid.



A)



B)

Figure 10.1. Propensity score distribution in the A) unmatched and B) matched cohorts.

10.2.2 Baseline Characteristics

Table 10.3, Table 10.4, Table 10.5, Table 10.6, and Table 10.7 display baseline variables for BEB-exposed and PAX-exposed patients in the unmatched cohort. The median age was higher in BEB-exposed patients (66 years; IQR 51 – 75) compared to PAX-exposed patients (61 years; IQR 47 – 71). Patients were primarily female (58.31% in BEB and 60.39% in PAX), White (82.92% in BEB and 80.63% in PAX), and non-Hispanic (73.92% in BEB and 62.84% in PAX). Common COVID-19 related characteristics included presence of a COVID-19 diagnosis anytime pre-index (80.25% in BEB and 54.18% in PAX), a COVID-19 positive test within 7 days pre-index (21.65% in BEB and 13.64% in PAX), and documentation of a COVID-19 vaccine (29.80% in BEB and 18.99% in PAX). Proportions of baseline comorbidities were generally larger in BEB-exposed compared to PAX-exposed patients. Common baseline comorbidities included aplastic anemia (24.79% in BEB and 12.16% in PAX), immunodeficiency (22.93% in BEB and 9.09% in PAX), hypertension (58.93% in BEB and 47.01% in PAX), other heart conditions (48.05% in BEB and 30.74% in PAX), obesity (31.53% in BEB and 29.49% in PAX), type 2 diabetes (27.18% in BEB and 18.26% in PAX), hematologic or solid malignancy except benign skin cancer (32.64% in BEB and 22.60% in PAX), anxiety and fear (33.81% in BEB and 31.88% in PAX), depression (29.19% in BEB and 24.17% in PAX), and CKD (24.33% in BEB and 10.32% in PAX).

Common baseline medications included past dexamethasone use (41.27% in BEB and 31.61% in PAX), past methylprednisolone use (36.67% in BEB and 32.78% in PAX), past prednisone use (36.14% in BEB and 29.43% in PAX), past triamcinolone use (28.75% in BEB and 24.04% in PAX), past fluticasone use (29.84% in BEB and 30.73% in PAX), past (60.44% in BEB and 44.84% in PAX) and present antihypertensive use (32.81% in BEB and 25.00% in PAX), past short-acting beta agonist (SABA) use (36.62% in BEB and 28.08% in PAX), and past lipid lowering agent use (45.69% in BEB and 31.25% in PAX).

Distributions between two groups for all four CEM variables were imbalanced with BEB patients more likely to be immunocompromised, older, have a documented COVID-19 vaccine, and have an ED encounter within 7 days: immunocompromised status (ASD= 0.350), age ≥ 65 years (ASD = 0.242), documented COVID-19 vaccination within 9 months pre-index (ASD = 0.206), and an ED encounter within 7 days pre-index (ASD = 0.311). Other notably imbalanced covariates included COVID-19 diagnosis anytime pre-index (ASD = 0.578; higher proportion of BEB patients), blood pressure category (ASD = 0.676; higher percentage of missing data for PAX patients), present methylprednisolone use (ASD = 0.763; higher proportion of BEB use), present hydrocortisone use (ASD = 0.443; higher proportion of BEB patients), past anticoagulant use (ASD = 0.440; higher proportion of BEB patients), and number of outpatient encounters within 7 days pre-index (ASD = 0.559; higher number of encounters for BEB patients).

Table 10.3. Baseline Demographic Characteristics and Lifestyle Variables in the Unmatched Cohorts

							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Index date month							0.274
February	95	0.15%	0	0.00%	95	0.13%	
March	582	0.92%	38	0.36%	620	0.84%	
April	3,902	6.19%	1,253	12.01%	5,155	7.02%	
May	12,585	19.96%	2,521	24.17%	15,106	20.56%	
June	12,652	20.07%	2,025	19.41%	14,677	19.97%	
July	18,812	29.84%	2,828	27.11%	21,640	29.45%	
August	14,420	22.87%	1,766	16.93%	16,186	22.03%	
Demographics							**ASD**
Patient age							0.239
Mean (SD), years	58.49 (16.04)		62.39 (16.59)				
Median (IQR), years	61 (47 - 71)		66 (51 - 75)				
Min, Max, years	12, 90		14, 92				
Age category							0.285
12-29 years	3,029	4.80%	385	3.69%	3,414	4.65%	
30-44 years	10,438	16.56%	1,443	13.83%	11,881	16.17%	
45-54 years	10,091	16.01%	1,217	11.67%	11,308	15.39%	
55-64 years	13,623	21.61%	1,857	17.80%	15,480	21.07%	
65-74 years	16,000	25.38%	2,873	27.54%	18,873	25.68%	
75-84 years	7,809	12.39%	1,970	18.89%	9,779	13.31%	
≥85 years	2,058	3.26%	686	6.58%	2,744	3.73%	
Female sex							0.042
Yes	38,074	60.39%	6,082	58.31%	44,156	60.09%	
Race							0.103
White	50,833	80.63%	8,649	82.92%	59,482	80.95%	
Black	5,491	8.71%	761	7.30%	6,252	8.51%	

							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Other	1,775	2.82%	162	1.55%	1,937	2.64%	
Unknown	4,949	7.85%	859	8.24%	5,808	7.90%	
Ethnicity							0.257
Hispanic	3,560	5.65%	585	5.61%	4,145	5.64%	
Not Hispanic	39,618	62.84%	7,711	73.92%	47,329	64.41%	
Unknown	19,870	31.52%	2,135	20.47%	22,005	29.95%	
Lifestyle variables							**ASD**
Smoking status 6 months pre-index							0.014
Yes	881	1.40%	163	1.56%	1,044	1.42%	
Smoking status >6 months pre-index							0.047
Yes	2,522	4.00%	519	4.98%	3,041	4.14%	
Smoking ever pre-index							0.019
Yes	4,086	6.48%	725	6.95%	4,811	6.55%	
Inactivity							0.048
Yes	81	0.13%	38	0.36%	119	0.16%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; CEM = coarsened exact matching; IQR = interquartile range; max = maximum; min = minimum; PAX = Paxlovid; SD = standard deviation.

Table 10.4. Baseline CEM and COVID-19 Variables in the Unmatched Cohorts

CEM variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Immunocompromised status (University of Pittsburgh Medical Center [UPMC])							0.350
Yes	20,657	32.76%	5,187	49.73%	25,844	35.17%	
Age ≥ 65							0.242
Yes	25,867	41.03%	5,529	53.01%	31,396	42.73%	
COVID-19 vaccination within 9 months pre-index							0.206
Yes	6,974	11.06%	1,912	18.33%	8,886	12.09%	
ED encounter within 7 days pre-index							0.311
Yes	5,130	8.14%	1,938	18.58%	7,068	9.62%	
COVID-19 related variables							**ASD**
COVID-19 diagnosis anytime pre-index							0.578
Yes	34,157	54.18%	8,371	80.25%	42,528	57.88%	
COVID-19 positive test: within 7 days pre-index							0.213
Yes	8,600	13.64%	2,258	21.65%	10,858	14.78%	
COVID-19 positive test: >7 days pre-index							0.015
Yes	2,432	3.86%	434	4.16%	2,866	3.90%	
COVID-19 vaccine: past (>9 months pre-index)							0.252
Yes	11,974	18.99%	3,108	29.80%	15,082	20.53%	
COVID-19 antibody therapy: present (within 3-6 months pre-index)							0.127
Yes	325	0.52%	200	1.92%	525	0.71%	
COVID-19 antibody therapy: past (>6 months pre-index)							0.042
Yes	386	0.61%	103	0.99%	489	0.67%	
COVID-19 related symptoms							**ASD**
Anosmia and parosmia							0.013
Yes	117	0.19%	14	0.13%	131	0.18%	
Cough							0.010
Yes	2,976	4.72%	516	4.95%	3,492	4.75%	
Fatigue							0.097

CEM variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	2,241	3.55%	583	5.59%	2,824	3.84%	
Fever or chills							0.075
Yes	2,535	4.02%	588	5.64%	3,123	4.25%	
Headache							0.042
Yes	522	0.83%	131	1.26%	653	0.89%	
Myalgia or joint pain							0.023
Yes	1,770	2.81%	335	3.21%	2,105	2.86%	
Nausea or vomiting							0.084
Yes	2,356	3.74%	574	5.50%	2,930	3.99%	
Dyspnea							0.102
Yes	1,630	2.59%	466	4.47%	2,096	2.85%	
Sore throat/pharyngitis							0.077
Yes	2,058	3.26%	500	4.79%	2,558	3.48%	
Diarrhea							0.029
Yes	609	0.97%	133	1.28%	742	1.01%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; CEM = coarsened exact matching; COVID-19 = coronavirus disease 2019; ED = early discontinuation; PAX = Paxlovid; SD = standard deviation.

Table 10.5. Baseline Clinical, Laboratory, and Comorbidity Variables in the Unmatched Cohorts

Clinical & laboratory variables							ASD
	PAX		BEB		Total		
BMI (kg/m^2)							0.083
Mean (SD), years	30.14 (7.11)		29.58 (6.77)				
Median (IQR), years	28.98 (25.11 – 33.90)		28.51 (24.81 – 33.26)				
Min, Max, years	11.65, 76.45		12.40, 71.94				
BMI category							0.347
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**	
Underweight: <18.5	547	0.87%	143	1.37%	690	0.94%	
Normal: 18.5-24	10,968	17.40%	2,278	21.84%	13,246	18.03%	
Overweight: 25-29	15,606	24.75%	3,055	29.29%	18,661	25.40%	
Obese: ≥30.0	21,265	33.73%	3,845	36.86%	25,110	34.17%	
Missing	14,662	23.26%	1,110	10.64%	15,772	21.46%	
MCQ eGFR: using last sCr pre-index							0.359
Mean (SD), years	95.75 (17.79)		87.59 (23.66)				
Median (IQR), years	95.52 (86.04 – 106.90)		90.23 (77.40 – 103.35)				
Min, Max, years	16.08, 161.87		14.37, 157.49				
MCQ eGFR: using last sCr pre-index							0.364
eGFR ≥90	33,499	53.13%	4,306	41.28%	37,805	51.45%	
eGFR 60-89	16,570	26.28%	3,188	30.56%	19,758	26.89%	
eGFR 30-59	1,704	2.70%	807	7.74%	2,511	3.42%	
eGFR <30	93	0.15%	271	2.60%	364	0.50%	
Missing	11,182	17.74%	1,859	17.82%	13,041	17.75%	
Blood pressure: category							0.676
Normotensive	2,148	3.41%	1,026	9.84%	3,174	4.32%	
Elevated	1,411	2.24%	704	6.75%	2,115	2.88%	
Stage 1	3,051	4.84%	1,138	10.91%	4,189	5.70%	
Stage 2	3,576	5.67%	1,891	18.13%	5,467	7.44%	
Missing	52,862	83.84%	5,672	54.38%	58,534	79.66%	
Oxygen saturation: category							0.413

Clinical & laboratory variables							ASD
	PAX		BEB		Total		
≥95%	1,822	2.89%	1,430	13.71%	3,252	4.43%	
85-95%	196	0.31%	102	0.98%	298	0.41%	
<85%	26	0.04%	15	0.14%	41	0.06%	
Missing	61,004	96.76%	8,884	85.17%	69,888	95.11%	
Comorbidities							**ASD**
Autoimmune							
Crohn's disease							0.066
Yes	739	1.17%	208	1.99%	947	1.29%	
Juvenile arthritis							0.000
Yes	78	0.12%	13	0.12%	91	0.12%	
Rheumatoid arthritis							0.142
Yes	2,488	3.95%	750	7.19%	3,238	4.41%	
Systemic lupus erythematosus							0.164
Yes	2,924	4.64%	911	8.73%	3,835	5.22%	
Ulcerative colitis							0.065
Yes	643	1.02%	187	1.79%	830	1.13%	
Blood Disorders							
Aplastic anemia							0.333
Yes	7,665	12.16%	2,586	24.79%	10,251	13.95%	
Immunodeficiency							0.364
Yes	2,656	4.21%	1,529	14.66%	4,185	5.70%	
Immunodeficiency (UPMC)							0.385
Yes	5,732	9.09%	2,392	22.93%	8,124	11.06%	
Sickle cell							0.006
Yes	159	0.25%	30	0.29%	189	0.26%	
Thalassemia							0.012
Yes	206	0.33%	42	0.40%	248	0.34%	
Circulatory							
Acute hemorrhagic cerebrovascular disease							0.114

Clinical & laboratory variables							ASD
	PAX		BEB		Total		
Yes	1,699	2.69%	508	4.87%	2,207	3.00%	
Cerebral infarction							0.180
Yes	2,331	3.70%	822	7.88%	3,153	4.29%	
Other cerebrovascular disease							0.182
Yes	3,320	5.27%	1,053	10.09%	4,373	5.95%	
Acute myocardial infarction							0.208
Yes	1,754	2.78%	762	7.31%	2,516	3.42%	
Coronary artery disease							0.292
Yes	4,082	6.47%	1,610	15.43%	5,692	7.75%	
Heart failure							0.346
Yes	2,725	4.32%	1,476	14.15%	4,201	5.72%	
Hypertension							0.241
Yes	29,636	47.01%	6,147	58.93%	35,783	48.70%	
Myocarditis or cardiomyopathy							0.235
Yes	1,768	2.80%	846	8.11%	2,614	3.56%	
Other heart condition							0.362
Yes	19,378	30.74%	5,012	48.05%	24,390	33.19%	
Peripheral vascular disease							0.238
Yes	5,193	8.24%	1,658	15.89%	6,851	9.32%	
Disability							
Cerebral palsy							0.040
Yes	100	0.16%	38	0.36%	138	0.19%	
Congenital malformation							0.241
Yes	6,191	9.82%	1,892	18.14%	8,083	11.00%	
Limitation of activities of daily living (ADL)							0.193
Yes	1,157	1.84%	563	5.40%	1,720	2.34%	
Neurodevelopmental disorders							0.009
Yes	2,986	4.74%	516	4.95%	3,502	4.77%	
Spinal cord injury							0.017

Clinical & laboratory variables							ASD
	PAX		BEB		Total		
Yes	92	0.15%	23	0.22%	115	0.16%	
Endocrine							
Obesity							0.044
Yes	18,592	29.49%	3,289	31.53%	21,881	29.78%	
Diabetes Type 1							0.098
Yes	1,051	1.67%	330	3.16%	1,381	1.88%	
Diabetes Type 2							0.214
Yes	11,511	18.26%	2,835	27.18%	14,346	19.52%	
Diabetes Type 1 or 2 (complicated)							0.224
Yes	6,484	10.28%	1,882	18.04%	8,366	11.39%	
Hepatic							
Alcoholic liver disease							0.039
Yes	1,529	2.43%	316	3.03%	1,845	2.51%	
Autoimmune hepatitis							0.054
Yes	99	0.16%	48	0.46%	147	0.20%	
Cirrhosis							0.174
Yes	567	0.90%	356	3.41%	923	1.26%	
Non-alcoholic fatty liver disease							0.070
Yes	4,092	6.49%	865	8.29%	4,957	6.75%	
Infectious							
Hepatitis B							0.083
Yes	206	0.33%	104	1.00%	310	0.42%	
Hepatitis C							0.077
Yes	956	1.52%	272	2.61%	1,228	1.67%	
HIV							0.059
Yes	1,193	1.89%	288	2.76%	1,481	2.02%	
Tuberculosis							0.045
Yes	161	0.26%	55	0.53%	216	0.29%	
Malignancy							

Clinical & laboratory variables							ASD
	PAX		BEB		Total		
Hematological oncology (except skin)							0.226
Yes	14,252	22.60%	3,405	32.64%	17,657	24.03%	
Metastatic							0.147
Yes	1,175	1.86%	461	4.42%	1,636	2.23%	
Radiation complication							0.102
Yes	597	0.95%	231	2.21%	828	1.13%	
Mental Health							
Anxiety and fear							0.040
Yes	20,102	31.88%	3,527	33.81%	23,629	32.16%	
Bipolar							0.092
Yes	1,181	1.87%	348	3.34%	1,529	2.08%	
Depression							0.114
Yes	15,240	24.17%	3,045	29.19%	18,285	24.88%	
Other mood disorder							0.082
Yes	1,105	1.75%	313	3.00%	1,418	1.93%	
Schizophrenia							0.088
Yes	628	1.00%	216	2.07%	844	1.15%	
Substance abuse							0.220
Yes	3,357	5.32%	1,187	11.38%	4,544	6.18%	
Suicidal ideation							0.109
Yes	1,459	2.31%	444	4.26%	1,903	2.59%	
Neurocognitive disorders							0.126
Yes	1,323	2.10%	449	4.30%	1,772	2.41%	
Pulmonary							
Alpha-1 antitrypsin deficiency							0.039
Yes	41	0.07%	22	0.21%	63	0.09%	
Asthma							0.060
Yes	11,380	18.05%	2,127	20.39%	13,507	18.38%	
Bronchopulmonary dysplasia							0.011

Clinical & laboratory variables							ASD
	PAX		BEB		Total		
Yes	1	0.00%	1	0.01%	2	0.00%	
COPD and bronchiectasis							0.098
Yes	6,851	10.87%	1,473	14.12%	8,324	11.33%	
Cystic fibrosis							0.044
Yes	117	0.19%	45	0.43%	162	0.22%	
Embolism							0.192
Yes	1,059	1.68%	536	5.14%	1,595	2.17%	
Hypertension							0.263
Yes	1,212	1.92%	772	7.40%	1,984	2.70%	
Interstitial disease							0.157
Yes	1,088	1.73%	459	4.40%	1,547	2.11%	
Renal							
CKD							0.378
Yes	6,506	10.32%	2,538	24.33%	9,044	12.31%	
End-stage renal disease (ESRD)							0.240
Yes	3,022	4.79%	1,173	11.25%	4,195	5.71%	
Transplant							
Organ stem cell							0.317
Yes	1,906	3.02%	1,147	11.00%	3,053	4.15%	
Graft versus host disease							0.048
Yes	58	0.09%	32	0.31%	90	0.12%	
Pregnancy variables							**ASD**
Pregnancy within 3 months pre-index							0.137
Yes	1,216	1.93%	449	4.30%	1,665	2.27%	
Pregnancy within 9 months pre-index							0.105
Yes	2,238	3.55%	600	5.75%	2,838	3.86%	
Pregnancy ever pre-index							0.088
Yes	10,703	16.98%	2,128	20.40%	12,831	17.46%	

Clinical & laboratory variables				ASD
	PAX	BEB	Total	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ED = early discontinuation; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; IQR = interquartile range; max = maximum; MCQ = Mayo Clinic quadratic; min = minimum; PAX = Paxlovid; sCr = serum creatinine; SD = standard deviation; UPMC = University of Pittsburgh Medical Center.

Table 10.6. Baseline Pharmacotherapy and Procedure-related Variables in the Unmatched Cohorts

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Antiemetics							
Present within 7 days pre-index							0.070
Yes	381	0.60%	134	1.28%	515	0.70%	
Past >7 days pre-index							0.004
Yes	9,322	14.79%	1,527	14.64%	10,849	14.76%	
Corticosteroids							
Beclomethasone: present (within 7 days pre-index)							0.005
Yes	35	0.06%	7	0.07%	42	0.06%	
Beclomethasone: past (>7 days pre-index)							0.031
Yes	1,103	1.75%	228	2.19%	1,331	1.81%	
Betamethasone: present (within 7 days pre-index)							0.016
Yes	96	0.15%	10	0.10%	106	0.14%	
Betamethasone: past (>7 days pre-index)							0.036
Yes	8,316	13.19%	1,250	11.98%	9,566	13.02%	
Budesonide: present (within 7 days pre-index)							0.002
Yes	244	0.39%	39	0.37%	283	0.39%	
Budesonide: past (>7 days pre-index)							0.092
Yes	4,379	6.95%	988	9.47%	5,367	7.30%	
Deflazacort: present (within 7 days pre-index)							0.006
Yes	1	0.00%	0	0.00%	1	0.00%	
Deflazacort: past (>7 days pre-index)							0.008
Yes	2	0.00%	1	0.01%	3	0.00%	
Dexamethasone: present (within 7 days pre-index)							0.356
Yes	706	1.12%	907	8.70%	1,613	2.20%	
Dexamethasone: past (>7 days pre-index)							0.202
Yes	19,929	31.61%	4,305	41.27%	24,234	32.98%	
Hydrocortisone: present (within 7 days pre-index)							0.443

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	140	0.22%	994	9.53%	1,134	1.54%	
Hydrocortisone: past (>7 days pre-index)							0.098
Yes	8,590	13.62%	1,790	17.16%	10,380	14.13%	
Methylprednisolone: present (within 7 days pre-index)							0.763
Yes	1,351	2.14%	2,862	27.44%	4,213	5.73%	
Methylprednisolone: past (>7 days pre-index)							0.082
Yes	20,664	32.78%	3,825	36.67%	24,489	33.33%	
Prednisolone: present (within 7 days pre-index)							0.265
Yes	41	0.07%	373	3.58%	414	0.56%	
Prednisolone: past (>7 days pre-index)							0.166
Yes	2,115	3.35%	733	7.03%	2,848	3.88%	
Prednisone: present (within 7 days pre-index)							0.029
Yes	1,193	1.89%	240	2.30%	1,433	1.95%	
Prednisone: past (>7 days pre-index)							0.143
Yes	18,555	29.43%	3,770	36.14%	22,325	30.38%	
Triamcinolone: present (within 7 days pre-index)							0.006
Yes	267	0.42%	40	0.38%	307	0.42%	
Triamcinolone: past (>7 days pre-index)							0.107
Yes	15,156	24.04%	2,999	28.75%	18,155	24.71%	
Mometasone: present (within 7 days pre-index)							0.008
Yes	64	0.10%	8	0.08%	72	0.10%	
Mometasone: past (>7 days pre-index)							0.019
Yes	3,633	5.76%	555	5.32%	4,188	5.70%	
Fluticasone: present (within 7 days pre-index)							0.002
Yes	1,314	2.08%	220	2.11%	1,534	2.09%	
Fluticasone: past (>7 days pre-index)							0.019
Yes	19,377	30.73%	3,113	29.84%	22,490	30.61%	
Anticoagulants							

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Present (within 6 months pre-index)							0.310
Yes	1,176	1.87%	911	8.73%	2,087	2.84%	
Past (>6 months pre-index)							0.440
Yes	3,455	5.48%	2,059	19.74%	5,514	7.50%	
Antidiabetic							
Insulin: present (within 6 months pre-index)							0.192
Yes	2,252	3.57%	839	8.04%	3,091	4.21%	
Insulin: past (>6 months pre-index)							0.364
Yes	6,210	9.85%	2,415	23.15%	8,625	11.74%	
Other: present (within 6 months pre-index)							0.037
Yes	5,276	8.37%	984	9.43%	6,260	8.52%	
Other: past (>6 months pre-index)							0.136
Yes	8,640	13.70%	1,952	18.71%	10,592	14.42%	
Antihypertensives							
Present (within 6 months pre-index)							0.173
Yes	15,762	25.00%	3,422	32.81%	19,184	26.11%	
Past (>6 months pre-index)							0.316
Yes	28,271	44.84%	6,305	60.44%	34,576	47.06%	
Antiviral							
Chloroquine: present (within 3-6 months pre-index)							0.006
Yes	3	0.00%	1	0.01%	4	0.01%	
Chloroquine: past (>6 months pre-index)							0.025
Yes	77	0.12%	5	0.05%	82	0.11%	
Hydroxychloroquine sulfate: present (within 3-6 months pre-index)							0.038
Yes	137	0.22%	45	0.43%	182	0.25%	
Hydroxychloroquine sulfate: past (>6 months pre-index)							0.102
Yes	973	1.54%	320	3.07%	1,293	1.76%	
Ivermectin: present (within 3-6 months pre-index)							0.005

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	24	0.04%	5	0.05%	29	0.04%	
Ivermectin: past (>6 months pre-index)							0.015
Yes	233	0.37%	49	0.47%	282	0.38%	
Molnupiravir: present (within 3-6 months pre-index)							0.011
Yes	4	0.01%	0	0.00%	4	0.01%	
Molnupiravir: past (>6 months pre-index)							0.011
Yes	4	0.01%	0	0.00%	4	0.01%	
Paxlovid: present (within 3-6 months pre-index)							0.006
Yes	18	0.03%	2	0.02%	20	0.03%	
Paxlovid: past (>6 months pre-index)							0.020
Yes	13	0.02%	0	0.00%	13	0.02%	
Remdesivir: present (within 3-6 months pre-index)							0.006
Yes	17	0.03%	4	0.04%	21	0.03%	
Remdesivir: past (>6 months pre-index)							0.036
Yes	247	0.39%	68	0.65%	315	0.43%	
Rituximab B-Cell							
Present (within 6 months pre-index)							0.054
Yes	342	0.54%	106	1.02%	448	0.61%	
Past (>6 months pre-index)							0.105
Yes	692	1.10%	260	2.49%	952	1.30%	
Bronchodilator							
Short-acting beta agonist (SABA): present (within 6 months pre-index)							0.393
Yes	7,015	11.13%	2,729	26.16%	9,744	13.26%	
SABA: past (>6 months pre-index)							0.183
Yes	17,701	28.08%	3,820	36.62%	21,521	29.29%	
Long-acting beta agonist (LABA): present (within 6 months pre-index)							0.037
Yes	2,249	3.57%	447	4.29%	2,696	3.67%	
LABA: past (>6 months pre-index)							0.085

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	6,048	9.59%	1,277	12.24%	7,325	9.97%	
Anticholinergic (ACH): present (within 6 months pre-index)							0.028
Yes	351	0.56%	82	0.79%	433	0.59%	
ACH: past (>6 months pre-index)							0.075
Yes	1,457	2.31%	373	3.58%	1,830	2.49%	
Theophylline: present (within 6 months pre-index)							0.007
Yes	16	0.03%	4	0.04%	20	0.03%	
Theophylline: past (>6 months pre-index)							0.059
Yes	86	0.14%	48	0.46%	134	0.18%	
CAR T-cell therapy							
Present (within 6 months pre-index)							0.004
Yes	9	0.01%	2	0.02%	11	0.01%	
Past (>6 months pre-index)							0.006
Yes	12	0.02%	3	0.03%	15	0.02%	
Convalescent Plasma							
Present (within 6 months pre-index)							0.000
Yes	0	0.00%	0	0.00%	0	0.00%	
Past (>6 months pre-index)							0.002
Yes	22	0.03%	4	0.04%	26	0.04%	
Abatacept							
Present (within 6 months pre-index)							0.023
Yes	39	0.06%	14	0.13%	53	0.07%	
Past (>6 months pre-index)							0.037
Yes	105	0.17%	37	0.35%	142	0.19%	
Anakinra							
Present (within 6 months pre-index)							0.000
Yes	6	0.01%	1	0.01%	7	0.01%	
Past (>6 months pre-index)							0.018

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	10	0.02%	5	0.05%	15	0.02%	
Tocilizumab							
Present (within 6 months pre-index)							0.024
Yes	30	0.05%	12	0.12%	42	0.06%	
Past (>6 months pre-index)							0.051
Yes	103	0.16%	46	0.44%	149	0.20%	
Immunosuppressive therapy							
Cyclosporine, everolimus, sirolimus, tacrolimus: present							0.360
Yes	320	0.51%	773	7.41%	1,093	1.49%	
Cyclosporine, everolimus, sirolimus, tacrolimus: past							0.371
Yes	1,387	2.20%	1,186	11.37%	2,573	3.50%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: present							0.219
Yes	737	1.17%	511	4.90%	1,248	1.70%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: past							0.352
Yes	2,045	3.24%	1,317	12.63%	3,362	4.58%	
Leukotrienes							
Present (within 6 months pre-index)							0.013
Yes	1,780	2.82%	318	3.05%	2,098	2.86%	
Past (>6 months pre-index)							0.037
Yes	5,249	8.33%	978	9.38%	6,227	8.47%	
Lipid-lowering							
Present (within 6 months pre-index)							0.154
Yes	10,798	17.13%	2,431	23.31%	13,229	18.00%	
Past (>6 months pre-index)							0.300
Yes	19,702	31.25%	4,766	45.69%	24,468	33.30%	
Programmed death ligands (PDLs)							

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Present (within 6 months pre-index)							0.053
Yes	83	0.13%	42	0.40%	125	0.17%	
Past (>6 months pre-index)							0.051
Yes	112	0.18%	49	0.47%	161	0.22%	
Tumor necrosis factor inhibitor (TNFXs)							
Present (within 6 months pre-index)							0.050
Yes	449	0.71%	125	1.20%	574	0.78%	
Past (>6 months pre-index)							0.079
Yes	936	1.48%	271	2.60%	1,207	1.64%	
Other Biologics							
Present (within 6 months pre-index)							0.066
Yes	287	0.46%	106	1.02%	393	0.53%	
Past (>6 months pre-index)							0.147
Yes	704	1.12%	341	3.27%	1,045	1.42%	
Procedure related variables							**ASD**
Radiation therapy							0.093
Yes	1,228	1.95%	361	3.46%	1,589	2.16%	
Transplant							
Organ							0.264
Yes	20	0.03%	362	3.47%	382	0.52%	
Hematopoietic							0.057
Yes	72	0.11%	42	0.40%	114	0.16%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; CAR-T = chimeric antigen receptor-modified T cell; PAX = paxlovid.

Table 10.7. Baseline Healthcare Utilization Variables in the Unmatched Cohorts

Healthcare utilization variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Inpatient encounter: 31-365 days pre-index							0.198
Yes	4,258	6.75%	1,313	12.59%	5,571	7.58%	
Number inpatient encounters: 31-365 days pre-index							0.202
0	58,790	93.25%	9,118	87.41%	67,908	92.42%	
1-2	3,228	5.12%	966	9.26%	4,194	5.71%	
3-5	755	1.20%	211	2.02%	966	1.31%	
6+	275	0.44%	136	1.30%	411	0.56%	
ED encounter: 8-365 days pre-index							0.194
Yes	10,579	16.78%	2,565	24.59%	13,144	17.89%	
Number ED encounters: 8-365 days pre-index							0.197
0	52,469	83.22%	7,866	75.41%	60,335	82.11%	
1-2	9,187	14.57%	2,159	20.70%	11,346	15.44%	
3-5	1,166	1.85%	338	3.24%	1,504	2.05%	
6+	226	0.36%	68	0.65%	294	0.40%	
Outpatient encounter: 8-365 days pre-index							0.149
Yes	57,594	91.35%	9,045	86.71%	66,639	90.69%	
Number outpatient encounters: 8-365 days pre-index							0.333
0	5,454	8.65%	1,386	13.29%	6,840	9.31%	
1-5	19,313	30.63%	2,320	22.24%	21,633	29.44%	
6-11	12,421	19.70%	1,552	14.88%	13,973	19.02%	
12-23	12,927	20.50%	1,897	18.19%	14,824	20.17%	
24+	12,933	20.51%	3,276	31.41%	16,209	22.06%	
Outpatient encounter: 7 days pre-index							0.349
Yes	46,314	73.46%	9,090	87.14%	55,404	75.40%	
Number outpatient encounters: 7 days pre-index							0.559
0	16,734	26.54%	1,341	12.86%	18,075	24.60%	
1-2	41,164	65.29%	6,355	60.92%	47,519	64.67%	

Healthcare utilization variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
3-5	4,995	7.92%	2,551	24.46%	7,546	10.27%	
6+	155	0.25%	184	1.76%	339	0.46%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; ED = early discontinuation; PAX = paxlovid.

Table 10.8, Table 10.9, Table 10.10, Table 10.11, and Table 10.12 display baseline variables for BEB-exposed and PAX-exposed patients in the matched cohort. The median age was 65 (IQR 50 – 74) and 65 (IQR 50 – 74) years in BEB-exposed and PAX-exposed patients, respectively. Similar to the unmatched cohort, patients were primarily female (60.24% in BEB and 60.53% in PAX), White (84.07% in BEB and 84.06% in PAX), and non-Hispanic (77.43% in BEB and 78.05% in PAX). Common COVID-19 related characteristics included presence of a COVID-19 diagnosis anytime pre-index (79.20% in BEB and 79.89% in PAX), a COVID-19 positive test within 7 days pre-index (21.49% in BEB and 23.08% in PAX), and documentation of a COVID-19 vaccine (27.65% in BEB and 27.89% in PAX). Common baseline comorbidities included aplastic anemia (19.86% in BEB and 20.41% in PAX), hypertension (54.76% in BEB and 55.02% in PAX), other heart conditions (43.93% in BEB and 44.57% in PAX), obesity (30.87% in BEB and 32.01% in PAX), type 2 diabetes (25.07% in BEB and 25.52% in PAX), hematologic or solid malignancy except benign skin cancer (33.22% in BEB and 32.68% in PAX), anxiety and fear (35.85% in BEB and 36.49% in PAX), depression (30.63% in BEB and 30.53% in PAX), and CKD (19.79% in BEB and 20.25% in PAX). Common baseline medications included past dexamethasone use (39.66% in BEB and 40.79% in PAX), past methylprednisolone use (33.12% in BEB and 32.86% in PAX), past prednisone use (34.36% in BEB and 34.29% in PAX), past triamcinolone use (29.17% in BEB and 29.21% in PAX), past fluticasone use (31.41% in BEB and 31.10% in PAX), past (57.59% in BEB and 57.99% in PAX) and present (30.26% in BEB and 30.48% in PAX) antihypertensive use, past (36.45% in BEB and 36.71% in PAX) and present (19.87% in BEB and 20.22% in PAX) SABA use, and past (42.73% in BEB and 42.71% in PAX) and present (21.57% in BEB and 21.16% in PAX) lipid lowering agent use. Almost perfect balance was achieved for all four CEM variables: immunocompromised status, age ≥ 65 years, COVID-19 vaccine within 9 months pre-index, and an ED encounter within 7 days pre-index. Adequate balance was achieved for all pre-specified covariates except for eGFR category (ASD = 0.202), blood pressure category (ASD = 0.347), and oxygen saturation category (ASD = 0.311).

Table 10.8. Baseline Demographic Characteristics and Lifestyle Variables in the Matched Cohorts

							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Index date month							0.054
February	8	0.14%	0	0.00%	8	0.07%	
March	28	0.48%	30	0.51%	58	0.50%	
April	691	11.86%	687	11.79%	1,378	11.82%	
May	1,387	23.80%	1,360	23.34%	2,747	23.57%	
June	1,138	19.53%	1,156	19.84%	2,294	19.68%	
July	1,568	26.91%	1,577	27.06%	3,145	26.99%	
August	1,007	17.28%	1,017	17.45%	2,024	17.37%	
Demographics							**ASD**
Patient age							0.009
Mean (SD), years	61.7 (16.6)		61.6 (16.7)				
Median (IQR), years	65 (50 - 74)		65 (50 - 74)				
Min, Max, years	14, 90		14, 92				
Age category							0.025
12-29 years	225	3.86%	247	4.24%	472	4.05%	
30-44 years	855	14.67%	840	14.42%	1,695	14.54%	
45-54 years	701	12.03%	719	12.34%	1,420	12.18%	
45-64 years	1,067	18.31%	1,042	17.88%	2,109	18.10%	
65-74 years	1,597	27.41%	1,586	27.22%	3,183	27.31%	
75-84 years	1,045	17.93%	1,058	18.16%	2,103	18.05%	
≥85 years	337	5.78%	335	5.75%	672	5.77%	
Female sex							0.006
Yes	3,527	60.53%	3,510	60.24%	7,037	60.38%	
Race							0.011
White	4,898	84.06%	4,899	84.07%	9,797	84.07%	
Black	342	5.87%	347	5.96%	689	5.91%	

Other	86	1.48%	79	1.36%	165	1.42%	
Unknown	501	8.60%	502	8.62%	1,003	8.61%	
Ethnicity							0.026
Hispanic	340	5.83%	323	5.54%	663	5.69%	
Not Hispanic	4,548	78.05%	4,512	77.43%	9,060	77.74%	
Unknown	939	16.11%	992	17.02%	1,931	16.57%	
Lifestyle variables							**ASD**
Smoking status 6 months pre-index							0.013
Yes	111	1.90%	101	1.73%	212	1.82%	
Smoking status >6 months pre-index							0.033
Yes	352	6.04%	308	5.29%	660	5.66%	
Smoking ever pre-index							0.003
Yes	473	8.12%	425	7.29%	898	7.71%	
Inactivity							0.031
Yes	20	0.34%	19	0.33%	39	0.33%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; IQR = interquartile range; max = maximum; min = minimum; PAX = paxlovid; SD = standard deviation

Table 10.9. Baseline CEM and COVID-19 Variables in the Matched Cohorts

CEM variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Immunocompromised status (UPMC)							0.000
Yes	2,791	47.90%	2,791	47.90%	5,582	47.90%	
Age ≥ 65							0.000
Yes	2,979	51.12%	2,979	51.12%	5,958	51.12%	
COVID-19 vaccination within 9 months pre-index							0.000
Yes	1,013	17.38%	1,013	17.38%	2,026	17.38%	
ED encounter within 7 days pre-index							0.000
Yes	1,022	17.54%	1,022	17.54%	2,044	17.54%	
COVID-19 related variables							**ASD**
COVID-19 diagnosis anytime pre-index							0.017
Yes	4,655	79.89%	4,615	79.20%	9,270	79.54%	
COVID-19 positive test: within 7 days pre-index							0.038
Yes	1,345	23.08%	1,252	21.49%	2,597	22.28%	
COVID-19 positive test: >7 days pre-index							0.018
Yes	265	4.55%	244	4.19%	509	4.37%	
COVID-19 vaccine: past (>9 months pre-index)							0.005
Yes	1,625	27.89%	1,611	27.65%	3,236	27.77%	
COVID-19 antibody therapy: present (within 3-6 months pre-index)							0.003
Yes	77	1.32%	79	1.36%	156	1.34%	
COVID-19 antibody therapy: past (>6 months pre-index)							0.010
Yes	49	0.84%	44	0.76%	93	0.80%	
COVID-19 related symptoms							**ASD**
Anosmia and parosmia							0.000
Yes	10	0.17%	10	0.17%	20	0.17%	
Cough							0.001
Yes	297	5.10%	298	5.11%	595	5.11%	
Fatigue							0.026

Yes	418	7.17%	380	6.52%	798	6.85%	
Fever or chills							0.014
Yes	401	6.88%	381	6.54%	782	6.71%	
Headache							0.016
Yes	107	1.84%	95	1.63%	202	1.73%	
Myalgia or joint pain							0.012
Yes	258	4.43%	244	4.19%	502	4.31%	
Nausea or vomiting							0.006
Yes	364	6.25%	356	6.11%	720	6.18%	
Dyspnea							0.010
Yes	290	4.98%	278	4.77%	568	4.87%	
Sore throat/pharyngitis							0.008
Yes	317	5.44%	307	5.27%	624	5.35%	
Diarrhea							0.021
Yes	107	1.84%	91	1.56%	198	1.70%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; CEM = coarsened extract matching; COVID-19 = coronavirus disease 2019; PAX = paxlovid; UPMC = University of Pittsburgh Medical Center.

Table 10.10. Baseline Clinical, Laboratory, and Comorbidity Variables in the Matched Cohorts

Clinical and laboratory variables							ASD
	PAX		BEB		Total		
BMI (kg/m^2)							0.002
Mean (SD), years	29.71 (7.01)		29.59 (6.80)				
Median (IQR), years	28.50 (24.80 - 33.35)		28.50 (24.70 - 33.28)				
Min, Max, years	12.48, 68.01		12.40, 71.94				
BMI category							0.057
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**	
Underweight: <18.5	69	1.18%	79	1.36%	148	1.27%	
Normal: 18.5-24	1,249	21.43%	1,276	21.90%	2,525	21.67%	
Overweight: 25-29	1,634	28.04%	1,642	28.18%	3,276	28.11%	
Obese: ≥30.0	2,079	35.68%	2,141	36.74%	4,220	36.21%	
Missing	796	13.66%	689	11.82%	1,485	12.74%	
MCQ eGFR: using last sCr pre-index							0.054
Mean (SD), years	92.24 (19.20)		90.43 (21.72)				
Median (IQR), years	92.63 (82.31 - 104.87)		91.98 (80.95 - 104.44)				
Min, Max, years	18.51, 159.67		14.78, 157.49				
MCQ eGFR: using last sCr pre-index							0.202
eGFR ≥90	2,847	48.86%	2,612	44.83%	5,459	46.84%	
eGFR 60-89	1,895	32.52%	1,725	29.60%	3,620	31.06%	
eGFR 30-59	285	4.89%	339	5.82%	624	5.35%	
eGFR <30	18	0.31%	98	1.68%	116	1.00%	
Missing	782	13.42%	1,053	18.07%	1,835	15.75%	
Blood pressure: category							0.347
Normotensive	297	5.10%	433	7.43%	730	6.26%	
Elevated	199	3.42%	305	5.23%	504	4.32%	
Stage 1	343	5.89%	552	9.47%	895	7.68%	
Stage 2	523	8.98%	983	16.87%	1,506	12.92%	
Missing	4,465	76.63%	3,554	60.99%	8,019	68.81%	
Oxygen saturation: category							0.311

≥95%	264	4.53%	772	13.25%	1,036	8.89%	
85-95%	48	0.82%	50	0.86%	98	0.84%	
<85%	10	0.17%	6	0.10%	16	0.14%	
Missing	5,505	94.47%	4,999	85.79%	10,504	90.13%	
Comorbidities							**ASD**
Autoimmune							
Crohn's disease							0.006
Yes	111	1.90%	106	1.82%	217	1.86%	
Juvenile arthritis							0.000
Yes	11	0.19%	11	0.19%	22	0.19%	
Rheumatoid arthritis							0.010
Yes	446	7.65%	431	7.40%	877	7.53%	
Systemic lupus erythematosus							0.012
Yes	525	9.01%	505	8.67%	1,030	8.84%	
Ulcerative colitis							0.012
Yes	98	1.68%	89	1.53%	187	1.60%	
Blood Disorder							
Aplastic anemia							0.014
Yes	1,189	20.41%	1,157	19.86%	2,346	20.13%	
Immunodeficiency							0.013
Yes	537	9.22%	559	9.59%	1,096	9.40%	
Immunodeficiency (UPMC)							0.001
Yes	1,052	18.05%	1,054	18.09%	2,106	18.07%	
Sickle cell							0.012
Yes	20	0.34%	16	0.27%	36	0.31%	
Thalassemia							0.005
Yes	24	0.41%	22	0.38%	46	0.39%	
Circulatory							
Acute hemorrhagic cerebrovascular disease							0.020
Yes	240	4.12%	264	4.53%	504	4.32%	
Cerebral infarction							0.003

Yes	430	7.38%	435	7.47%	865	7.42%	
Other cerebrovascular disease							0.026
Yes	463	7.95%	505	8.67%	968	8.31%	
Acute myocardial infarction							0.014
Yes	378	6.49%	358	6.14%	736	6.32%	
Coronary artery disease							0.005
Yes	768	13.18%	758	13.01%	1,526	13.09%	
Heart failure							0.013
Yes	653	11.21%	629	10.79%	1,282	11.00%	
Hypertension							0.005
Yes	3,206	55.02%	3,191	54.76%	6,397	54.89%	
Myocarditis cardiomyopathy							0.004
Yes	335	5.75%	341	5.85%	676	5.80%	
Other heart condition							0.013
Yes	2,597	44.57%	2,560	43.93%	5,157	44.25%	
Peripheral vascular disease							0.017
Yes	797	13.68%	832	14.28%	1,629	13.98%	
Disability							
Cerebral palsy							0.009
Yes	19	0.33%	22	0.38%	41	0.35%	
Congenital malformation							0.012
Yes	1,057	18.14%	1,031	17.69%	2,088	17.92%	
Limitation of ADL							0.012
Yes	305	5.23%	290	4.98%	595	5.11%	
Neurodevelopmental disorders							0.009
Yes	297	5.10%	309	5.30%	606	5.20%	
Spinal cord injury							0.016
Yes	9	0.15%	13	0.22%	22	0.19%	
Endocrine							
Obesity							0.024
Yes	1,865	32.01%	1,799	30.87%	3,664	31.44%	

Diabetes Type 1							0.014
Yes	167	2.87%	154	2.64%	321	2.75%	
Diabetes Type 2							0.010
Yes	1,487	25.52%	1,461	25.07%	2,948	25.30%	
Diabetes Type 1 or 2 (complicated)							0.016
Yes	886	15.21%	853	14.64%	1,739	14.92%	
Hepatic							
Alcoholic liver disease							0.011
Yes	153	2.63%	143	2.45%	296	2.54%	
Autoimmune hepatitis							0.005
Yes	28	0.48%	26	0.45%	54	0.46%	
Cirrhosis							0.006
Yes	131	2.25%	126	2.16%	257	2.21%	
Non-alcoholic fatty liver disease							0.001
Yes	454	7.79%	453	7.77%	907	7.78%	
Infectious							
Hepatitis B							0.008
Yes	40	0.69%	44	0.76%	84	0.72%	
Hepatitis C							0.022
Yes	134	2.30%	154	2.64%	288	2.47%	
HIV							0.011
Yes	197	3.38%	186	3.19%	383	3.29%	
Tuberculosis							0.018
Yes	39	0.67%	31	0.53%	70	0.60%	
Malignancy							
Hematological oncology (except skin)							0.012
Yes	1,904	32.68%	1,936	33.22%	3,840	32.95%	
Metastatic							0.001
Yes	246	4.22%	247	4.24%	493	4.23%	
Radiation complication							0.001
Yes	114	1.96%	113	1.94%	227	1.95%	

Mental Health							
	Anxiety and fear						0.013
Yes	2,126	36.49%	2,089	35.85%	4,215	36.17%	
	Bipolar						0.012
Yes	195	3.35%	183	3.14%	378	3.24%	
	Depression						0.002
Yes	1,779	30.53%	1,785	30.63%	3,564	30.58%	
	Other mood disorder						0.019
Yes	147	2.52%	165	2.83%	312	2.68%	
	Schizophrenia						0.016
Yes	129	2.21%	116	1.99%	245	2.10%	
	Substance abuse						0.016
Yes	658	11.29%	628	10.78%	1,286	11.03%	
	Suicidal ideation						0.019
Yes	286	4.91%	263	4.51%	549	4.71%	
Neurocognitive disorders							0.007
Yes	237	4.07%	245	4.20%	482	4.14%	
Pulmonary							
	Alpha-1 antitrypsin deficiency						0.008
Yes	11	0.19%	9	0.15%	20	0.17%	
	Asthma						0.009
Yes	1,297	22.26%	1,275	21.88%	2,572	22.07%	
	Bronchopulmonary dysplasia						0.000
Yes	0	0.00%	0	0.00%	0	0.00%	
	COPD and bronchiectasis						0.002
Yes	815	13.99%	810	13.90%	1,625	13.94%	
	Cystic fibrosis						0.003
Yes	20	0.34%	19	0.33%	39	0.33%	
	Embolism						0.004
Yes	270	4.63%	265	4.55%	535	4.59%	
	Hypertension						0.005

Yes	318	5.46%	311	5.34%	629	5.40%	
Interstitial disease							0.012
Yes	178	3.05%	190	3.26%	368	3.16%	
Renal							
CKD							0.012
Yes	1,180	20.25%	1,153	19.79%	2,333	20.02%	
ESRD							0.017
Yes	571	9.80%	542	9.30%	1,113	9.55%	
Transplant							
Organ stem cell							0.030
Yes	269	4.62%	307	5.27%	576	4.94%	
Graft versus host disease							0.007
Yes	13	0.22%	15	0.26%	28	0.24%	
Pregnancy variables							**ASD**
Pregnancy within 3 months pre-index							0.017
Yes	258	4.43%	238	4.08%	496	4.26%	
Pregnancy within 9 months pre-index							0.014
Yes	350	6.01%	331	5.68%	681	5.84%	
Pregnancy ever pre-index							0.003
Yes	1,249	21.43%	1,243	21.33%	2,492	21.38%	

Abbreviations: ADL = activities of daily living; ASD = absolute standardized difference; BEB = bebtelovimab; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; IQR = interquartile range; max = maximum; MCQ = Mayo Clinic quadratic; min = minimum; PAX = paxlovid; sCr = serum creatinine; SD = standard deviation; UPMC = University of Pittsburgh Medical Center.

Table 10.11. Baseline Pharmacotherapy and Procedure-related Variables in the Matched Cohorts

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Antiemetics							
Present (within 7 days pre-index)							0.011
Yes	67	1.15%	74	1.27%	141	1.21%	
Past (>7 days pre-index)							0.007
Yes	745	12.79%	758	13.01%	1,503	12.90%	
Corticosteroids							
Beclomethasone: present (within 7 days pre-index)							0.015
Yes	4	0.07%	2	0.03%	6	0.05%	
Beclomethasone: past (>7 days pre-index)							0.005
Yes	129	2.21%	133	2.28%	262	2.25%	
Betamethasone: present (within 7 days pre-index)							0.005
Yes	7	0.12%	8	0.14%	15	0.13%	
Betamethasone: past (>7 days pre-index)							0.008
Yes	691	11.86%	707	12.13%	1,398	12.00%	
Budesonide: present (within 7 days pre-index)							0.003
Yes	20	0.34%	21	0.36%	41	0.35%	
Budesonide: past (>7 days pre-index)							0.021
Yes	589	10.11%	552	9.47%	1,141	9.79%	
Deflazacort: present (within 7 days pre-index)							0.000
Yes	0	0.00%	0	0.00%	0	0.00%	
Deflazacort: past (>7 days pre-index)							0.019
Yes	0	0.00%	1	0.02%	1	0.01%	
Dexamethasone: present (within 7 days pre-index)							0.006
Yes	210	3.60%	204	3.50%	414	3.55%	
Dexamethasone: past (>7 days pre-index)							0.023
Yes	2,377	40.79%	2,311	39.66%	4,688	40.23%	
Hydrocortisone: present (within 7 days pre-index)							0.013

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	95	1.63%	105	1.80%	200	1.72%	
Hydrocortisone: past (>7 days pre-index)							0.020
Yes	911	15.63%	954	16.37%	1,865	16.00%	
Methylprednisolone: present (within 7 days pre-index)							0.017
Yes	758	13.01%	725	12.44%	1,483	12.73%	
Methylprednisolone: past (>7 days pre-index)							0.005
Yes	1,915	32.86%	1,930	33.12%	3,845	32.99%	
Prednisolone: present (within 7 days pre-index)							0.032
Yes	40	0.69%	57	0.98%	97	0.83%	
Prednisolone: past (>7 days pre-index)							0.012
Yes	334	5.73%	350	6.01%	684	5.87%	
Prednisone: present (within 7 days pre-index)							0.018
Yes	114	1.96%	129	2.21%	243	2.09%	
Prednisone: past (>7 days pre-index)							0.001
Yes	1,998	34.29%	2,002	34.36%	4,000	34.32%	
Triamcinolone: present (within 7 days pre-index)							0.009
Yes	29	0.50%	33	0.57%	62	0.53%	
Triamcinolone: past (>7 days pre-index)							0.001
Yes	1,702	29.21%	1,700	29.17%	3,402	29.19%	
Mometasone: present (within 7 days pre-index)							0.026
Yes	9	0.15%	4	0.07%	13	0.11%	
Mometasone: past (>7 days pre-index)							0.023
Yes	302	5.18%	333	5.71%	635	5.45%	
Fluticasone: present (within 7 days pre-index)							0.004
Yes	117	2.01%	114	1.96%	231	1.98%	
Fluticasone: past (>7 days pre-index)							0.007
Yes	1,812	31.10%	1,830	31.41%	3,642	31.25%	
Anticoagulants							

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Present (within 6 months pre-index)							0.002
Yes	348	5.97%	345	5.92%	693	5.95%	
Past (>6 months pre-index)							0.000
Yes	893	15.33%	892	15.31%	1,785	15.32%	
Antidiabetic							
Insulin: present (within 6 months pre-index)							0.018
Yes	399	6.85%	373	6.40%	772	6.62%	
Insulin: past (>6 months pre-index)							0.023
Yes	1,139	19.55%	1,086	18.64%	2,225	19.09%	
Other: present (within 6 months pre-index)							0.018
Yes	576	9.89%	545	9.35%	1,121	9.62%	
Other: past (>6 months pre-index)							0.014
Yes	1,032	17.71%	1,001	17.18%	2,033	17.44%	
Antihypertensives							
Present (within 6 months pre-index)							0.005
Yes	1,776	30.48%	1,763	30.26%	3,539	30.37%	
Past (>6 months pre-index)							0.008
Yes	3,379	57.99%	3,356	57.59%	6,735	57.79%	
Antivirals							
Chloroquine: present (within 3-6 months pre-index)							0.000
Yes	1	0.02%	1	0.02%	2	0.02%	
Chloroquine: past (>6 months pre-index)							0.057
Yes	12	0.21%	1	0.02%	13	0.11%	
Hydroxychloroquine sulfate: present (within 3-6 months pre-index)							0.019
Yes	28	0.48%	21	0.36%	49	0.42%	
Hydroxychloroquine sulfate: past (>6 months pre-index)							0.002
Yes	169	2.90%	171	2.93%	340	2.92%	
Ivermectin: present (within 3-6 months pre-index)							0.026

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	0	0.00%	2	0.03%	2	0.02%	
Ivermectin: past (>6 months pre-index)							0.006
Yes	20	0.34%	22	0.38%	42	0.36%	
Molnupiravir: present (within 3-6 months pre-index)							0.019
Yes	1	0.02%	0	0.00%	1	0.01%	
Molnupiravir: past (>6 months pre-index)							0.000
Yes	0	0.00%	0	0.00%	0	0.00%	
Paxlovid: present (within 3-6 months pre-index)							0.008
Yes	3	0.05%	2	0.03%	5	0.04%	
Paxlovid: past (>6 months pre-index)							0.019
Yes	1	0.02%	0	0.00%	1	0.01%	
Remdesivir: present (within 3-6 months pre-index)							0.035
Yes	8	0.14%	2	0.03%	10	0.09%	
Remdesivir: past (>6 months pre-index)							0.002
Yes	34	0.58%	35	0.60%	69	0.59%	
Rituximab B-cell							
Present (within 6 months pre-index)							0.004
Yes	56	0.96%	54	0.93%	110	0.94%	
Past (>6 months pre-index)							0.004
Yes	128	2.20%	125	2.15%	253	2.17%	
Bronchodilator							
SABA: present (within 6 months pre-index)							0.009
Yes	1,178	20.22%	1,158	19.87%	2,336	20.04%	
SABA: past (>6 months pre-index)							0.005
Yes	2,139	36.71%	2,124	36.45%	4,263	36.58%	
LABA: present (within 6 months pre-index)							0.002
Yes	270	4.63%	268	4.60%	538	4.62%	
LABA: past (>6 months pre-index)							0.019

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	783	13.44%	746	12.80%	1,529	13.12%	
ACH: present (within 6 months pre-index)							0.002
Yes	51	0.88%	50	0.86%	101	0.87%	
ACH: past (>6 months pre-index)							0.015
Yes	221	3.79%	205	3.52%	426	3.66%	
Theophylline: present (within 6 months pre-index)							0.037
Yes	4	0.07%	0	0.00%	4	0.03%	
Theophylline: past (>6 months pre-index)							0.006
Yes	19	0.33%	17	0.29%	36	0.31%	
CAR T-cell therapy							
Present (within 6 months pre-index)							0.026
Yes	2	0.03%	0	0.00%	2	0.02%	
Past (>6 months pre-index)							0.030
Yes	5	0.09%	1	0.02%	6	0.05%	
Convalescent plasma							
Present (within 6 months pre-index)							0.000
Yes	0	0.00%	0	0.00%	0	0.00%	
Past (>6 months pre-index)							0.008
Yes	3	0.05%	2	0.03%	5	0.04%	
Abatacept							
Present (within 6 months pre-index)							0.024
Yes	10	0.17%	5	0.09%	15	0.13%	
Past (>6 months pre-index)							0.000
Yes	19	0.33%	19	0.33%	38	0.33%	
Anakinra							
Present (within 6 months pre-index)							0.026
Yes	2	0.03%	0	0.00%	2	0.02%	
Past (>6 months pre-index)							0.011

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Yes	2	0.03%	1	0.02%	3	0.03%	
Tocilizumab							
Present (within 6 months pre-index)							0.012
Yes	6	0.10%	4	0.07%	10	0.09%	
Past (>6 months pre-index)							0.011
Yes	27	0.46%	23	0.39%	50	0.43%	
Immunosuppressive therapy							
Cyclosporine, everolimus, sirolimus, tacrolimus: present							0.020
Yes	114	1.96%	131	2.25%	245	2.10%	
Cyclosporine, everolimus, sirolimus, tacrolimus: past							0.025
Yes	301	5.17%	334	5.73%	635	5.45%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: present							0.007
Yes	159	2.73%	166	2.85%	325	2.79%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: past							0.010
Yes	443	7.60%	459	7.88%	902	7.74%	
Leukotrienes							
Present (within 6 months pre-index)							0.010
Yes	180	3.09%	190	3.26%	370	3.17%	
Past (>6 months pre-index)							0.018
Yes	542	9.30%	572	9.82%	1,114	9.56%	
Lipid-lowering							
Present (within 6 months pre-index)							0.010
Yes	1,233	21.16%	1,257	21.57%	2,490	21.37%	
Past (>6 months pre-index)							0.000
Yes	2,489	42.71%	2,490	42.73%	4,979	42.72%	
PDLs							
Present (within 6 months pre-index)							0.000
Yes	20	0.34%	20	0.34%	40	0.34%	

Pharmacotherapy variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Past (>6 months pre-index)							0.017
Yes	19	0.33%	25	0.43%	44	0.38%	
TNFXs							
Present (within 6 months pre-index)							0.008
Yes	77	1.32%	72	1.24%	149	1.28%	
Past (>6 months pre-index)							0.003
Yes	167	2.87%	164	2.81%	331	2.84%	
Other biologics							
Present (within 6 months pre-index)							0.011
Yes	47	0.81%	53	0.91%	100	0.86%	
Past (>6 months pre-index)							0.013
Yes	122	2.09%	133	2.28%	255	2.19%	
Procedure related variables							**ASD**
Radiation therapy							0.009
Yes	200	3.43%	210	3.60%	410	3.52%	
Transplant							
Organ							0.003
Yes	18	0.31%	19	0.33%	37	0.32%	
Hematopoietic							0.000
Yes	18	0.31%	18	0.31%	36	0.31%	

Abbreviations: ACH = anticholinergic; ASD = absolute standardized difference; BEB = bebtelovimab; CAR-T = chimeric antigen receptor-modified T cell; LABA = long-acting beta-agonist; PAX = Paxlovid; PDL = programmed death ligand; SABA = short-acting beta-agonist; TNFX = tumor necrosis factor inhibitor.

Table 10.12. Baseline Healthcare Utilization Variables in the Matched Cohorts

Healthcare utilization variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
Inpatient encounter: 31-365 days pre-index							0.007
Yes	611	10.49%	599	10.28%	1,210	10.38%	
Number inpatient encounters: 31-365 days pre-index							0.022
0	5,216	89.51%	5,228	89.72%	10,444	89.62%	
1-2	479	8.22%	461	7.91%	940	8.07%	
3-5	95	1.63%	92	1.58%	187	1.60%	
6+	37	0.63%	46	0.79%	83	0.71%	
ED encounter: 8-365 days pre-index							0.018
Yes	1,375	23.60%	1,330	22.82%	2,705	23.21%	
Number ED encounters: 8-365 days pre-index							0.022
0	4,452	76.40%	4,497	77.18%	8,949	76.79%	
1-2	1,160	19.91%	1,116	19.15%	2,276	19.53%	
3-5	173	2.97%	177	3.04%	350	3.00%	
6+	42	0.72%	37	0.63%	79	0.68%	
Outpatient encounter: 8-365 days pre-index							0.001
Yes	5,264	90.34%	5,263	90.32%	10,527	90.33%	
Number outpatient encounters: 8-365 days pre-index							0.003
0	563	9.66%	564	9.68%	1,127	9.67%	
1-5	1,296	22.24%	1,294	22.21%	2,590	22.22%	
6-11	938	16.10%	945	16.22%	1,883	16.16%	
12-23	1,215	20.85%	1,212	20.80%	2,427	20.83%	
24+	1,815	31.15%	1,812	31.10%	3,627	31.12%	
Outpatient encounter: 7 days pre-index							0.029
Yes	4,947	84.90%	5,006	85.91%	9,953	85.40%	
Number outpatient encounters: 7 days pre-index							0.032
0	880	15.10%	821	14.09%	1,701	14.60%	
1-2	3,622	62.16%	3,696	63.43%	7,318	62.79%	

Healthcare utilization variables							ASD
	PAX		BEB		Total		
	Frequency	%	Frequency	%	Frequency	%	
3-5	1,263	21.67%	1,245	21.37%	2,508	21.52%	
6+	62	1.06%	65	1.12%	127	1.09%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; ED = early discontinuation; PAX = paxlovid.

10.3 Outcome Data

10.3.1 COVID-19 Treatments During Follow-up

Administration of COVID-19 treatments within 30 days after the index date was uncommon in both the unmatched and matched cohorts (Table 10.13). A subsequent BEB dose was administered in 3.47% and 4.46% of BEB-exposed patients in the unmatched and matched cohorts, respectively. A subsequent PAX dose was administered in 1.81% and 2.09% of PAX-exposed patients in the unmatched and matched cohorts, respectively.

Table 10.13. COVID-19 Treatment Administration during Follow-up in the Unmatched and Matched Cohorts

	Unmatched						Matched					
	PAX		BEB		Total		PAX		BEB		Total	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
COVID-19 convalescent plasma												
No	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Yes	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Bamlanivimab/etesevimab												
No	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Yes	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Bebtelovimab												
No	62,817	99.63%	10,069	96.53%	72,886	99.19%	5,759	98.83%	5,567	95.54%	11,326	97.19%
Yes	231	0.37%	362	3.47%	593	0.81%	68	1.17%	260	4.46%	328	2.81%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Casirivimab/imdevimab												
No	63,047	100.00%	10,431	100.00%	73,478	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Yes	1	0.00%	0	0.00%	1	0.00%	0	0.00%	0	0.00%	0	0.00%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Sotrovimab												
No	63,042	99.99%	10,430	99.99%	73,472	99.99%	5,825	99.97%	5,827	100.00%	11,652	99.98%
Yes	6	0.01%	1	0.01%	7	0.01%	2	0.03%	0	0.00%	2	0.02%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Tixagevimab/cilgavimab												
No	63,015	99.95%	10,419	99.88%	73,434	99.94%	5,818	99.85%	5,819	99.86%	11,637	99.85%
Yes	33	0.05%	12	0.12%	45	0.06%	9	0.15%	8	0.14%	17	0.15%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Tocilizumab												
No	63,039	99.99%	10,426	99.95%	73,465	99.98%	5,826	99.98%	5,824	99.95%	11,650	99.97%
Yes	9	0.01%	5	0.05%	14	0.02%	1	0.02%	3	0.05%	4	0.03%

	Unmatched						Matched					
	PAX		BEB		Total		PAX		BEB		Total	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Hydroxychloroquine												
No	62,991	99.91%	10,410	99.80%	73,401	99.89%	5,814	99.78%	5,820	99.88%	11,634	99.83%
Yes	57	0.09%	21	0.20%	78	0.11%	13	0.22%	7	0.12%	20	0.17%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Ivermectin												
No	63,038	99.98%	10,430	99.99%	73,468	99.99%	5,826	99.98%	5,826	99.98%	11,652	99.98%
Yes	10	0.02%	1	0.01%	11	0.01%	1	0.02%	1	0.02%	2	0.02%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Molnupiravir												
No	62,964	99.87%	10,426	99.95%	73,390	99.88%	5,815	99.79%	5,822	99.91%	11,637	99.85%
Yes	84	0.13%	5	0.05%	89	0.12%	12	0.21%	5	0.09%	17	0.15%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Nirmatrelvir/ritonavir												
No	61,904	98.19%	10,401	99.71%	72,305	98.40%	5,705	97.91%	5,800	99.54%	11,505	98.72%
Yes	1,144	1.81%	30	0.29%	1,174	1.60%	122	2.09%	27	0.46%	149	1.28%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%
Remdesivir												
No	62,917	99.79%	10,386	99.57%	73,303	99.76%	5,785	99.28%	5,802	99.57%	11,587	99.43%
Yes	131	0.21%	45	0.43%	176	0.24%	42	0.72%	25	0.43%	67	0.57%
Total	63,048	100.00%	10,431	100.00%	73,479	100.00%	5,827	100.00%	5,827	100.00%	11,654	100.00%

Abbreviations: BEB = bebtelovimab; COVID-19 = coronavirus disease 2019; PAX = paxlovid.

10.3.2 Number of Events and Cumulative Incidence for Primary and Secondary Outcomes

In the unmatched cohort, there was a cumulative incidence of 2.30% (95% confidence interval [CI]: 2.02%, 2.61%) and a cumulative incidence of 1.09% (95% CI: 1.01%, 1.17%) for primary outcome events in BEB-exposed and PAX-exposed patients, respectively (Table 10.14). Among secondary outcomes, there was a cumulative incidence of 2.24% (95% CI: 1.97%, 2.55%) and 1.07% (95% CI: 0.99%, 1.16%) for hospitalizations, a cumulative incidence of 5.31% (95% CI: 4.89%, 5.76%) and 3.18% (95% CI: 3.04%, 3.32%) for ED visits, and a cumulative incidence of 0.09% (95% CI: 0.04%, 0.16%) and 0.03% (95% CI: 0.01%, 0.04%) for death in BEB-exposed and PAX-exposed patients, respectively.

In the matched cohort, there was a cumulative incidence of 2.03% (95% CI: 1.68%, 2.42%) and 1.84% (95% CI: 1.51%, 2.21%) for primary outcome events in BEB-exposed and PAX-exposed patients, respectively. Among secondary outcomes, there was a cumulative incidence of 1.94% (95% CI: 1.60%, 2.33%) and 1.82% (95% CI: 1.49%, 2.20%) for hospitalizations, 5.08% (95% CI: 4.53%, 5.68%) and 4.58% (95% CI: 4.06%, 5.15%) for ED visits, and a cumulative incidence of 0.10% (95% CI: 0.04%, 0.22%) and 0.02% (95% CI: 0.00%, 0.10%) for death in BEB-exposed and PAX-exposed patients, respectively.

Table 10.14. Cumulative Incidence for Primary and Secondary Outcomes in the Unmatched and Matched Cohorts

Outcome	Exposure	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL
Unmatched cohorts						
Primary analysis						
Hospitalization OR Death	BEB	10,431	240	2.30%	2.02%	2.61%
	PAX	63,048	686	1.09%	1.01%	1.17%
Secondary analyses						
Hospitalization	BEB	10,431	234	2.24%	1.97%	2.55%
	PAX	63,048	677	1.07%	0.99%	1.16%
ED visit	BEB	10,431	554	5.31%	4.89%	5.76%
	PAX	63,048	2,003	3.18%	3.04%	3.32%
Death	BEB	10,431	9	0.09%	0.04%	0.16%
	PAX	63,048	16	0.03%	0.01%	0.04%
Matched cohorts						
Primary analysis						
Hospitalization OR Death	BEB	5,827	118	2.03%	1.68%	2.42%
	PAX	5,827	107	1.84%	1.51%	2.21%
Secondary analyses						
Hospitalization	BEB	5,827	113	1.94%	1.60%	2.33%
	PAX	5,827	106	1.82%	1.49%	2.20%
ED visit	BEB	5,827	296	5.08%	4.53%	5.68%

Outcome	Exposure	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL
	PAX	5,827	267	4.58%	4.06%	5.15%
Death	BEB	5,827	6	0.10%	0.04%	0.22%
	PAX	5,827	1	0.02%	0.00%	0.10%

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; PAX = Paxlovid;.

Note: For the Risk Difference analyses, PAX is the reference category.

10.4 Main Results

RDs for primary and secondary outcomes in the unmatched and matched cohorts are presented in Table 10.15. In the matched cohorts, BEB was noninferior to PAX for the primary outcome based on the *a priori* specified NI margin of 1.795% for the UCL. The RD was 0.19% with a UCL that was within the *a priori* specified margin (95% LCL -0.31%, 95% UCL 0.69%). In the matched cohorts BEB (compared to PAX) was not associated with increased risks of hospitalization (RD 0.12%; 95% LCL -0.37%, 95% UCL 0.61%), an ED visit (RD 0.50%; 95% LCL -0.28%, 95% UCL 1.28%), or death (RD 0.086%; 95% LCL -0.003%, 95% UCL 0.175%).

Table 10.15. Risk Differences for Primary and Secondary Outcomes in the Unmatched and Matched Cohorts

Outcome	Exposure	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
Unmatched cohorts				
Primary analysis				
Hospitalization OR Death	BEB	1.21%	0.91%	1.51%
	PAX			
Secondary analyses				
Hospitalization	BEB	1.17%	0.87%	1.46%
	PAX			
ED visit	BEB	2.13%	1.68%	2.59%
	PAX			
Death	BEB	0.061%	0.003%	0.119%
	PAX			
Matched cohorts				
Primary analysis				
Hospitalization OR Death	BEB	0.19%	-0.31%	0.69%
	PAX			
Secondary analyses				
Hospitalization	BEB	0.12%	-0.37%	0.61%
	PAX			
ED visit	BEB	0.50%	-0.28%	1.28%

Outcome	Exposure	Risk Difference (RD, PAX = reference)		
		RD	95% LCL	95% UCL
	PAX			
Death	BEB	0.086%	-0.003%	0.175%
	PAX			

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; ED = early discontinuation; PAX = paxlovid.
Note: For the Risk Difference analyses, PAX is the reference category.

10.5 Other Analyses

10.5.1 Subgroup Analyses

Results from subgroup analyses are displayed in Table 10.16. There was no evidence of effect modification by subgroups for age ≥ 65 years, immunocompromised status, COVID-19 vaccine, or ED visit within 7 days pre-index.

Table 10.16. Results from Subgroup Analyses

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
Subgroup: Age ≥ 65 years (yes/no)										
Primary analysis										
Hospitalization OR Death	BEB	All	5,827	118	2.03%	1.68%	2.42%	0.19%	-0.31%	0.69%
	PAX		5,827	107	1.84%	1.51%	2.21%			
	BEB	Condition Present	2,979	61	2.05%	1.57%	2.62%	-0.03%	-0.76%	0.69%
	PAX		2,979	62	2.08%	1.60%	2.66%			
	BEB	Condition Absent	2,848	57	2.00%	1.52%	2.59%	0.42%	-0.27%	1.11%
	PAX		2,848	45	1.58%	1.15%	2.11%			
Secondary analyses										
Hospitalization	BEB	All	5,827	113	1.94%	1.60%	2.33%	0.12%	-0.37%	0.61%
	PAX		5,827	106	1.82%	1.49%	2.20%			
	BEB	Condition Present	2,979	59	1.98%	1.51%	2.55%	-0.07%	-0.78%	0.65%
	PAX		2,979	61	2.05%	1.57%	2.62%			
	BEB	Condition Absent	2,848	54	1.90%	1.43%	2.47%	0.32%	-0.36%	0.99%
	PAX		2,848	45	1.58%	1.15%	2.11%			
ED visit	BEB	All	5,827	296	5.08%	4.53%	5.68%	0.50%	-0.28%	1.28%
	PAX		5,827	267	4.58%	4.06%	5.15%			
	BEB	Condition Present	2,979	164	5.51%	4.71%	6.39%	0.70%	-0.42%	1.83%
	PAX		2,979	143	4.80%	4.06%	5.63%			
	BEB	Condition Absent	2,848	132	4.63%	3.89%	5.47%	0.28%	-0.80%	1.36%
	PAX		2,848	124	4.35%	3.63%	5.17%			
Death	BEB	All	5,827	6	0.10%	0.04%	0.22%	0.086%	-0.003%	0.175%
	PAX		5,827	1	0.02%	0.00%	0.10%			
	BEB	Condition Present	2,979	2	0.07%	0.01%	0.24%	0.034%	-0.080%	0.147%
	PAX		2,979	1	0.03%	0.00%	0.19%			
	BEB		2,848	4	0.14%	0.04%	0.36%	0.140%	0.003%	0.278%

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
	PAX	Condition Absent	2,848	0	0.00%	0.00%	0.13%			
Subgroup: Immunocompromised (yes/no)										
Primary analysis										
Hospitalization OR Death	BEB	All	5,827	118	2.03%	1.68%	2.42%	0.19%	-0.31%	0.69%
	PAX		5,827	107	1.84%	1.51%	2.21%			
	BEB	Condition Present	2,791	71	2.54%	1.99%	3.20%	0.18%	-0.63%	0.99%
	PAX		2,791	66	2.36%	1.83%	3.00%			
	BEB	Condition Absent	3,036	47	1.55%	1.14%	2.05%	0.20%	-0.40%	0.80%
	PAX		3,036	41	1.35%	0.97%	1.83%			
Secondary analyses										
Hospitalization	BEB	All	5,827	113	1.94%	1.60%	2.33%	0.12%	-0.37%	0.61%
	PAX		5,827	106	1.82%	1.49%	2.20%			
	BEB	Condition Present	2,791	66	2.36%	1.83%	3.00%	0.04%	-0.76%	0.83%
	PAX		2,791	65	2.33%	1.80%	2.96%			
	BEB	Condition Absent	3,036	47	1.55%	1.14%	2.05%	0.20%	-0.40%	0.80%
	PAX		3,036	41	1.35%	0.97%	1.83%			
ED visit	BEB	All	5,827	296	5.08%	4.53%	5.68%	0.50%	-0.28%	1.28%
	PAX		5,827	267	4.58%	4.06%	5.15%			
	BEB	Condition Present	2,791	146	5.23%	4.43%	6.12%	0.39%	-0.75%	1.54%
	PAX		2,791	135	4.84%	4.07%	5.70%			
	BEB	Condition Absent	3,036	150	4.94%	4.20%	5.77%	0.59%	-0.47%	1.65%
	PAX		3,036	132	4.35%	3.65%	5.13%			
Death	BEB	All	5,827	6	0.10%	0.04%	0.22%	0.086%	-0.003%	0.175%
	PAX		5,827	1	0.02%	0.00%	0.10%			
	BEB	Condition Present	2,791	6	0.21%	0.08%	0.47%	0.179%	-0.006%	0.365%
	PAX		2,791	1	0.04%	0.00%	0.20%			
	BEB		3,036	0	0.00%	0.00%	0.12%	0.000%	0.000%	0.000%

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
	PAX	Condition Absent	3,036	0	0.00%	0.00%	0.12%			
Subgroup: COVID-19 vaccine (yes/undetermined)										
Primary analysis										
Hospitalization OR Death	BEB	All	5,827	118	2.03%	1.68%	2.42%	0.19%	-0.31%	0.69%
	PAX		5,827	107	1.84%	1.51%	2.21%			
	BEB	Condition Present	1,013	19	1.88%	1.13%	2.91%	0.30%	-0.84%	1.43%
	PAX		1,013	16	1.58%	0.91%	2.55%			
	BEB	Condition Absent	4,814	99	2.06%	1.67%	2.50%	0.17%	-0.39%	0.72%
	PAX		4,814	91	1.89%	1.52%	2.32%			
Secondary analyses										
Hospitalization	BEB	All	5,827	113	1.94%	1.60%	2.33%	0.12%	-0.37%	0.61%
	PAX		5,827	106	1.82%	1.49%	2.20%			
	BEB	Condition Present	1,013	19	1.88%	1.13%	2.91%	0.30%	-0.84%	1.43%
	PAX		1,013	16	1.58%	0.91%	2.55%			
	BEB	Condition Absent	4,814	94	1.95%	1.58%	2.38%	0.08%	-0.46%	0.63%
	PAX		4,814	90	1.87%	1.51%	2.29%			
ED visit	BEB	All	5,827	296	5.08%	4.53%	5.68%	0.50%	-0.28%	1.28%
	PAX		5,827	267	4.58%	4.06%	5.15%			
	BEB	Condition Present	1,013	64	6.32%	4.90%	8.00%	2.86%	0.99%	4.74%
	PAX		1,013	35	3.46%	2.42%	4.77%			
	BEB	Condition Absent	4,814	232	4.82%	4.23%	5.46%	0.00%	-0.86%	0.86%
	PAX		4,814	232	4.82%	4.23%	5.46%			
Death	BEB	All	5,827	6	0.10%	0.04%	0.22%	0.086%	-0.003%	0.175%
	PAX		5,827	1	0.02%	0.00%	0.10%			
	BEB	Condition Present	1,013	1	0.10%	0.00%	0.55%	0.099%	-0.095%	0.292%
	PAX		1,013	0	0.00%	0.00%	0.36%			
	BEB		4,814	5	0.10%	0.03%	0.24%	0.083%	-0.017%	0.183%

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
	PAX	Condition Absent	4,814	1	0.02%	0.00%	0.12%			
Subgroup: Emergency department visit within 7 days pre-index (yes/no)										
Primary analysis										
Hospitalization OR Death	BEB	All	5,827	118	2.03%	1.68%	2.42%	0.19%	-0.31%	0.69%
	PAX		5,827	107	1.84%	1.51%	2.21%			
	BEB	Condition Present	1,022	39	3.82%	2.73%	5.18%	0.98%	-0.58%	2.53%
	PAX		1,022	29	2.84%	1.91%	4.05%			
	BEB	Condition Absent	4,805	79	1.64%	1.30%	2.04%	0.02%	-0.49%	0.53%
	PAX		4,805	78	1.62%	1.29%	2.02%			
Secondary analyses										
Hospitalization	BEB	All	5,827	113	1.94%	1.60%	2.33%	0.12%	-0.37%	0.61%
	PAX		5,827	106	1.82%	1.49%	2.20%			
	BEB	Condition Present	1,022	38	3.72%	2.64%	5.07%	0.88%	-0.66%	2.42%
	PAX		1,022	29	2.84%	1.91%	4.05%			
	BEB	Condition Absent	4,805	75	1.56%	1.23%	1.95%	-0.04%	-0.54%	0.46%
	PAX		4,805	77	1.60%	1.27%	2.00%			
ED visit	BEB	All	5,827	296	5.08%	4.53%	5.68%	0.50%	-0.28%	1.28%
	PAX		5,827	267	4.58%	4.06%	5.15%			
	BEB	Condition Present	1,022	131	12.82%	10.83%	15.02%	0.68%	-2.18%	3.55%
	PAX		1,022	124	12.13%	10.19%	14.29%			
	BEB	Condition Absent	4,805	165	3.43%	2.94%	3.99%	0.46%	-0.25%	1.16%
	PAX		4,805	143	2.98%	2.51%	3.50%			
Death	BEB	All	5,827	6	0.10%	0.04%	0.22%	0.086%	-0.003%	0.175%
	PAX		5,827	1	0.02%	0.00%	0.10%			
	BEB	Condition Present	1,022	1	0.10%	0.00%	0.54%	0.098%	-0.094%	0.290%
	PAX		1,022	0	0.00%	0.00%	0.36%			
	BEB		4,805	5	0.10%	0.03%	0.24%	0.083%	-0.017%	0.183%

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference)		
								RD	95% LCL	95% UCL
	PAX	Condition Absent	4,805	1	0.02%	0.00%	0.12%			

Abbreviations: 95% LCL = 95% confidence interval lower confidence limit; 95% UCL = 95% confidence interval upper confidence limit; BEB = bebtelovimab; COVID-19 = coronavirus disease 2019; ED = early discontinuation; PAX = paxlovid.

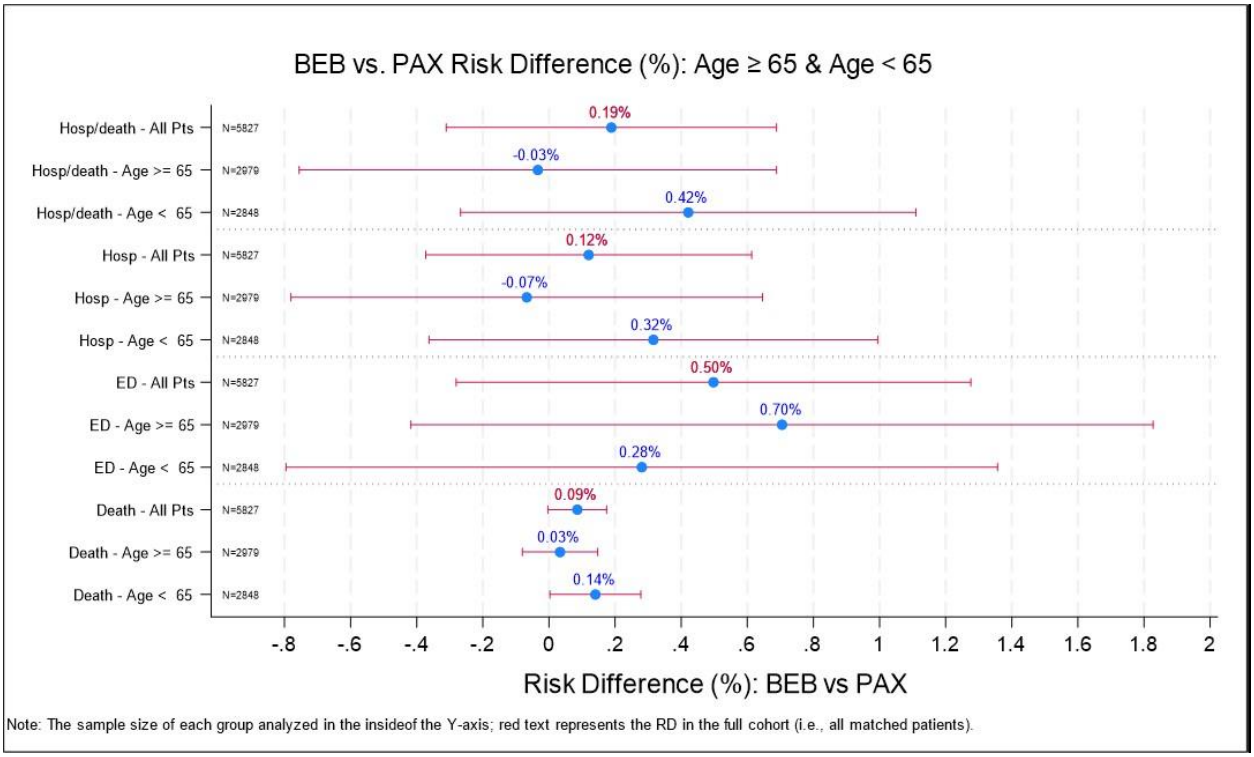


Figure 10.2. BEB vs. PAX risk difference (%): age ≥ 65 and age < 65.

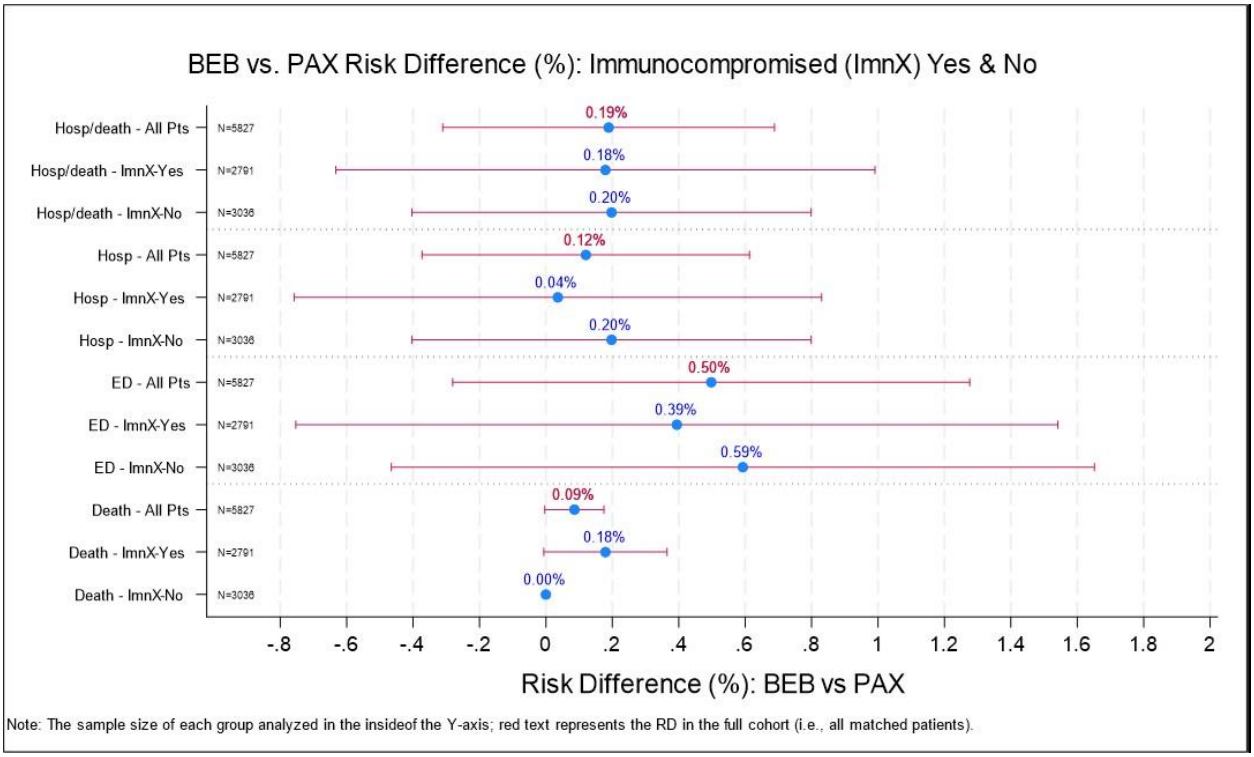


Figure 10.3. BEB vs. PAX risk difference (%): immunocompromised (ImnX) Yes and No.

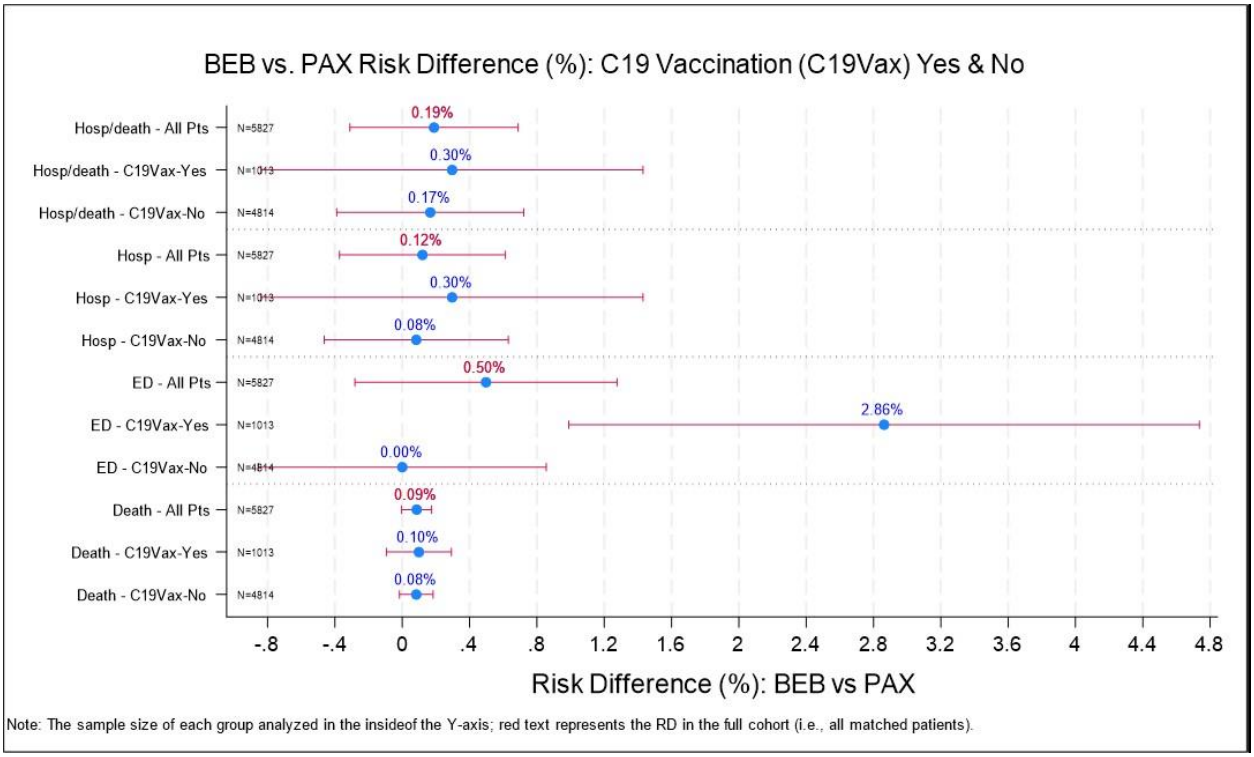


Figure 10.4. BEB vs. PAX risk difference (%): COVID-19 vaccination Yes and No.

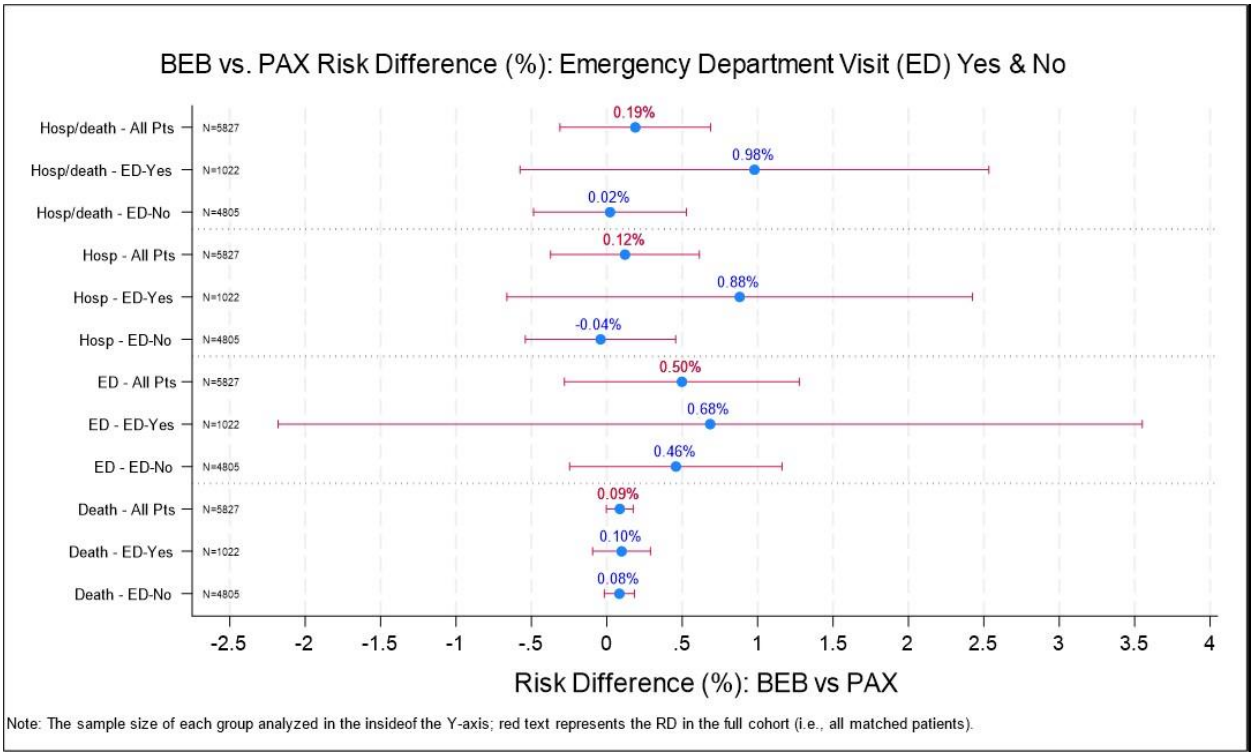


Figure 10.5. **BEB vs. PAX risk difference (%): emergency department visit Yes and No.**

10.5.2 Sensitivity Analyses

Among patients included in the matched cohorts, the same primary and secondary analyses were conducted for the sensitivity analyses described below.

10.5.2.1 Results of Sensitivity Analyses to Mitigate Potential Channeling Bias

In this analysis, the index date was imputed or "lagged" to the primary index date plus 1 day. By systematically lagging the index date 1 day forward in time for all study cohort members, we thereby excluded patients who had an event very early during follow-up and mitigated bias related to disease severity at the time of BEB or PAX treatment. The results are presented in Table 10.17 below. For convenience, the results table includes results using the primary analytic methodology and results pertaining to this sensitivity analysis.

For the primary outcome (hospitalization or death within 30 days post-index), 14 events occurred on the first day of follow-up (i.e., Day 1) for patients treated with BEB (number of Day 1 events=7) and PAX (number of Day 1 events =7). These events were excluded from the sensitivity analysis. While this resulted in a reduction in the cumulative incidence (i.e., the risk) of the composite outcome in both groups, the RD (and 95% CI) was essentially unchanged compared to the RD (95% CI) using the primary methodology.

The results for the hospitalization and death outcomes followed the same pattern as the primary composite outcome. That is, the cumulative incidence was reduced by excluding Day 1 events; however, the RD was consistent with RD from the primary methodology. For the ED outcome, we observed differential exclusion of treatment events on Day 1. Approximately 14% and 8% of events were excluded on Day 1 for BEB and PAX treated patients, respectively. While the observed RD was attenuated, the 95% CIs were mostly overlapping with the 95% CI using the primary methodology.

Table 10.17. Results from Sensitivity Analyses to Mitigate Potential Channeling Bias

Outcome	Methodology	Exposure	Number of Patients Analyzed	Number of Patients with Events	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
Primary analysis										
Hospitalization OR Death	**Primary**	BEB	5,827	118	2.03%	1.68%	2.42%	0.19%	-0.31%	0.69%
		PAX	5,827	107	1.84%	1.51%	2.21%			
Hospitalization OR Death	**Excluding Events on Day 1**	BEB	5,827	111	1.90%	1.57%	2.29%	0.19%	-0.30%	0.67%
		PAX	5,827	100	1.72%	1.40%	2.08%			
Secondary analyses										
Hospitalization	**Primary**	BEB	5,827	113	1.94%	1.60%	2.33%	0.12%	-0.37%	0.61%
		PAX	5,827	106	1.82%	1.49%	2.20%			
Hospitalization	**Excluding Events on Day 1**	BEB	5,827	107	1.84%	1.51%	2.21%	0.14%	-0.34%	0.62%
		PAX	5,827	99	1.70%	1.38%	2.06%			
ED visit	**Primary**	BEB	5,827	296	5.08%	4.53%	5.68%	0.50%	-0.28%	1.28%
		PAX	5,827	267	4.58%	4.06%	5.15%			
ED visit	**Excluding Events on Day 1**	BEB	5,827	255	4.38%	3.87%	4.93%	0.15%	-0.58%	0.89%
		PAX	5,827	246	4.22%	3.72%	4.77%			
Death	**Primary**	BEB	5,827	6	0.10%	0.04%	0.22%	0.086%	-0.003%	0.175%
		PAX	5,827	1	0.02%	0.00%	0.10%			
Death	**Excluding Events on Day 1**	BEB	5,827	5	0.09%	0.03%	0.20%	0.069%	-0.014%	0.151%
		PAX	5,827	1	0.02%	0.0004%	0.10%			

Abbreviations: BEB=bebtelovimab; PAX=Paxlovid; 95% LCL=95% confidence interval lower confidence limit; 95% UCL=95% confidence interval upper confidence limit.

Note: For the Risk Difference analyses, PAX is the reference category.

10.5.2.2. Results of Sensitivity Analyses to Assess the Impact of Unmeasured Confounding

The E-value results are presented in Table 10.18 below. The results table includes E-value results pertaining to both the RD (i.e., the primary effect estimate) and the RR. E-value results on the RR scale are intended to augment interpretation regarding the magnitude of unmeasured confounding needed to modify the observed RR to a different value – which is not currently available on the RD scale.

For the primary outcome (hospitalization or death within 30 days post-index), considering the confounders included in the propensity score generating model, an unmeasured confounder with an association of at least 1.44 (i.e., E-value=1.44) with the exposure and outcome would be required to fully attenuate (i.e., RD=0.0) the observed RD=0.19% (95% CI -0.31%, 0.69%).

On the RR scale, the strength of association an unmeasured confounder would need to have with the exposure and outcome to shift the observed RR (RR=1.10; 95% CI=0.85-1.43) to a RR=0.5 is at least 3.84. Unmeasured confounding with a magnitude > 2.0 and >3.0 would be required to shift the observed RR to RRs of 1.5 and 2.0, respectively.

The minimum magnitude of unmeasured confounding required to nullify the observed treatment effect for the hospitalization and ED outcomes is similar with the primary outcome (E-value for hospitalization=1.33; E-Value for ED visit=1.46). For the death outcome, given the small number of observed deaths (BEB [n=6]; PAX [n=1]), the observed treatment effect (RD=0.086%) has limited precision to estimate a valid standard error using traditional asymptotic statistical methods. This occurs because the standard error calculation assumes sample sizes are large enough for the normal approximation to be valid. Therefore, the estimation of the magnitude of unmeasured confounding needed to nullify or expunge the observed treatment effect for the death outcome is limited.

Table 10.18. Results of Sensitivity Analyses to Assess the Impact of Unmeasured Confounding

Outcome	Unmeasured Confounding Required to Nullify the Observed Treatment Effect: Risk Difference Scale		Unmeasured Confounding Required to Change the Observed Treatment Effect: Risk Ratio Scale				
	E-Value RD=0.0	E-Value RD 95% CI Includes 0	Observed RR (95% CI)	E-Value True RR=0.5	E-Value True RR=1.0	E-Value True RR=1.5	E-Value True RR=2.0
Primary analysis							
Hospitalization OR Death	1.44	1.00	1.10 (0.85-1.43)	3.84	1.44	2.06	3.03
Secondary analyses							
Hospitalization	1.33	1.00	1.06 (0.82-1.39)	3.69	1.33	2.16	3.16
ED visit	1.46	1.00	1.11 (0.94-1.30)	3.86	1.46	2.04	3.01
Death	11.48	1.00	6.00 (0.72-49.82)	23.49	11.48	7.46	5.45

Abbreviations: 95% CI = 95% Confidence Interval; RD = Risk Difference; RR = Risk Ratio.

10.5.2.3. Results of Sensitivity Analyses to Assess the Impact of Missing Baseline Covariate Data

The results are presented in Table 10.19 below.

BMI and eGFR were the only two variables that met the pre-specified missing value criteria for imputation in the primary analysis cohort before matching (BEB [N=10,431]; PAX [N=63,048]). The missingness for BMI and eGFR was 21% and 18%, respectively. Given a non-monotonic missingness pattern was observed for these two variables, imputation was performed by multivariate imputation using chained equations (MICE).

The imputation model included the missing variables (i.e., BMI and eGFR) and other variables used to predict the imputed values for BMI and eGFR. The predictor variables included the exposure variable (BEB vs. PAX), the primary composite outcome variable, pre-specified baseline covariates, and empirically identified baseline covariates (identified using HDPS methodology). Since cubic splines were ultimately desired for inclusion in the propensity score generating model, BMI and eGFR were included in the imputation model as cubic splines. Linear regression-based MICE was used to generate twenty imputation datasets (m=20) with imputed values for BMI and eGFR. Except for the outcome variable, he prediction variables included in the imputation model were the same as those included in the PS generating model.

Multiple imputation was conducted using the "Across" approach and the "Within" approach. In the "Across" approach, the PSs are averaged over m imputed datasets to obtain an average PS. The average PS is then used in one of the imputed datasets to obtain one estimate of the treatment effect (i.e., the risk difference). Alternatively, the "Within" approach uses the PS form each imputed dataset to obtain m treatment effect estimates. These estimates are then combined using Rubin's rules.

For the "Across" approach, after estimating of the average PS, the matched cohorts included 5,755 matched pairs compared to 5,872 matched pairs when using the primary analytic methodology. For the "Within" approach, PS matching was conducted within each imputed data set (m=20). Sample sizes pertaining to each m matched cohort are not presented.

The "Across" multiple imputation approach resulted in a reduced risk of the primary outcome (hospitalization or death within 30 days post-index) for BEB and PAX treated patients. The RD was slightly magnified (away from the "null") from 0.19% to 0.31%; however, the 95% CIs for both approaches showed considerable overlap. The "Within" multiple imputation approach resulted in an attenuated RD (from 0.19% to 0.06%); however, the 95% CIs for both approaches showed considerable overlap. The multiple imputation findings for the secondary outcomes were similar with those observed for the primary composite outcome in that there were overlapping confidence intervals with the primary methodology.

Table 10.19. Sensitivity Analyses to Assess the Impact of Missing Baseline Covariate Data

Outcome	Analysis	Exposure	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
Primary analysis										
Hospitalization OR Death	**Multiple Imputation "Across"**	BEB	5,755	114	1.98%	1.64%	2.37%	0.31%	-0.18%	0.80%
		PAX	5,755	96	1.67%	1.35%	2.03%			
	Multiple Imputation "Within"	BEB						0.06%	-0.49%	0.62%
		PAX								
Secondary analyses										
Hospitalization	**Multiple Imputation "Across"**	BEB	5,755	110	1.91%	1.57%	2.30%	0.26%	-0.22%	0.74%
		PAX	5,755	95	1.65%	1.34%	2.01%			
	Multiple Imputation "Within"	BEB						0.02%	-0.53%	0.57%
		PAX								
ED visit	**Multiple Imputation "Across"**	BEB	5,755	296	5.14%	4.59%	5.75%	-0.14%	-0.95%	0.67%
		PAX	5,755	304	5.28%	4.72%	5.89%			
	Multiple Imputation "Within"	BEB						0.28%	-0.60%	1.17%
		PAX								
Death	**Multiple Imputation "Across"**	BEB	5,755	4	0.07%	0.02%	0.18%	0.000%	-0.096%	0.096%
		PAX	5,755	4	0.07%	0.02%	0.18%			
	Multiple Imputation "Within"	BEB						0.023%	-0.076%	0.121%
		PAX								

Outcome	Analysis	Exposure	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL

Abbreviations: 95% LCL=95% confidence interval lower confidence limit; 95% UCL=95% confidence interval upper confidence limit; AM=analysis model (i.e., PS generating model); BEB=bebtelovimab; BMI=Body Mass Index; eGFR=estimated glomerular filtration rate; HR=heart rate; IM=imputation model; PAX=Paxlovid; Y=hospitalization or death outcome variable.

Note: For the Risk Difference analyses, PAX is the reference category.

10.5.3 Supplemental Analyses in TriNetX Linked Network

Results from the supplemental analyses using the TriNetX Linked Network are described in the Report on Supplemental Analyses in TriNetX Linked Network, which can be found in Annex 2.

10.6 Adverse Events/Adverse Reactions

This is a non-interventional study based on secondary data; therefore, no Individual Case Safety Report reporting is required. This study has no protocol-defined adverse events, so a summary of adverse events was not included in this study report.

11 Discussion

11.1 Key Results

We evaluated the effectiveness of BEB compared to PAX for patients with COVID-19. The treatment effect (i.e., the RD) was estimated for 30-day all-cause hospitalization OR death (primary outcome). The null hypothesis was that BEB was inferior to PAX given the *a priori* specified non-inferiority margin. Secondary analyses were conducted to estimate the treatment effect for all-cause hospitalization, all-cause death, and all-cause ED encounter. Hypothesis testing was not conducted for the secondary outcomes. Subgroup and sensitivity analyses were conducted to assess potential effect modification and bias.

For the primary analysis, we observed the 95% UCL of BEB vs. PAX risk difference excluded the non-inferiority margin (1.795%) and therefore concluded BEB was not inferior to PAX. The risk of hospitalization or death was approximately 2% in both groups. Hospitalizations comprised ~97% of events compared to deaths (~3%). For the secondary analyses, we observed no statistical difference in the risk of hospitalization, ED encounter, or death for patients exposed to BEB compared to PAX. The risk of each outcome in BEB was approximately 2%, 5%, and <1%, respectively. Overall, the results for specific sub-groups of interest (i.e., stratified analyses by age ≥ 65 years, immunocompromised status, COVID-19 vaccination status, and ED visit) were consistent with the observed results for the primary (matched) cohort. With respect to the assessment of bias, both channeling bias related to COVID-19 severity and unmeasured confounding related to missing BMI and eGFR values do not appear to pose major threats to validity. Additionally, an assessment of the potential impact of unmeasured confounding showed that moderate/strong unmeasured confounding would be needed to change the conclusion of the study (i.e., to make BEB inferior to PAX).

To contextualize these findings, results of the present study were compared to those from a cohort study that compared the effectiveness of BEB to PAX within the Mayo Clinic health system (Razonable et al. 2022). Importantly, the present study and the Mayo Clinic study were conducted during the Omicron variant era. The main (composite) outcome in the Mayo Clinic study was hospitalization, oxygen utilization, or death within 30-days following treatment with BEB or PAX. Unlike the present study, differences in baseline patient characteristics, to mitigate channeling bias, were not accounted for in the Mayo Clinic study. The risk of the primary outcome in the present study (BEB 0.02 or 2.0%; PAX 0.018 or 1.8%) was higher than the risk reported in the Mayo Clinic study (BEB 0.014 or 1.4%; PAX 0.012 or 1.2%). However, the observed RD for the present study (0.19% [-0.31%,0.69%]) was consistent with that reported in the Mayo Clinic study (0.28% [-0.59%,1.15%]). In both the Mayo Clinic study and the present study (prior to matching), patients who were treated with BEB (vs PAX) were older and a higher percentage of patients had comorbidities associated with experiencing severe COVID-19 illness.

The observed risk of hospitalization or death in the present study may be further contextualized by two additional studies that utilized an untreated comparator group (McCreary et al. 2022; Hammond et al. 2022). McCreary et al. reported the 28-day risk of hospitalization or death was 3.1% for patients treated with BEB. Hammond et al., reported the risk of COVID-19 related

hospitalization, for patients included in a randomized trial, was 0.77% for patients treated with PAX. Despite differences in the outcome definition in these studies, both findings closely paralleled the observed risk for BEB treated patients (2.3% unmatched cohort; 2.0% matched cohort) and PAX treated patients (i.e., 1.1% unmatched cohort; 1.8% matched cohort) in the present study.

Results from the channeling bias sensitivity analysis were consistent with the results observed with the primary methodology. Channeling bias, related to COVID-19 severity, did not appear to pose a major threat to the validity of the effect estimates for the primary and secondary outcomes. The observed differential exclusion of events and attenuated risk difference for the ED outcome are noted; however, given the overlapping CIs, the overall interpretation of the treatment effect remains unchanged compared to the results with the primary methodology.

The E-value analyses showed that weak to moderate unmeasured confounding with a magnitude of at least 1.44 could nullify the observed treatment effect for hospitalization or death (produce a risk difference equal to 0), given the relatively rare incidence of the primary composite outcome (<2.0%) and small observed treatment effect (RD=0.19%). Although methods to determine the magnitude of unmeasured confounding needed to move the upper confidence limit (0.69) to the pre-specified non-inferiority margin (1.795) are not available on the risk-difference scale, the amount of unmeasured confounding needed to move the association in favor of PAX on the relative risk scale was evaluated. Those results suggested an unmeasured confounder with a moderate to strong association with the exposure and outcome (> 2.0) would be needed to produce a relative risk of 1.5 or greater. The magnitude of unmeasured confounding needed to nullify the observed treatment effect for the hospitalization and ED outcomes is similar. This considered together with results of sensitivity analyses assessing the influence of unmeasured disease severity or other variables that may lead to channeling bias and unmeasured vaccine status suggest that study findings are robust to unmeasured confounding.

The results from the multiple imputation sensitivity analysis were consistent with the results observed with the primary methodology. The impact of missing BMI and eGFR is evident on the cumulative incidence and RD estimates; however, the overall interpretation of the findings remains unchanged. The multiple imputation results were similar when using the “Across” approach and the ‘Within” approach.

11.2 Limitations

This study has several limitations. Regarding missing data, healthcare encounters, including COVID-19 vaccinations, that occurred outside the HCO network were not captured. This may have resulted in incomplete healthcare utilization profiles and potentially missing exposure, confounder, and outcome data. Strategies to mitigate missing data and other sources of information bias were incorporated into the study design and study methodology. These comprised the following: inclusion of only patients who regularly received care at the contributing HCOs, using medication records to classify the study cohorts, conducting subgroup analyses for patients with documented evidence of COVID-19 vaccination, and conducting sensitivity analyses, using multiple imputation, to account for missing baseline covariate data.

The impact of potentially missing outcome data will be assessed in future analyses using EHR data linked to health insurance claims data.

To mitigate confounding bias (e.g., by COVID-19 illness severity), the study cohorts were restricted to patients who were not hospitalized within 30 days prior to receiving BEB or PAX. Additional confounding control was achieved using CEM on highly selected and *a priori* defined baseline variables in conjunction with PS matching on a broader set of baseline covariates. Sensitivity analyses were conducted to assess the potential impact of unmeasured confounding. These analyses showed the observed study results were robust to unmeasured confounding related to disease severity and missing BMI and eGFR data. They also showed strong unmeasured confounding would be required to substantially change the study conclusion.

With respect to exposure misclassification, the ability to identify monoclonal antibody and antiviral administrations in the TriNetX Dataworks USA Network is an 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 health insurance claims data only, where insurance claims for BEB and other products made available under EUA are likely missing. 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 (e.g., 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 risk difference (in favor of BEB) with a narrower CI, and 3) an increased likelihood of rejecting the null hypothesis and establishing noninferiority 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 (i.e., COVID-19) the severity of the outcome (i.e., hospitalization or death), and the context of disease occurrence (i.e., COVID-19 acquired during a global pandemic with heightened awareness of potential harm). Another form of measurable exposure misclassification may occur if the exposure, as classified on the index date, is followed by post-index antibody or antiviral therapy. To address this form of exposure misclassification, we described the use of non-index monoclonal antibody and antiviral treatment during follow-up for patients in both cohorts. The results show that 1.2% and 0.5% of patients treated with PAX and BEB on the index data received the other therapy (PAX or BEB), respectively, during the 30-day follow-up period. Less than 1% of patients in both groups received remdesivir or any other antiviral/antibody therapy post-index.

To mitigate outcome misclassification, eligibility requirements were incorporated to restrict the study cohorts to include only patients who regularly received care within the TriNetX HCO network. Additionally, future analyses will be conducted among patients with linked EHR and health insurance claims data.

To evaluate the consistency of the treatment effect for specific subgroups of patients compared to the treatment effect for the overall study population (i.e., effect modification), the primary and secondary analyses were stratified by matched pairs who were age ≥ 65 years, immunocompromised, and who had a pre-index ED visit or documentation of receiving a

COVID-19 vaccine in the last 9 months. Overall, the results from the sub-group analyses were consistent with the observed results for the primary matched cohort.

Noninferiority testing for the primary composite outcome was conducted. The *a priori* defined noninferiority margin of 1.795% was based on a sample size of 1,390 patients in each treatment arm which provided 90% power to reject the null hypothesis. This further assumed the incidence of hospitalization or death was 1.4% for BEB and 1.2% for PAX (Razonable et al. 2022), whereas the observed sample size in each group and the risk of the primary outcome were 5,827 and ~2%, respectively. We also observed the primary outcome risk was 2.03% and 1.84% for patients treated with BEB and PAX, respectively. Thus, given the observed outcome risk and sample size, the present study had adequate power to establish noninferiority, using the *a priori* established noninferiority margin (i.e., 1.795%).

11.3 Interpretation

The results showed that BEB was not inferior to PAX with respect to 30-day hospitalization or death. Likewise, there was no statistical difference between BEB and PAX for the primary and secondary outcomes. The primary findings were not substantially different in the subgroups analyzed and the primary treatment effect was robust when different methods to assess bias were applied. For example, channeling bias related to COVID-19 severity did not appear to pose a major threat to validity. Similarly, the primary study findings were consistent with analyses that included imputed BMI and eGFR data. Finally, strong unmeasured confounding would be required to appreciably change the conclusion.

11.4 Generalisability

Generalizability is the ability to apply the results of a study to other populations. Patients included in the TriNetX Dataworks USA Network have been 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 high-risk 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.

12 Other Information

Not applicable.

13 Conclusions

In this study of patients with COVID-19 during the period of high prevalence for the Omicron BA.4 and BA.5 subvariants in the US, we found the risk of hospitalization or death was not greater for patients treated with BEB compared to patients treated with PAX. Similarly, the risk of the secondary outcomes (i.e., hospitalization, ED visit, and death) was not different for patients treated with BEB and PAX. Furthermore, the study findings were (i) consistent for important patient subgroups (e.g., immunocompromised and COVID-19 vaccinated) and (ii) robust to a variety of bias assessments. When administered to patients who were at high risk for progression to severe COVID-19 illness, the incidence of hospitalization or death was not greater for patients treated with BEB compared to patients treated with PAX.

14 References

Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 booster vaccines against COVID-19-related symptoms, hospitalization and death in England. *Nat Med*. 2022;28(4):831-837.

[ASPR] Administration for Strategic Preparedness and Response. 2022. Allocation of Bamlanivimab/Etesevimab and REGEN-COV Therapeutics Paused 2022 [Available from: https://aspr.hhs.gov/COVID-19/Therapeutics/updates/Pages/important-update-24January2022.aspx.

[ASPR] Administration for Strategic Preparedness and Response. 2023a. Important information about bamlanivimab (updated April 7, 2023). Available from: https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Bamlanivimab/Pages/default.aspx.

[ASPR] Administration for Strategic Preparedness and Response. 2023b. Important information about REGEN-COV (updated April 7, 2023). Available from: https://aspr.hhs.gov/COVID-19/Therapeutics/Products/REGEN-COV/Pages/default.aspx.

[CDC] Centers for Disease Control and Prevention. 2022a. Estimated COVID-19 burden 2022 (updated August 12, 2022). Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html.

[CDC] Centers for Disease Control and Prevention. 2022b. COVID data tracker 2022. Available from: https://covid.cdc.gov/covid-data-tracker.

[CDC] Centers for Disease Control and Prevention. 2022c. Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare professionals 2022. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html.

Choi YJ, Park JY, Lee HS, et al. Variable effects of underlying diseases on the prognosis of patients with COVID-19. *PLoS One*. 2021;16(7):e0254258.

Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Arch Acad Emerg Med*. 2020;8(1):e35.

[FDA] Food and Drug Administration. 2016. Non-inferiority clinical trials to establish effectiveness: Guidance for Industry 2016 Available from: https://www.fda.gov/media/78504/download.

[FDA] Food and Drug Administration. 2021a. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of COVID-19 in certain adults. 2021 Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain.

[FDA] Food and Drug Administration. 2021b. Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19 2021. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19.

[FDA] Food and Drug Administration. 2022a. FDA announces bebtelovimab is not currently authorized in any US region 2022. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region.

[FDA] Food and Drug Administration. 2022b. Coronavirus (COVID-19) update: FDA authorizes new monoclonal antibody for treatment of COVID-19 that retains activity against omicron variant 2022. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains.

[FDA] Food and Drug Administration. 2022c. FDA updates sotrovimab emergency use authorization 2022. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization.

[FDA] Food and Drug Administration. 2023. FDA approves first oral antiviral for treatment of COVID-19 in adults 2023. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-antiviral-treatment-covid-19-adults#:~:text=Today%2C%20the%20U.S.%20Food%20and,19%2C%20including%20hospitalization%20or%20death.

Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. *Stat Med*. 2019;38(26):5120-5132.

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med*. 2022;386(15):1397-1408.

Hodge D, Marra F, Marzolini C, et al. Drug interactions: a review of the unseen danger of experimental COVID-19 therapies. *J Antimicrob Chemother*. 2020;75(12):3417-3424.

Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 omicron sublineages. *Nature*. 2022;604(7906):553-556.

Khairat S, Zou B, Adler-Milstein J. Factors and reasons associated with low COVID-19 vaccine uptake among highly hesitant communities in the US. *Am J Infect Control*. 2022;50(3):262-267.

Kompaniyets L, Pennington AF, Goodman AB, et al. Underlying medical conditions and severe illness among 540,667 adults hospitalized with COVID-19, March 2020-March 2021. *Prev Chronic Dis*. 2021;18:E66.

Linden A, Mathur MB, VanderWeele TJ. Conducting sensitivity analysis for unmeasured confounding in observational studies using E-values: the evalue package. *The Stata Journal*. 2020;20:162-175.

Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385(7):585-594.

Mauri L, D'Agostino RB, Sr. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med*. 2017;377(14):1357-1367.

McCreary EK, Kip KE, Collins K, et al. Evaluation of bebtelovimab for treatment of COVID-19 during the SARS-CoV-2 omicron variant era. *Open Forum Infect Dis*. 2022;9(10):ofac517.

Monto AS. The future of SARS-CoV-2 vaccination - lessons from influenza. *N Engl J Med*. 2021;385(20):1825-1827.

Nguyen KH, Nguyen K, Corlin L, et al. Changes in COVID-19 vaccination receipt and intention to vaccinate by socioeconomic characteristics and geographic area, United States, January 6 - March 29, 2021. *Ann Med*. 2021;53(1):1419-1428.

[NIH] National Institutes of Health. Therapeutic management of nonhospitalized adults with COVID-19. 2022 Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/.

Parasher A. COVID-19: current understanding of its pathophysiology, clinical presentation and treatment. *Postgrad Med J*. 2021;97(1147):312-320.

Pei S, Yamana TK, Kandula S, et al. Burden and characteristics of COVID-19 in the United States during 2020. *Nature*. 2021;598(7880):338-341.

Razonable RR, O'Horo JC, Hanson SN, et al. Comparable outcomes for bebtelovimab and ritonavir-boosted nirmatrelvir treatment in high-risk patients with coronavirus disease-2019 during severe acute respiratory syndrome coronavirus 2 BA.2 omicron epoch. *J Infect Dis*. 2022;226(10):1683-1687.

Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512-22.

VanderWeele TJ, Ding P. sensitivity analysis in observational research: introducing the E-Value. *Ann Intern Med*. 2017;167(4):268-274.

VanderWeele TJ, Ding P, Mathur M. Technical Considerations in the Use of the E-Value. Journal of Causal Inference. 2019.

Wagner CE, Saad-Roy CM, Morris SE, et al. Vaccine nationalism and the dynamics and control of SARS-CoV-2. *Science*. 2021;373(6562):eabj7364.

[WHO] World Health Organization Working Group. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e197.

15 Annex 1. List of Standalone Documents

No.	Document Reference No.	Date	Title
1.	v1	17 February 2023	LY3853113 RWE Final Report Code List

16 Annex 2. Report on Supplemental Analyses in TriNetX Linked Network

16.1 A2.1. Rationale and Background

On 11 February 2022, the FDA issued an EUA for BEB, an antibody used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who were 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 were not available or clinically appropriate (FDA 2022).

Recognizing the limitations of the available clinical data, conditions of the letter of authorization required Eli Lilly and Company to submit a protocol for a clinical trial to collect additional information on BEB effectiveness outcomes. A cohort study using data from the TriNetX Dataworks USA EHR Network, as described in Sections 1 through 14 of this final study report, was conducted to address research questions regarding the effectiveness of BEB prior to its de-authorization on 30 November 2022.

To further assess the robustness of findings from the study conducted in the TriNetX Dataworks USA Network, supplemental analyses were conducted in the TriNetX Linked Network. The TriNetX Linked Network includes a subset of patients from the TriNetX Dataworks USA Network EHR database who also have linked closed health insurance claims data and linked mortality data, allowing the ascertainment of hospitalizations, deaths, and other healthcare services that occurred outside of the site-specific care setting of the HCOs contributing EHR data to the TriNetX Dataworks USA Network.

16.2 A2.2. Research Questions and Objectives

The primary and secondary objective of the supplemental analyses were the same as in the study conducted in the TriNetX Dataworks USA Network. The primary objective was to estimate the 30-day RD and 95% CI of a composite outcome of all-cause hospitalization or all-cause death, for patients who received BEB compared with patients who received PAX. The secondary objective was 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 and RD and corresponding 95% CIs were reported for all outcomes. Hypothesis testing was not conducted for the supplemental analyses (i.e., an a priori NI margin was not specified).

16.3 A2.3. Research Methods

16.3.1 A2.3.1. Study Design

The study objectives for the supplemental analyses in the TriNetX Linked Network were assessed using a cohort study design among patients with EHR data linked to health insurance claims (claims) data within the TriNetX Linked Network. Major aspects of the study design

remained the same as in the cohort study conducted in the TriNetX Dataworks USA Network; minor modifications that were made in the supplemental analyses are described below in Sections 16.3.2 (A2.3.2) through 16.3.7 (A2.3.7).

16.3.2 A2.3.2. Study Cohort

The study cohort for the supplemental analyses was constructed using similar methodology as described in Section 9.2.1. However, the variables used to classify each inclusion/exclusion criterion were ascertained from either EHR data, claims data, or both. The specific data source for each variable is provided below.

The study cohorts included patients who received BEB or PAX during the index period (i.e., 16 February 2022 to 31 August 2022). The index date was 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 were 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 index date were excluded. Therefore, a patient was allowed to be included in only one cohort. Inclusion and exclusion criteria were as follows:

1. BEB or PAX exposure during index period (index date):
    a. *Ascertained from EHR and claims data.*
2. At least 12 years old (i.e., age ≥ 12 years) as of the index date:
    a. *Ascertained from EHR data only.*
3. 12 months of continuous insurance enrollment pre-index (with no gaps >45 days) with medical and pharmacy coverage AND “EHR activity” 6-36 months pre-index:
    a. *Ascertained from EHR and claims data.*
4. No inpatient admission within 30 days pre-index (inclusive of index date):
    a. *Ascertained from EHR and claims data.*
5. No hospice care within 30 days pre-index (inclusive of index date):
    a. *Ascertained from EHR and claims data.*
6. No treatment indicated or used for COVID-19 within 90 days pre-index (inclusive of index date) - excluding BEB/PAX on the index date:
    a. *Ascertained from EHR and claims data.*
7. No supplemental or chronic oxygen therapy within 30 days pre-index (inclusive of index date):
    a. *Ascertained from EHR and claims data.*

16.3.3 A2.3.3. Outcomes

Each outcome was ascertained and classified using the same methodology as in the TriNetX Dataworks USA Network study, as described in Section 9.4.3.

All outcomes were classified using both EHR and claims data. Evidence of the outcome in either data source (i.e., EHR or claims) classified the outcome status as present (yes). If there was no evidence of the outcome in either data source, the outcome status was classified as absent (no).

All-cause hospitalization

All-cause hospitalization was classified using both EHR and claims data using the methodology described in Section 9.4.3.

All-cause mortality

All-cause mortality was classified using both EHR and claims data using the methodology described in Section 9.4.3. In addition to EHR recorded deaths, the TriNetX Linked Network uses de-identified tokenization to connect and source additional mortality data from private obituary information, closed or private claims, and the Social Security Administration Death Master File.

Emergency Department (ED) visit

The ED outcome was classified using both EHR and claims data using the methodology described in Section 9.4.3.

16.3.4 A2.3.4. Baseline Covariates

The classification of baseline covariates followed similar methodology as in the TriNetX Dataworks USA Network study, as described in Section 9.4.5. The specific data source for each variable is listed below (i.e., EHR data only, claims data only, EHR and claims data).

For binary covariates classified using both EHR and claims data (e.g., COVID-19 diagnosis), evidence in either data source (i.e., EHR or claims) classified the covariate status as present (yes). If there was no evidence of the covariate in either data source, the covariate status was classified as absent (no).

Demographics

- Age – EHR data only
- Sex – EHR data only
- Race – EHR data only

Clinical parameters

- Blood pressure (BP) – EHR data only
- Oxygen saturation – EHR data only
- Body mass index (BMI) – EHR data only

Smoking status

- Smoking status – EHR and claims data

Laboratory data

- Serum creatinine – EHR data only

Comorbidities

- Baseline comorbidities – EHR and claims data

COVID-19 diagnosis

- COVID-19 diagnosis – EHR and claims data

COVID-19 symptoms

- COVID-19 related symptoms – EHR and claims data

Pharmacotherapy

- Baseline pharmacotherapy – EHR and claims data

Healthcare resource utilization

- Baseline healthcare resource utilization – EHR and claims data

16.3.5 A2.3.5. Follow-Up and Censoring

Follow-up and censoring followed similar methodology as in the TriNetX Dataworks USA Network study, as described in Section 9.2.2. Follow-up began on the day after index date (i.e., index date plus one day) and continued until 30-days post-index.

Using an ITT approach, the exposure status (i.e., BEB or PAX) classified on the index date was carried forward for the entire 30-day follow-up period. With this approach, all patients in the study cohorts were included in the analysis set, regardless of post-index use of convalescent plasma, monoclonal antibody therapy, antiviral therapy, or insurance disenrollment.

Using both EHR and claims data, we described the frequency and proportion of patients who received any of the following: post-index convalescent plasma; monoclonal antibody therapy; and antiviral treatment indicated, authorized, or used to treat or prevent COVID-19 (excluding BEB/PAX on the index date). We also described the frequency and proportion of patients with insurance disenrollment during follow-up.

16.3.6 A2.3.6. Data Sources

The TriNetX Linked Network is described in detail in Section 9.5.2. The TriNetX Linked Network includes patients from TriNetX Dataworks USA Network who also have linked closed health insurance claims data and linked mortality data. 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. Among patients in the TriNetX Linked Network, approximately 48% have commercial insurance, 31% have Managed Medicaid, 6% have Medicare Advantage, and 15% have multiple types of insurances.

16.3.7 A2.3.7. Statistical Analysis Plan

Method to Control for Confounding

The method to control for confounding followed the same methodology as in the TriNetX Dataworks USA Network study, as described in Section 9.9.2.2. However, baseline covariates

were ascertained from both EHR and claims data. For the empirically identified baseline covariates used to generate the HDPS, we first deleted duplicate baseline records (i.e., codes) from EHR and claims data that occurred on the same (pre-index) date. This was done to prevent "double counting" codes that existed in both the EHR data and claims data.

16.3.8 A2.3.8. Analysis

Baseline Characteristics

The methodology described for the TriNetX Dataworks USA Network study in Section 9.9.2.3 was used to describe and analyze baseline characteristics.

Primary and Secondary Analyses

The methodology described for the TriNetX Dataworks USA Network study in Section 9.9.2.4 was used to describe and analyze the primary and secondary outcomes. However, hypotheses testing was not applicable to the supplemental analyses using the TriNetX Linked Network.

Subgroup Analyses

The methodology described for the TriNetX Dataworks USA Network study in Section 9.9.4 was used for the subgroup analyses.

Sensitivity Analyses

The methodology described for the TriNetX Dataworks USA Network study in Section 9.9.5 was used for the sensitivity analyses.

16.4 A2.4. Results

16.4.1 A2.4.1. Participants

Before applying patient qualification criteria, 5,462 BEB-exposed and 14,501 PAX-exposed patients were identified. After applying patient qualification criteria, 1,998 BEB-exposed and 3,301 PAX-exposed patients remained in the unmatched cohorts (Table.A2.1). After conducting HDPS matching, 37.5% of BEB-exposed patients were retained, resulting in 750 BEB-exposed and 750 PAX-exposed patients in the matched cohorts.

Table.A2.1. Patient Disposition for Supplemental Analyses

Patient Identification Criteria – Inclusion/Exclusion		BEB			PAX		
		N	% Excluded	% Retained	N	% Excluded	% Retained
1	Exposure to BEB or PAX during index period	5,462			14,501		
2	Age ≥12 years at index date	5,461	0.02%	99.98%	14,230	1.87%	98.13%
3	12 months of continuous insurance enrollment pre-index and "EHR activity" 6-36 months pre-index	2,517	53.9%	46.1%	3,694	74.0%	26.0%
4	No inpatient admission within 30 days pre-index	2,260	10.2%	89.8%	3,551	3.9%	96.1%
5	No hospice care within 30 days pre-index	2,251	0.4%	99.6%	3,542	0.3%	99.7%
6	No exposure to monoclonal antibody or antiviral within 90 days pre-index	2,070	8.0%	92.0%	3,344	5.6%	94.4%
7	No supplemental or chronic oxygen therapy within 30 days pre-index	1,998	3.5%	96.5%	3,301	1.3%	98.7%
	Total in unmatched cohorts	**1,998**			**3,301**		
8	HDPS Matching (1:1) using a caliper of 0.01 & common support	750	62.5%	37.5%	750	77.3%	22.7%
	Total in matched cohorts	**750**			**750**		

Abbreviations: BEB = bebtelovimab; EHR = electronic health record; HDPS = high dimensional propensity score; PAX = paxlovid.

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

16.4.2 A2.4.2. Descriptive Data

16.4.2.1 A2.4.2.1. CEM Matching Rate and Propensity Score Distribution

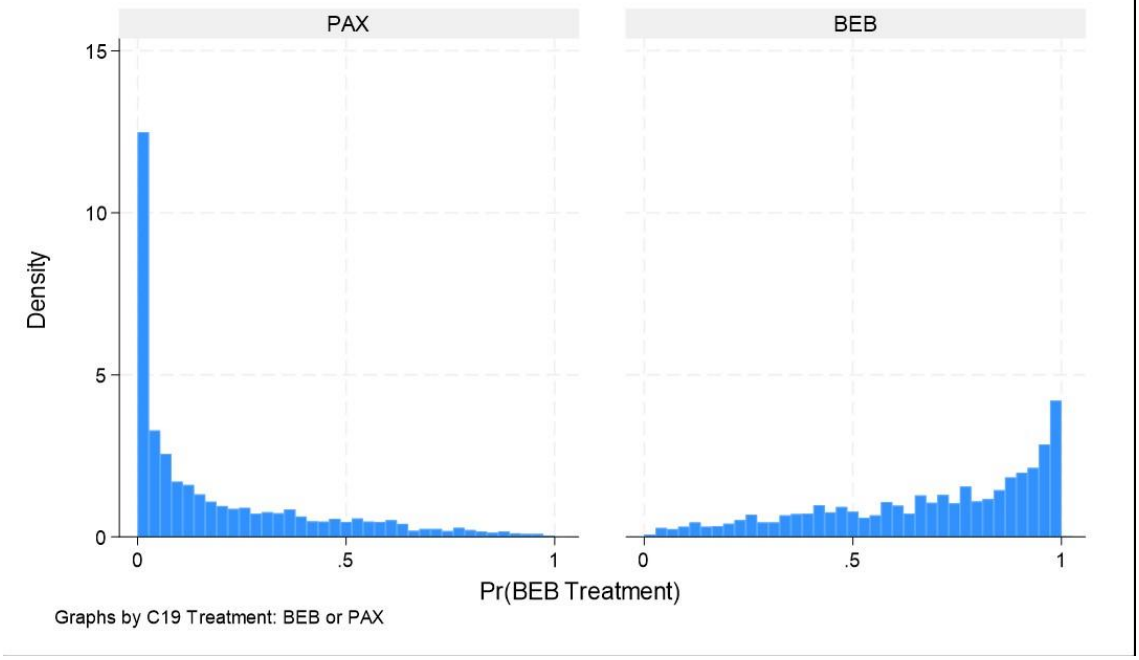
Table.A2.2 presents patient distribution within CEM categories. The proportion of patients in each category within the BEB and PAX cohorts is the same after matching. Similar to the PS distribution in the unmatched cohorts in the TriNetX Dataworks USA Network, the different shapes of the distributions presented in part A of Figure.A2.1 indicate that BEB and PAX were prescribed to different patient populations. PAX treated patients represented a more clearly defined but skewed distributed patient population and were less likely to receive BEB as indicated by the right-skewed distribution. BEB patients were not as clearly defined, as indicated by a lesser-skewed distribution. The overlap of the PS distribution between BEB-exposed and PAX-exposed patients notably improved after HDPS matching. PS distributions in the matched cohorts appear to be more normally distributed compared to the matched cohorts in the TriNetX Dataworks USA Network.

Table.A2.2. Distribution of Patients within CEM Categories for Supplemental Analyses in Unmatched and Matched Cohorts

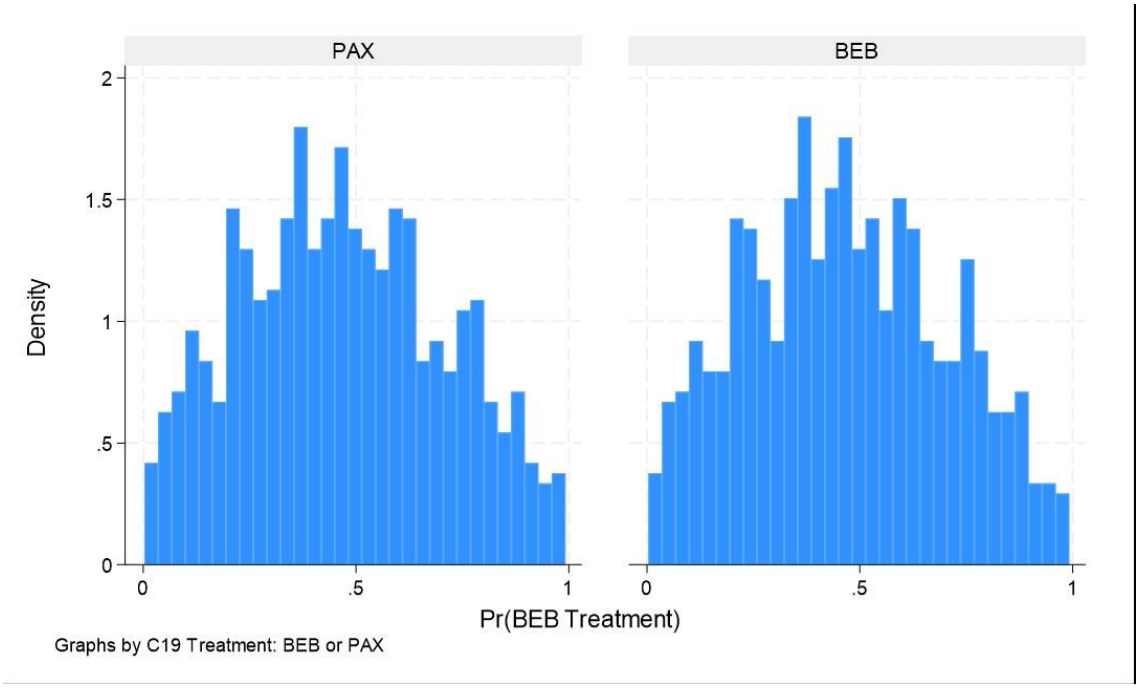
CEM Category	CEM Categories				PAX		BEB		Total	
	Immunocompromised Status	Age ≥ 65	COVID-19 Vaccination within 9 Months Pre-index	ED Visit within 7 Days Pre-index	Frequency	%	Frequency	%	Frequency	%
Unmatched cohorts										
1	No	No	No	No	655	19.8%	264	13.2%	919	17.3%
2	No	No	No	Yes	183	5.5%	193	9.7%	376	7.1%
3	No	No	Yes	No	469	14.2%	138	6.9%	607	11.5%
4	No	No	Yes	Yes	42	1.3%	77	3.9%	119	2.2%
5	No	Yes	No	No	145	4.4%	59	3.0%	204	3.8%
6	No	Yes	No	Yes	18	0.5%	39	2.0%	57	1.1%
7	No	Yes	Yes	No	153	4.6%	49	2.5%	202	3.8%
8	No	Yes	Yes	Yes	7	0.2%	20	1.0%	27	0.5%
9	Yes	No	No	No	444	13.5%	264	13.2%	708	13.4%
10	Yes	No	No	Yes	95	2.9%	192	9.6%	287	5.4%
11	Yes	No	Yes	No	501	15.2%	222	11.1%	723	13.6%
12	Yes	No	Yes	Yes	28	0.8%	123	6.2%	151	2.8%
13	Yes	Yes	No	No	250	7.6%	145	7.3%	395	7.5%
14	Yes	Yes	No	Yes	29	0.9%	85	4.3%	114	2.2%
15	Yes	Yes	Yes	No	268	8.1%	90	4.5%	358	6.8%
16	Yes	Yes	Yes	Yes	14	0.4%	38	1.9%	52	1.0%
Total					3,301	62.3%	1,998	37.7%	5,299	100.0%
Matched cohorts										
1	No	No	No	No	148	19.7%	148	19.7%	296	19.7%
2	No	No	No	Yes	89	11.9%	89	11.9%	178	11.9%
3	No	No	Yes	No	68	9.1%	68	9.1%	136	9.1%
4	No	No	Yes	Yes	20	2.7%	20	2.7%	40	2.7%
5	No	Yes	No	No	18	2.4%	18	2.4%	36	2.4%
6	No	Yes	No	Yes	6	0.8%	6	0.8%	12	0.8%

CEM Category	CEM Categories				PAX		BEB		Total	
	Immunocompromised Status	Age ≥ 65	COVID-19 Vaccination within 9 Months Pre-index	ED Visit within 7 Days Pre-index	Frequency	%	Frequency	%	Frequency	%
7	No	Yes	Yes	No	15	2.0%	15	2.0%	30	2.0%
8	No	Yes	Yes	Yes	2	0.3%	2	0.3%	4	0.3%
9	Yes	No	No	No	123	16.4%	123	16.4%	246	16.4%
10	Yes	No	No	Yes	50	6.7%	50	6.7%	100	6.7%
11	Yes	No	Yes	No	103	13.7%	103	13.7%	206	13.7%
12	Yes	No	Yes	Yes	15	2.0%	15	2.0%	30	2.0%
13	Yes	Yes	No	No	43	5.7%	43	5.7%	86	5.7%
14	Yes	Yes	No	Yes	14	1.9%	14	1.9%	28	1.9%
15	Yes	Yes	Yes	No	35	4.7%	35	4.7%	70	4.7%
16	Yes	Yes	Yes	Yes	1	0.1%	1	0.1%	2	0.1%
Total					750	50.0%	750	50.0%	1,500	100.0%

Abbreviations: BEB = bebtelovimab; CEM = coarsened exact matching; COVID-19 = coronavirus disease 2019; ED = early discontinuation; PAX = paxlovid.



A)



B)

Figure.A2.1. Propensity score distribution for supplemental analyses in the A) unmatched and B) matched cohorts.

16.4.2.2 A2.4.2.2. Baseline Characteristics

Table.A2.3, Table.A2.4, Table.A2.5, Table.A2.6, and Table.A2.7 display baseline variables for BEB-exposed and PAX-exposed patients in the unmatched cohorts. The mean age was 55 (SD 16) and 54 (SD 17) years in BEB-exposed and PAX-exposed patients, respectively. Patients were primarily female (61.7% in BEB and 61.9% in PAX) and White (71.0% in BEB and 73.8% in PAX). The addition of the linked claims data resulted in higher proportions of patients with a COVID-19 diagnosis and documentation of previous COVID-19 vaccination than observed in the main analysis (COVID diagnosis: 82.25% in BEB and 54.18% in PAX in the main analyses versus 98.2% in BEB and 62.0% in PAX in the linked supplemental analysis; COVID-19 vaccination: 29.80% in BEB and 18.99% in PAX in the main analysis versus 44.4% in BEB and 41.0% in PAX in the linked supplemental analysis). Common baseline comorbidities included aplastic anemia (32.9% in BEB and 25.3% in PAX), immunodeficiency (25.4% in BEB and 14.0% in PAX), hypertension (56.5% in BEB and 52.0% in PAX), other heart conditions (58.3% in BEB and 48.3% in PAX), obesity (60.4% in BEB and 49.1% in PAX), type 2 diabetes (36.6% in BEB and 26.3% in PAX), hematologic or solid malignancy except benign skin cancer (39.5% in BEB and 35.2% in PAX), anxiety and fear (53.6% in BEB and 47.2% in PAX), depression (45.8% in BEB and 38.9% in PAX), asthma (31.4% in BEB and 30.2% in PAX), COPD and bronchiectasis (24.7% in BEB and 20.1% in PAX), and CKD (21.5% in BEB and 14.0% in PAX), all of which had larger proportions compared to the unmatched cohorts in the main analysis.

Higher proportions of medication use were observed among cohorts created with the addition of the linked insurance claims vs. EHR data alone. Medication history in the cohorts created using the additional linked data showed higher proportions of BEB patients with a history of exposure to antiemetics (52.6% in BEB and 37.7% in PAX) and steroids (largest difference observed with dexamethasone, 54.3% in BEB and 46.0% in PAX). Patients exposed to BEB also had more past (20.6% in BEB, 13.6% in PAX) and present (9.8% in BEB and 6.5% in PAX) insulin use, past (68.7% in BEB and 58.0% in PAX) and present (52.2% in BEB and 44.6% in PAX) antihypertensive use, past SABA use (49.2% in BEB and 46.2% in PAX), past (51.2% in BEB and 44.2% in PAX), and present (41.2% in BEB and 35.5% in PAX) lipid lowering agent use.

Distributions between the treatment groups for three of the four CEM variables were imbalanced: immunocompromised status (ASD= 0.174), documented COVID-19 vaccination within 9 months pre-index (ASD = 0.143), and an ED encounter within 7 days pre-index (ASD = 0.619). Other notably imbalanced covariates included COVID-19 diagnosis anytime pre-index (ASD = 1.016), eGFR category (ASD = 0.400), immunodeficiency (ASD = 0.309), past antiemetic use (ASD = 0.302), and present cyclosporine, everolimus, sirolimus, or tacrolimus use (ASD = 0.303).

Table.A2.3. Baseline Demographic Characteristics and Lifestyle Variables for Supplemental Analyses in the Unmatched Cohorts

							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Index date month							0.277
February	10	0.3%	4	0.2%	14	0.3%	
March	30	0.9%	15	0.8%	45	0.8%	
April	119	3.6%	170	8.5%	289	5.5%	
May	534	16.2%	401	20.1%	935	17.6%	
June	650	19.7%	498	24.9%	1,148	21.7%	
July	1,039	31.5%	516	25.8%	1,555	29.3%	
August	919	27.8%	394	19.7%	1,313	24.8%	
Demographics							**ASD**
Patient age							
Mean (SD), years	54 (17)		55 (16)		54 (17)		0.002
Age category							0.011
12-29 years	297	9.0%	154	7.7%	451	8.5%	
30-44 years	618	18.7%	406	20.3%	1,024	19.3%	
45-54 years	597	18.1%	347	17.4%	944	17.8%	
55-64 years	905	27.4%	566	28.3%	1,471	27.8%	
65-74 years	496	15.0%	318	15.9%	814	15.4%	
75-84 years	264	8.0%	154	7.7%	418	7.9%	
≥85 years	124	3.8%	53	2.7%	177	3.3%	
Female sex							0.005
Yes	2,044	61.9%	1,232	61.7%	3,276	61.8%	
Race							0.078
White	2,435	73.8%	1,419	71.0%	3,854	72.7%	
Black	409	12.4%	241	12.1%	650	12.3%	
Unknown	457	13.8%	338	16.9%	795	15.0%	

							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Lifestyle variables							**ASD**
Smoking status 6 months pre-index							0.027
Yes	215	6.5%	144	7.2%	359	6.8%	
Smoking status >6 months pre-index							0.023
Yes	615	18.6%	390	19.5%	1,005	19.0%	
Smoking ever pre-index							0.027
Yes	635	19.2%	406	20.3%	1,041	19.6%	
Inactivity							0.035
Yes	8	0.2%	9	0.5%	17	0.30%	

Abbreviations: ASD = absolute standardized differences; BEB = bebtelovimab; PAX = Paxlovid; SD = standard deviation.

Table.A2.4. Baseline CEM and COVID-19 Variables for Supplemental Analyses in the Unmatched Cohorts

CEM variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Immunocompromised status (University of Pittsburgh Medical Center [UPMC])							0.174
Yes	1,629	49.3%	1,159	58.0%	2,788	52.6%	
Age ≥ 65							0.011
Yes	884	26.8%	525	26.3%	1,409	26.6%	
COVID-19 vaccination within 9 months pre-index							0.143
Yes	1,482	44.9%	757	37.9%	2,239	42.3%	
ED encounter within 7 days pre-index							0.619
Yes	416	12.6%	767	38.4%	1,183	22.3%	
COVID-19 related variables							**ASD**
COVID-19 diagnosis anytime pre-index							1.016
Yes	2,048	62.0%	1,962	98.2%	4,010	75.7%	
COVID-19 positive test: within 7 days pre-index							0.115
Yes	345	10.5%	284	14.2%	629	11.9%	
COVID-19 positive test: >7 days pre-index							0.070
Yes	89	2.7%	79	4.0%	168	3.2%	
COVID-19 vaccine: past (>9 months pre-index)							0.070
Yes	1,352	41.0%	887	44.4%	2,239	42.3%	
COVID-19 MABs: present (within 6 months pre-index)							0.136
Yes	20	0.6%	44	2.2%	64	1.2%	
COVID-19 MABs: past (>6 months pre-index)							0.167
Yes	36	1.1%	72	3.6%	108	2.0%	
COVID-19 related symptoms							**ASD**
Anosmia and parosmia							0.043
Yes	9	0.3%	11	0.6%	20	0.4%	
Cough							0.155
Yes	17	0.5%	47	2.4%	64	1.2%	

CEM variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Fatigue							0.226
Yes	165	5.0%	222	11.1%	387	7.3%	
Fever or chills							0.259
Yes	233	7.1%	302	15.1%	535	10.1%	
Headache							0.078
Yes	8	0.2%	16	0.8%	24	0.5%	
Myalgia or joint pain							0.150
Yes	133	4.0%	150	7.5%	283	5.3%	
Nausea or vomiting							0.159
Yes	179	5.4%	192	9.6%	371	7.0%	
Dyspnea							0.236
Yes	138	4.2%	205	10.3%	343	6.5%	
Sore throat/pharyngitis							0.207
Yes	170	5.1%	214	10.7%	384	7.2%	
Diarrhea							0.075
Yes	42	1.3%	45	2.3%	87	1.6%	

Abbreviations: BEB = bebtelovimab; CEM = coarsened exact matching; COVID-19 = coronavirus disease 2019; PAX = paxlovid.

Table.A2.5. Baseline Clinical, Laboratory, and Comorbidity Variables for Supplemental Analyses in the Unmatched Cohorts

Clinical & laboratory variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
BMI category							0.051
Underweight: <18.5	28	0.8%	19	1.0%	47	0.9%	
Normal: 18.5-24	320	9.7%	161	8.1%	481	9.1%	
Overweight: 25-29	417	12.6%	254	12.7%	671	12.7%	
Obese: ≥30.0	769	23.3%	448	22.4%	1,217	23.0%	
Missing	1,767	53.5%	1,116	55.9%	2,883	54.4%	
MCQ eGFR: using last sCr pre-index							0.400
eGFR ≥90	1,707	51.7%	755	37.8%	2,462	46.5%	
eGFR 60-89	625	18.9%	274	13.7%	899	17.0%	
eGFR 30-59	118	3.6%	67	3.4%	185	3.5%	
eGFR <30	9	0.3%	35	1.8%	44	0.8%	
Missing	842	25.5%	867	43.4%	1,709	32.3%	
Blood pressure: category							0.003
Normotensive	112	3.4%	54	2.7%	166	3.1%	
Elevated	60	1.8%	36	1.8%	96	1.8%	
Stage1	114	3.5%	70	3.5%	184	3.5%	
Stage2	140	4.2%	90	4.5%	230	4.3%	
Missing	2,875	87.1%	1,748	87.5%	4,623	87.2%	
Oxygen saturation: category							0.038
≥95%	203	6.1%	126	6.3%	329	6.2%	
85-95%	18	0.5%	19	1.0%	37	0.7%	
<85%	2	0.1%	1	0.1%	3	0.1%	
Missing	3,078	93.2%	1,852	92.7%	4,930	93.0%	
Comorbidities							**ASD**
Autoimmune							

Clinical & laboratory variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Crohn's disease							0.069
Yes	56	1.7%	54	2.7%	110	2.1%	
Juvenile arthritis							0.005
Yes	9	0.3%	6	0.3%	15	0.3%	
Rheumatoid arthritis							0.106
Yes	192	5.8%	171	8.6%	363	6.9%	
Systemic lupus erythematosus							0.103
Yes	185	5.6%	164	8.2%	349	6.6%	
Ulcerative colitis							0.062
Yes	52	1.6%	49	2.5%	101	1.9%	
Blood Disorders							
Aplastic anemia							0.168
Yes	835	25.3%	657	32.9%	1,492	28.2%	
Immunodeficiency							0.309
Yes	186	5.6%	298	14.9%	484	9.1%	
Immunodeficiency (UPMC)							0.289
Yes	463	14.0%	508	25.4%	971	18.3%	
Sickle cell							0.016
Yes	25	0.8%	18	0.9%	43	0.8%	
Thalassemia							0.013
Yes	16	0.5%	8	0.4%	24	0.5%	
Circulatory							
Acute hemorrhagic cerebrovascular disease							0.042
Yes	144	4.4%	105	5.3%	249	4.7%	
Cerebral infarction							0.064
Yes	177	5.4%	138	6.9%	315	5.9%	
Other cerebrovascular disease							0.117

Clinical & laboratory variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Yes	363	11.0%	298	14.9%	661	12.5%	
Acute myocardial infarction							0.199
Yes	124	3.8%	170	8.5%	294	5.5%	
Coronary artery disease							0.240
Yes	393	11.9%	414	20.7%	807	15.2%	
Heart failure							0.275
Yes	316	9.6%	382	19.1%	698	13.2%	
Hypertension							0.091
Yes	1,716	52.0%	1,129	56.5%	2,845	53.7%	
Myocarditis or cardiomyopathy							0.189
Yes	192	5.8%	221	11.1%	413	7.8%	
Other heart condition							0.201
Yes	1,596	48.3%	1,165	58.3%	2,761	52.1%	
Peripheral vascular disease							0.130
Yes	533	16.1%	424	21.2%	957	18.1%	
Disability							
Cerebral palsy							0.022
Yes	29	0.9%	22	1.1%	51	1.0%	
Congenital malformation							0.167
Yes	491	14.9%	425	21.3%	916	17.3%	
Limitation of activities of daily living (ADL)							0.150
Yes	101	3.1%	124	6.2%	225	4.2%	
Neurodevelopmental disorders							0.030
Yes	311	9.4%	206	10.3%	517	9.8%	
Spinal cord injury							0.008
Yes	22	0.7%	12	0.6%	34	0.6%	
Endocrine							

Clinical & laboratory variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Obesity							0.228
Yes	1,622	49.1%	1,207	60.4%	2,829	53.4%	
Diabetes Type 1							0.079
Yes	165	5.0%	137	6.9%	302	5.7%	
Diabetes Type 2							0.223
Yes	869	26.3%	732	36.6%	1,601	30.2%	
Diabetes Type 1 or 2 (complicated)							0.200
Yes	656	19.9%	567	28.4%	1,223	23.1%	
Hepatic							
Alcoholic liver disease							0.100
Yes	127	3.8%	120	6.0%	247	4.7%	
Autoimmune hepatitis							0.034
Yes	7	0.2%	8	0.4%	15	0.3%	
Cirrhosis							0.099
Yes	58	1.8%	66	3.3%	124	2.3%	
Non-alcoholic fatty liver disease							0.196
Yes	438	13.3%	411	20.6%	849	16.0%	
Infectious							
Hepatitis B							0.093
Yes	25	0.8%	36	1.8%	61	1.2%	
Hepatitis C							0.030
Yes	71	2.2%	52	2.6%	123	2.3%	
HIV							0.006
Yes	47	1.4%	27	1.4%	74	1.4%	
Tuberculosis							0.012
Yes	20	0.6%	14	0.7%	34	0.6%	
Malignancy							

Clinical & laboratory variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Hematological oncology (except skin)							0.089
Yes	1,162	35.2%	789	39.5%	1,951	36.8%	
Metastatic							0.068
Yes	82	2.5%	73	3.7%	155	2.9%	
Radiation complication							0.066
Yes	111	3.4%	93	4.7%	204	3.8%	
Mental Health							
Anxiety and fear							0.127
Yes	1,559	47.2%	1,070	53.6%	2,629	49.6%	
Bipolar							0.080
Yes	201	6.1%	163	8.2%	364	6.9%	
Depression							0.141
Yes	1,283	38.9%	915	45.8%	2,198	41.5%	
Other mood disorder							0.000
Yes	114	3.5%	69	3.5%	183	3.5%	
Schizophrenia							0.072
Yes	73	2.2%	68	3.4%	141	2.7%	
Substance abuse							0.070
Yes	434	13.1%	312	15.6%	746	14.1%	
Suicidal ideation							0.046
Yes	119	3.6%	90	4.5%	209	3.9%	
Neurocognitive disorders							0.056
Yes	155	4.7%	119	6.0%	274	5.2%	
Pulmonary							
Alpha-1 antitrypsin deficiency							0.063
Yes	0	0.0%	4	0.2%	4	0.1%	
Asthma							0.027

Clinical & laboratory variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Yes	997	30.2%	628	31.4%	1,625	30.7%	
Bronchopulmonary dysplasia							0.045
Yes	0	0.0%	2	0.1%	2	0.0%	
COPD and bronchiectasis							0.110
Yes	665	20.1%	494	24.7%	1,159	21.9%	
Cystic fibrosis							0.056
Yes	10	0.3%	14	0.7%	24	0.5%	
Embolism							0.127
Yes	94	2.8%	107	5.4%	201	3.8%	
Hypertension							0.213
Yes	124	3.8%	178	8.9%	302	5.7%	
Interstitial disease							0.091
Yes	126	3.8%	115	5.8%	241	4.5%	
Renal							
CKD							0.197
Yes	463	14.0%	430	21.5%	893	16.9%	
ESRD							0.283
Yes	44	1.3%	138	6.9%	182	3.4%	
Transplant							
Organ stem cell							0.259
Yes	171	5.2%	249	12.5%	420	7.9%	
Graft versus host disease							0.008
Yes	6	0.2%	3	0.2%	9	0.2%	
Pregnancy variables							**ASD**
Pregnancy within 3 months pre-index							0.130
Yes	85	2.6%	101	5.1%	186	3.5%	
Pregnancy within 9 months pre-index							0.173

Clinical & laboratory variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Yes	105	3.2%	139	7.0%	244	4.6%	
Pregnancy ever pre-index							0.088
Yes	814	24.7%	570	28.5%	1,384	26.1%	

Abbreviations: ADL = activities of daily living; ASD = absolute standardized difference; BEB = bebtelovimab; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; MCQ = Mayo Clinic quadratic; PAX = paxlovid; sCr = serum creatinine; UPMC = University of Pittsburgh Medical Center.

Table.A2.6. Baseline Pharmacotherapy and Procedure-related Variables for Supplemental Analyses in the Unmatched Cohorts

Pharmacotherapy variables	PAX N=3,301		BEB N=1,998		Total N=5,299		ASD
	Frequency	%	Frequency	%	Frequency	%	
Antiemetics							
Present (within 7 days pre-index)							0.209
Yes	60	1.8%	116	5.8%	176	3.3%	
Past (>7 days pre-index)							0.302
Yes	1,246	37.7%	1,051	52.6%	2,297	43.4%	
Corticosteroids							
Beclomethasone: present (within 7 days pre-index)							0.025
Yes	1	0.0%	0	0.0%	1	0.0%	
Beclomethasone: past (>7 days pre-index)							0.028
Yes	101	3.1%	71	3.6%	172	3.2%	
Betamethasone: present (within 7 days pre-index)							0.037
Yes	9	0.3%	10	0.5%	19	0.4%	
Betamethasone: past (>7 days pre-index)							0.036
Yes	701	21.2%	395	19.8%	1,096	20.7%	
Budesonide: present (within 7 days pre-index)							0.052
Yes	23	0.7%	24	1.2%	47	0.9%	
Budesonide: past (>7 days pre-index)							0.013
Yes	404	12.2%	236	11.8%	640	12.1%	
Deflazacort: present (within 7 days pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Deflazacort: past (>7 days pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Dexamethasone: present (within 7 days pre-index)							0.148
Yes	52	1.6%	80	4.0%	132	2.5%	
Dexamethasone: past (>7 days pre-index)							0.165

Pharmacotherapy variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Yes	1,520	46.0%	1,084	54.3%	2,604	49.1%	
Hydrocortisone: present (within 7 days pre-index)							0.191
Yes	12	0.4%	54	2.7%	66	1.2%	
Hydrocortisone: past (>7 days pre-index)							0.001
Yes	887	26.9%	538	26.9%	1,425	26.9%	
Methylprednisolone: present (within 7 days pre-index)							0.189
Yes	59	1.8%	105	5.3%	164	3.1%	
Methylprednisolone: past (>7 days pre-index)							0.130
Yes	1,669	50.6%	1,139	57.0%	2,808	53.3%	
Prednisolone: present (within 7 days pre-index)							0.112
Yes	45	1.4%	60	3.0%	105	2.0%	
Prednisolone: past (>7 days pre-index)							0.076
Yes	1,346	40.8%	890	44.5%	2,236	42.2%	
Prednisone: present (within 7 days pre-index)							0.074
Yes	147	4.5%	122	6.1%	269	5.1%	
Prednisone: past (>7 days pre-index)							0.079
Yes	1,755	53.2%	1,141	57.1%	2,896	54.7%	
Triamcinolone: present (within 7 days pre-index)							0.067
Yes	20	0.6%	25	1.3%	45	0.8%	
Triamcinolone: past (>7 days pre-index)							0.058
Yes	1,375	41.7%	890	44.5%	2,265	42.7%	
Mometasone: present (within 7 days pre-index)							0.003
Yes	7	0.2%	4	0.2%	11	0.2%	
Mometasone: past (>7 days pre-index)							0.072
Yes	416	12.6%	206	10.3%	622	11.7%	
Fluticasone: present (within 7 days pre-index)							0.050
Yes	115	3.5%	89	4.5%	204	3.8%	

Pharmacotherapy variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Fluticasone: past (>7 days pre-index)							0.015
Yes	1,617	49.0%	964	48.2%	2,581	48.7%	
Anticoagulants							
Present (within 6 months pre-index)							0.259
Yes	131	4.0%	213	10.7%	344	6.5%	
Past (>6 months pre-index)							0.252
Yes	257	7.8%	317	15.9%	574	10.8%	
Antidiabetic							
Insulin: present (within 6 months pre-index)							0.121
Yes	215	6.5%	196	9.8%	411	7.8%	
Insulin: past (>6 months pre-index)							0.188
Yes	448	13.6%	412	20.6%	860	16.2%	
Other: present (within 6 months pre-index)							0.100
Yes	522	15.8%	392	19.6%	914	17.2%	
Other: past (>6 months pre-index)							0.157
Yes	677	20.5%	543	27.2%	1,220	23.0%	
Antihypertensives							
Present (within 6 months pre-index)							0.152
Yes	1,471	44.6%	1,042	52.2%	2,513	47.4%	
Past (>6 months pre-index)							0.222
Yes	1,916	58.0%	1,372	68.7%	3,288	62.0%	
Antiviral							
Chloroquine: present (within 3-6 months pre-index)							0.025
Yes	1	0.0%	0	0.0%	1	0.0%	
Chloroquine: past (>6 months pre-index)							0.021
Yes	8	0.2%	3	0.2%	11	0.2%	
Hydroxychloroquine sulfate: present (within 3-6 months pre-index)							0.072

Pharmacotherapy variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Yes	8	0.2%	15	0.8%	23	0.4%	
Hydroxychloroquine sulfate: past (>6 months pre-index)							0.073
Yes	78	2.4%	72	3.6%	150	2.8%	
Ivermectin: present (within 3-6 months pre-index)							0.010
Yes	1	0.0%	1	0.1%	2	0.0%	
Ivermectin: past (>6 months pre-index)							0.065
Yes	43	1.3%	43	2.2%	86	1.6%	
Molnupiravir: present (within 3-6 months pre-index)							0.025
Yes	1	0.0%	0	0.0%	1	0.0%	
Molnupiravir: past (>6 months pre-index)							0.040
Yes	1	0.0%	3	0.2%	4	0.1%	
Paxlovid: present (within 3-6 months pre-index)							0.065
Yes	7	0.2%	0	0.0%	7	0.1%	
Paxlovid: past (>6 months pre-index)							0.049
Yes	4	0.1%	0	0.0%	4	0.1%	
Remdesivir: present (within 3-6 months pre-index)							0.010
Yes	1	0.0%	1	0.1%	2	0.0%	
Remdesivir: past (>6 months pre-index)							0.062
Yes	24	0.7%	27	1.4%	51	1.0%	
Rituximab B-Cell							
Present (within 6 months pre-index)							0.024
Yes	39	1.2%	29	1.5%	68	1.3%	
Past (>6 months pre-index)							0.044
Yes	63	1.9%	51	2.6%	114	2.2%	
Bronchodilator							
SABA: present (within 6 months pre-index)							0.120
Yes	691	20.9%	520	26.0%	1,211	22.9%	

Pharmacotherapy variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
SABA: past (>6 months pre-index)							0.060
Yes	1,526	46.2%	984	49.2%	2,510	47.4%	
LABA: present (within 6 months pre-index)							0.044
Yes	268	8.1%	187	9.4%	455	8.6%	
LABA: past (>6 months pre-index)							0.010
Yes	569	17.2%	352	17.6%	921	17.4%	
ACH: present (within 6 months pre-index)							0.003
Yes	55	1.7%	34	1.7%	89	1.7%	
ACH: past (>6 months pre-index)							0.062
Yes	155	4.7%	122	6.1%	277	5.2%	
Theophylline: present (within 6 months pre-index)							0.049
Yes	4	0.1%	0	0.0%	4	0.1%	
Theophylline: past (>6 months pre-index)							0.035
Yes	8	0.2%	9	0.5%	17	0.3%	
CAR T-cell therapy							
Present (within 6 months pre-index)							0.035
Yes	2	0.1%	0	0.0%	2	0.0%	
Past (>6 months pre-index)							0.024
Yes	4	0.1%	1	0.10%	5	0.10%	
Convalescent Plasma							
Present (within 6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Past (>6 months pre-index)							0.071
Yes	0	0.0%	5	0.3%	5	0.1%	
Abatacept							
Present (within 6 months pre-index)							0.006
Yes	4	0.1%	2	0.1%	6	0.1%	

Pharmacotherapy variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Past (>6 months pre-index)							0.004
Yes	6	0.2%	4	0.2%	10	0.2%	
Anakinra							
Present (within 6 months pre-index)							0.055
Yes	0	0.0%	3	0.2%	3	0.1%	
Past (>6 months pre-index)							0.071
Yes	0	0.0%	5	0.3%	5	0.1%	
Tocilizumab							
Present (within 6 months pre-index)							0.029
Yes	3	0.1%	4	0.2%	7	0.1%	
Past (>6 months pre-index)							0.064
Yes	2	0.1%	7	0.4%	9	0.2%	
Immunosuppressive therapy							
Cyclosporine, everolimus, sirolimus, tacrolimus: present (within 6 months pre-index)							0.303
Yes	58	1.8%	166	8.3%	224	4.2%	
Cyclosporine, everolimus, sirolimus, tacrolimus: past (>6 months pre-index)							0.234
Yes	150	4.5%	214	10.7%	364	6.9%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: present (within 6 months pre-index)							0.230
Yes	74	2.2%	141	7.1%	215	4.1%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: past (>6 months pre-index)							0.234
Yes	174	5.3%	235	11.8%	409	7.7%	
Leukotrienes							
Present (within 6 months pre-index)							0.113
Yes	214	6.5%	191	9.6%	405	7.6%	
Past (>6 months pre-index)							0.087
Yes	547	16.6%	398	19.9%	945	17.8%	

Pharmacotherapy variables							**ASD**
	PAX N=3,301		**BEB N=1,998**		**Total N=5,299**		
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**	
Lipid-lowering							
Present (within 6 months pre-index)							0.117
Yes	1,172	35.5%	832	41.2%	1,995	37.6%	
Past (>6 months pre-index)							0.141
Yes	1,459	44.2%	1,023	51.2%	2,482	46.8%	
PDLs							
Present (within 6 months pre-index)							0.004
Yes	6	0.2%	4	0.2%	10	0.2%	
Past (>6 months pre-index)							0.039
Yes	11	0.3%	12	0.6%	23	0.4%	
TNFXs							
Present (within 6 months pre-index)							0.027
Yes	54	1.6%	40	2.0%	94	1.8%	
Past (>6 months pre-index)							0.068
Yes	71	2.2%	65	3.3%	136	2.6%	
Other Biologics							
Present (within 6 months pre-index)							0.047
Yes	39	1.2%	35	1.8%	74	1.4%	
Past (>6 months pre-index)							0.119
Yes	49	1.5%	66	3.3%	115	2.2%	
Procedure related variables							**ASD**
Radiation therapy							0.066
Yes	131	4.0%	107	5.4%	238	4.5%	
Transplant							
Organ							0.300
Yes	3	0.1%	91	4.6%	94	1.8%	

Pharmacotherapy variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Hematopoietic							0.015
Yes	6	0.2%	5	0.3%	11	0.2%	

Abbreviations: ACH = anticholinergic; ASD = absolute standardized difference; BEB = bebtelovimab; CAR-T = chimeric antigen receptor-modified T cell; LABA = long-acting beta-agonist; PAX = Paxlovid; PDL = programmed death ligand; SABA = short-acting beta-agonist; TNFX = tumor necrosis factor inhibitor.

Table.A2.7. Baseline Healthcare Utilization Variables for Supplemental Analyses in the Unmatched Cohorts

Healthcare utilization variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
Inpatient encounter: 31-365 days pre-index							0.268
Yes	552	16.7%	555	27.8%	1,107	20.9%	
Number inpatient encounters: 31-365 days pre-index							0.258
0	2,749	83.3%	1,443	72.2%	4,192	79.1%	
1-2	229	6.9%	213	10.7%	442	8.3%	
3-5	153	4.6%	146	7.3%	299	5.6%	
6+	170	5.1%	196	9.8%	366	6.9%	
ED encounter: 8-365 days pre-index							0.252
Yes	1,164	35.3%	951	47.6%	2,115	39.9%	
Number ED encounters: 8-365 days pre-index							0.289
0	2,137	64.7%	1,047	52.4%	3,184	60.1%	
1-2	829	25.1%	579	29.0%	1,408	26.6%	
3-5	243	7.4%	254	12.7%	497	9.4%	
6+	92	2.8%	118	5.9%	210	4.0%	
Outpatient encounter: 8-365 days pre-index							0.008
Yes	3,240	98.2%	1,959	98.0%	5,199	98.1%	
Number outpatient encounters: 8-365 days pre-index							0.126
0	61	1.8%	39	2.0%	100	1.9%	
1-5	414	12.5%	273	13.7%	687	13.0%	
6-11	560	17.0%	450	22.5%	1,010	19.1%	
12-23	980	29.7%	575	28.8%	1,555	29.3%	
24+	1,286	39.0%	661	33.1%	1,947	36.7%	
Outpatient encounter: 7 days pre-index							0.288
Yes	2,737	82.9%	1,417	70.9%	4,154	78.4%	
Number outpatient encounters: 7 days pre-index							0.196
0	564	17.1%	581	29.1%	1,145	21.6%	

Healthcare utilization variables							ASD
	PAX N=3,301		BEB N=1,998		Total N=5,299		
	Frequency	%	Frequency	%	Frequency	%	
1-2	2,302	69.7%	1,159	58.0%	3,461	65.3%	
3-5	415	12.6%	240	12.0%	655	12.4%	
6+	20	0.6%	18	0.9%	38	0.7%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; ED = early discontinuation; PAX = Paxlovid.

Table.A2.8, Table.A2.9, Table.A2.10, Table.A2.11, and Table.A2.12 display baseline variables for BEB-exposed and PAX-exposed patients in the matched cohorts. The mean age was 51 (SD 16) and 52 (SD 16) years in BEB-exposed and PAX-exposed patients, respectively. Similar to the unmatched cohorts, patients were primarily female (62.5% in both BEB and PAX) and White (71.5% in BEB and 73.1% in PAX). Common COVID-19 related characteristics included presence of a COVID-19 diagnosis anytime pre-index (95.5% in BEB and 96.9% in PAX) and documentation of a COVID-19 vaccine (43.2% in BEB and 40.3% in PAX). Common baseline comorbidities included aplastic anemia (26.0% in BEB and 26.3% in PAX), hypertension (50.3% in BEB and 50.0% in PAX), other heart conditions (48.9% in BEB and 47.3% in PAX), obesity (56.9% in both BEB and PAX), type 2 diabetes (29.1% in BEB and 28.8% in PAX), hematologic or solid malignancy except benign skin cancer (35.1% in BEB and 34.5% in PAX), anxiety and fear (50.7% in BEB and 52.4% in PAX), depression (44.9% in BEB and 46.5% in PAX), asthma (30.9% in BEB and 30.4% in PAX), and COPD and bronchiectasis (22.4% in BEB and 20.5% in PAX). Common baseline medications included past antiemetic use (45.7% in BEB and 45.5% in PAX), past dexamethasone use (52.0% in BEB and 51.9% in PAX), past methylprednisolone use (50.0% in BEB and 54.1% in PAX), past prednisolone use (38.8% in BEB and 41.6% in PAX), past prednisone use (54.5% in BEB and 55.6% in PAX), past triamcinolone use (39.5% in BEB and 41.1% in PAX), past fluticasone use (46.8% in BEB and 44.1% in PAX), past (60.9% in BEB and 58.8% in PAX) and present (46.1% in BEB and 44.4% in PAX) antihypertensive use, past SABA use (46.8% in BEB and 47.2% in PAX), and past (42.0% in BEB and 40.1% in PAX) and present (31.7% in BEB and 31.5% in PAX) lipid lowering agent use. Perfect balance was achieved for all four CEM variables: immunocompromised status, age ≥ 65 years, COVID-19 vaccine within 9 months pre-index, and an ED encounter within 7 days pre-index. Adequate balance was achieved for all pre-specified covariates except for eGFR category (ASD = 0.323) and organ transplant (ASD = 0.131), with the BEB cohort having more patients with missing eGFR data and more patients with a history of organ transplant.

Table.A2.8. Baseline Demographic Characteristics and Lifestyle Variables for Supplemental Analyses in the Matched Cohorts

	PAX N=750		BEB N=750		Total N=1,500		ASD
	Frequency	%	Frequency	%	Frequency	%	
Index date month							0.030
February	1	0.1%	1	0.1%	2	0.1%	
March	6	0.8%	7	0.9%	13	0.9%	
April	42	5.6%	34	4.5%	76	5.1%	
May	138	18.4%	137	18.3%	275	18.3%	
June	176	23.5%	170	22.7%	346	23.1%	
July	199	26.5%	213	28.4%	412	27.5%	
August	188	25.1%	188	25.1%	376	25.1%	
Demographics							**ASD**
Patient Age							0.023
Mean (SD)	52 (16)		51 (16)		51 (16)		
Age Category							0.025
12-29 years	77	10.3%	84	11.2%	161	10.7%	
30-44 years	167	22.3%	166	22.1%	333	22.2%	
45-54 years	147	19.6%	147	19.6%	294	19.6%	
55-64 years	225	30.0%	219	29.2%	444	29.6%	
65-74 years	72	9.6%	85	11.3%	157	10.5%	
75-84 years	52	6.9%	34	4.5%	86	5.7%	
≥85 years	10	1.3%	15	2.0%	25	1.7%	
Female sex							0.000
Yes	469	62.5%	469	62.5%	938	62.5%	
Race							0.034
White	548	73.1%	536	71.5%	1,084	72.3%	
Black	90	12.0%	95	12.7%	185	12.3%	
Unknown	112	14.9%	119	15.9%	231	15.4%	
Lifestyle variables							**ASD**

	PAX N=750		BEB N=750		Total N=1,500		ASD
	Frequency	%	Frequency	%	Frequency	%	
Smoking status 6 months pre-index							0.042
Yes	61	8.1%	70	9.3%	131	8.7%	
Smoking status >6 months pre-index							0.029
Yes	159	21.2%	168	22.4%	327	21.8%	
Smoking ever pre-index							0.025
Yes	167	22.3%	175	23.3%	342	22.8%	
Inactivity							0.052
Yes	1	0.1%	0	0.0%	1	0.1%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; PAX = Paxlovid; SD = standard deviation.

Table.A2.9. Baseline CEM and COVID-19 Variables for Supplemental Analyses in the Matched Cohorts

CEM variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Immunocompromised status (UPMC)							0.000
Yes	384	51.2%	384	51.2%	768	51.2%	
Age ≥65							0.000
Yes	134	17.9%	134	17.9%	268	17.9%	
COVID-19 vaccination within 9 months pre-index							0.000
Yes	259	34.5%	259	34.5%	518	34.5%	
ED encounter within 7 days pre-index							0.000
Yes	197	26.3%	197	26.3%	394	26.3%	
COVID-19 related variables							**ASD**
COVID-19 diagnosis anytime pre-index							0.077
Yes	727	96.9%	716	95.5%	1,443	96.2%	
COVID-19 positive test: within 7 days pre-index							0.032
Yes	91	12.1%	99	13.2%	190	12.7%	
COVID-19 positive test: >7 days pre-index							0.035
Yes	25	3.3%	30	4.0%	55	3.7%	
COVID-19 vaccine past (>9 months pre-index)							0.059
Yes	302	40.3%	324	43.2%	626	41.7%	
COVID-19 MABs present (within 6 months pre-index)							0.043
Yes	8	1.1%	5	0.7%	13	0.9%	
COVID-19 MABs past (>6 months pre-index)							0.033
Yes	18	2.4%	22	2.9%	40	2.7%	
COVID-19 related symptoms							**ASD**
Anosmia and parosmia							0.020
Yes	4	0.5%	3	0.4%	7	0.5%	
Cough							0.030
Yes	7	0.9%	5	0.7%	12	0.8%	

CEM variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Fatigue							0.020
Yes	56	7.5%	60	8.0%	116	7.7%	
Fever or chills							0.008
Yes	95	12.7%	97	12.9%	192	12.8%	
Headache							0.073
Yes	2	0.3%	6	0.8%	8	0.5%	
Myalgia or joint pain							0.027
Yes	47	6.3%	52	6.9%	99	6.6%	
Nausea or vomiting							0.046
Yes	75	10.0%	65	8.7%	140	9.3%	
Dyspnea							0.032
Yes	48	6.4%	54	7.2%	102	6.8%	
Sore throat/pharyngitis							0.000
Yes	65	8.7%	65	8.7%	130	8.7%	
Diarrhea							0.054
Yes	14	1.9%	9	1.2%	23	1.5%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; COVID-19 = coronavirus disease-2019; CEM = coarsened exact matching; ED = early discontinuation; MAB = monocolonal antibodies; PAX = paxlovid; UPMC = University of Pittsburgh Medical Center.

Table A2.10. Baseline Clinical, Laboratory, and Comorbidity Variables for Supplemental Analyses in the Matched Cohorts

Clinical and laboratory variables							**ASD**
	PAX N=750		**BEB N=750**		**Total N=1,500**		
BMI category							0.098
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**	
Underweight: <18.5	7	0.9%	6	0.8%	13	0.9%	
Normal: 18.5-24	80	10.7%	67	8.9%	147	9.8%	
Overweight: 25-29	92	12.3%	90	12.0%	182	12.1%	
Obese: ≥30.0	206	27.5%	177	23.6%	383	25.5%	
Missing	365	48.7%	410	54.7%	775	51.7%	
MCQ eGFR: using last sCr pre-index							0.323
eGFR ≥90	375	50.0%	292	38.9%	667	44.5%	
eGFR 60-89	108	14.4%	69	9.2%	177	11.8%	
eGFR 30-59	18	2.4%	16	2.1%	34	2.3%	
eGFR <30	4	0.5%	9	1.2%	13	0.9%	
Missing	245	32.7%	364	48.5%	609	40.6%	
Blood pressure: category							0.076
Normotensive	41	5.5%	24	3.2%	65	4.3%	
Elevated	22	2.9%	15	2.0%	37	2.5%	
Stage1	33	4.4%	31	4.1%	64	4.3%	
Stage2	49	6.5%	38	5.1%	87	5.8%	
Missing	605	80.7%	642	85.6%	1,247	83.1%	
Oxygen saturation: category							0.000
≥95%	53	7.1%	47	6.3%	100	6.7%	
85-95%	5	0.7%	7	0.9%	12	0.8%	
<85%	0	0.0%	0	0.0%	0	0.0%	
Missing	692	92.3%	696	92.8%	1,388	92.5%	
Comorbidities							**ASD**
Autoimmune							

Clinical and laboratory variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
Crohn's disease							0.033
Yes	22	2.9%	18	2.4%	40	2.7%	
Juvenile arthritis							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Rheumatoid arthritis							0.026
Yes	57	7.6%	52	6.9%	109	7.3%	
Systemic lupus erythematosus							0.016
Yes	55	7.3%	52	6.9%	107	7.1%	
Ulcerative colitis							0.027
Yes	15	2.0%	18	2.4%	33	2.2%	
Blood disorder							
Aplastic anemia							0.006
Yes	197	26.3%	195	26.0%	392	26.1%	
Immunodeficiency							0.014
Yes	63	8.4%	66	8.8%	129	8.6%	
Immunodeficiency (UPMC)							0.000
Yes	136	18.1%	136	18.1%	272	18.1%	
Sickle cell							0.030
Yes	7	0.9%	5	0.7%	12	0.8%	
Thalassemia							0.000
Yes	4	0.5%	4	0.5%	8	0.5%	
Circulatory							
Acute hemorrhagic cerebrovascular disease							0.028
Yes	27	3.6%	31	4.1%	58	3.9%	
Cerebral infarction							0.030
Yes	42	5.6%	37	4.9%	79	5.3%	
Other cerebrovascular disease							0.065
Yes	87	11.6%	72	9.6%	159	10.6%	
Acute myocardial infarction							0.017

Clinical and laboratory variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
Yes	44	5.9%	47	6.3%	91	6.1%	
Coronary artery disease							0.015
Yes	112	14.9%	116	15.5%	228	15.2%	
Heart failure							0.054
Yes	81	10.8%	94	12.5%	175	11.7%	
Hypertension							0.005
Yes	375	50.0%	377	50.3%	752	50.1%	
Myocarditis cardiomyopathy							0.000
Yes	53	7.1%	53	7.1%	106	7.1%	
Other heart condition							0.032
Yes	355	47.3%	367	48.9%	722	48.1%	
Peripheral vascular disease							0.041
Yes	120	16.0%	109	14.5%	229	15.3%	
Disability							
Cerebral palsy							0.047
Yes	7	0.9%	4	0.5%	11	0.7%	
Congenital malformation							0.074
Yes	142	18.9%	121	16.1%	263	17.5%	
Limitation of activities of daily living (ADL)							0.015
Yes	26	3.5%	24	3.2%	50	3.3%	
Neurodevelopmental disorders							0.017
Yes	84	11.2%	80	10.7%	164	10.9%	
Spinal cord injury							0.016
Yes	6	0.8%	5	0.7%	11	0.7%	
Endocrine							
Obesity							0.000
Yes	427	56.9%	427	56.9%	854	56.9%	
Diabetes Type 1							0.046
Yes	38	5.1%	46	6.1%	84	5.6%	

Clinical and laboratory variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
Diabetes Type 2							0.006
Yes	216	28.8%	218	29.1%	434	28.9%	
Diabetes Type 1 or 2 (complicated)							0.019
Yes	159	21.2%	165	22.0%	324	21.6%	
Hepatic							
Alcoholic liver disease							0.037
Yes	28	3.7%	23	3.1%	51	3.4%	
Autoimmune hepatitis							0.023
Yes	3	0.4%	2	0.3%	5	0.3%	
Cirrhosis							0.019
Yes	16	2.1%	14	1.9%	30	2.0%	
Non-alcoholic fatty liver disease							0.000
Yes	124	16.5%	124	16.5%	248	16.5%	
Infectious							
Hepatitis B							0.024
Yes	10	1.3%	8	1.1%	18	1.2%	
Hepatitis C							0.000
Yes	18	2.4%	18	2.4%	36	2.4%	
HIV							0.024
Yes	10	1.3%	8	1.1%	18	1.2%	
Tuberculosis							0.037
Yes	5	0.7%	3	0.4%	8	0.5%	
Malignancy							
Hematological oncology (except skin)							0.011
Yes	259	34.5%	263	35.1%	522	34.8%	
Metastatic							0.043
Yes	16	2.1%	21	2.8%	37	2.5%	
Radiation complication							0.013
Yes	32	4.3%	30	4.0%	62	4.1%	

Clinical and laboratory variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
Mental health							
Anxiety and fear							0.035
Yes	393	52.4%	380	50.7%	773	51.5%	
Bipolar							0.063
Yes	69	9.2%	56	7.5%	125	8.3%	
Depression							0.032
Yes	349	46.5%	337	44.9%	686	45.7%	
Other mood disorder							0.039
Yes	25	3.3%	20	2.7%	45	3.0%	
Schizophrenia							0.041
Yes	23	3.1%	18	2.4%	41	2.7%	
Substance abuse							0.000
Yes	111	14.8%	111	14.8%	222	14.8%	
Suicidal ideation							0.007
Yes	32	4.3%	33	4.4%	65	4.3%	
Neurocognitive disorders							0.006
Yes	41	5.5%	42	5.6%	83	5.5%	
Pulmonary							
Alpha-1 antitrypsin deficiency							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Asthma							0.012
Yes	228	30.4%	232	30.9%	460	30.7%	
Bronchopulmonary dysplasia							0.073
Yes	0	0.0%	2	0.3%	2	0.1%	
COPD and bronchiectasis							0.045
Yes	154	20.5%	168	22.4%	322	21.5%	
Cystic fibrosis							0.023
Yes	2	0.3%	3	0.4%	5	0.3%	
Embolism							0.035

Clinical and laboratory variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
Yes	31	4.1%	26	3.5%	57	3.8%	
Hypertension							0.024
Yes	37	4.9%	41	5.5%	78	5.2%	
Interstitial disease							0.013
Yes	31	4.1%	33	4.4%	64	4.3%	
Renal							
CKD							0.022
Yes	124	16.5%	118	15.7%	242	16.1%	
ESRD							0.056
Yes	18	2.4%	25	3.3%	43	2.9%	
Transplant							
Organ stem cell							0.079
Yes	38	5.1%	52	6.9%	90	6.0%	
Graft versus host disease							0.052
Yes	1	0.1%	0	0.0%	1	0.1%	
Pregnancy variables							**ASD**
Pregnancy within 3 months pre-index							0.047
Yes	27	3.6%	34	4.5%	61	4.1%	
Pregnancy within 9 months pre-index							0.072
Yes	33	4.4%	45	6.0%	78	5.2%	
Pregnancy ever pre-index							0.064
Yes	186	24.8%	207	27.6%	393	26.2%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; MCQ = Mayo Clinic quadratic; PAX = paxlovid; sCr = serum creatinine; SD = standard deviation; UPMC = University of Pittsburgh Medical Center.

Table.A2.11. Baseline Pharmacotherapy and Procedure-related Variables for Supplemental Analyses in the Matched Cohorts

Pharmacotherapy variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Antiemetics							
Present (within 7 days pre-index)							0.033
Yes	30	4.0%	35	4.7%	65	4.3%	
Past (>7 days pre-index)							0.005
Yes	341	45.5%	343	45.7%	684	45.6%	
Corticosteroids							
Beclomethasone: present (within 7 days pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Beclomethasone: past (>7 days pre-index)							0.061
Yes	20	2.7%	28	3.7%	48	3.2%	
Betamethasone: present (within 7 days pre-index)							0.042
Yes	4	0.5%	2	0.3%	6	0.4%	
Betamethasone: past (>7 days pre-index)							0.023
Yes	154	20.5%	161	21.5%	315	21.0%	
Budesonide: present (within 7 days pre-index)							0.028
Yes	6	0.8%	8	1.1%	14	0.9%	
Budesonide: past (>7 days pre-index)							0.037
Yes	83	11.1%	92	12.3%	175	11.7%	
Deflazacort: present (within 7 days pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Deflazacort: past (>7 days pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Dexamethasone: present (within 7 days pre-index)							0.031
Yes	21	2.8%	25	3.3%	46	3.1%	
Dexamethasone: past (>7 days pre-index)							0.003
Yes	389	51.9%	390	52.0%	779	51.9%	

Pharmacotherapy variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Hydrocortisone: present (within 7 days pre-index)							0.013
Yes	9	1.2%	8	1.1%	17	1.1%	
Hydrocortisone: past (>7 days pre-index)							0.009
Yes	175	23.3%	178	23.7%	353	23.5%	
Methylprednisolone: present (within 7 days pre-index)							0.009
Yes	18	2.4%	19	2.5%	37	2.5%	
Methylprednisolone: past (>7 days pre-index)							0.083
Yes	406	54.1%	375	50.0%	781	52.1%	
Prednisolone: present (within 7 days pre-index)							0.022
Yes	10	1.3%	12	1.6%	22	1.5%	
Prednisolone: past (>7 days pre-index)							0.057
Yes	312	41.6%	291	38.8%	603	40.2%	
Prednisone: present (within 7 days pre-index)							0.039
Yes	42	5.6%	49	6.5%	91	6.1%	
Prednisone: past (>7 days pre-index)							0.021
Yes	417	55.6%	409	54.5%	826	55.1%	
Triamcinolone: present (within 7 days pre-index)							0.013
Yes	8	1.1%	7	0.9%	15	1.0%	
Triamcinolone: past (>7 days pre-index)							0.033
Yes	308	41.1%	296	39.5%	604	40.3%	
Mometasone: present (within 7 days pre-index)							0.030
Yes	1	0.1%	2	0.3%	3	0.2%	
Mometasone: past (>7 days pre-index)							0.027
Yes	76	10.1%	70	9.3%	146	9.7%	
Fluticasone: present (within 7 days pre-index)							0.097
Yes	41	5.5%	26	3.5%	67	4.5%	
Fluticasone: past (>7 days pre-index)							0.054
Yes	331	44.1%	351	46.8%	682	45.5%	

Pharmacotherapy variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Anticoagulants							
Present (within 6 months pre-index)							0.023
Yes	45	6.0%	41	5.5%	86	5.7%	
Past (>6 months pre-index)							0.014
Yes	71	9.5%	68	9.1%	139	9.3%	
Antidiabetic							
Insulin: present (within 6 months pre-index)							0.015
Yes	54	7.2%	57	7.6%	111	7.4%	
Insulin: past (>6 months pre-index)							0.000
Yes	108	14.4%	108	14.4%	216	14.4%	
Other: present (within 6 months pre-index)							0.004
Yes	115	15.3%	116	15.5%	231	15.4%	
Other: past (>6 months pre-index)							0.000
Yes	163	21.7%	163	21.7%	326	21.7%	
Antihypertensives							
Present (within 6 months pre-index)							0.035
Yes	333	44.4%	346	46.1%	679	45.3%	
Past (>6 months pre-index)							0.044
Yes	441	58.8%	457	60.9%	898	59.9%	
Antivirals							
Chloroquine: present (within 3-6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Chloroquine: past (>6 months pre-index)							0.052
Yes	0	0.0%	1	0.1%	1	0.1%	
Hydroxychloroquine sulfate: present (within 3-6 months pre-index)							0.023
Yes	2	0.3%	3	0.4%	5	0.3%	
Hydroxychloroquine sulfate: past (>6 months pre-index)							0.024
Yes	23	3.1%	20	2.7%	43	2.9%	

Pharmacotherapy variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Ivermectin: present (within 3-6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Ivermectin: past (>6 months pre-index)							0.041
Yes	11	1.5%	15	2.0%	26	1.7%	
Molnupiravir: present (within 3-6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Molnupiravir: past (>6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Paxlovid: present (within 3-6 months pre-index)							0.090
Yes	3	0.4%	0	0.0%	3	0.2%	
Paxlovid: past (>6 months pre-index)							0.052
Yes	1	0.1%	0	0.0%	1	0.1%	
Remdesivir: present (within 3-6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Remdesivir: past (>6 months pre-index)							0.036
Yes	8	1.1%	11	1.5%	19	1.3%	
Rituximab B-cell							
Present (within 6 months pre-index)							0.034
Yes	12	1.6%	9	1.2%	21	1.4%	
Past (>6 months pre-index)							0.029
Yes	16	2.1%	13	1.7%	29	1.9%	
Bronchodilator							
SABA: present (within 6 months pre-index)							0.050
Yes	189	25.2%	173	23.1%	362	24.1%	
SABA: past (>6 months pre-index)							0.008
Yes	354	47.2%	351	46.8%	705	47.0%	
LABA: present (within 6 months pre-index)							0.025
Yes	61	8.1%	56	7.5%	117	7.8%	

Pharmacotherapy variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
LABA: past (>6 months pre-index)							0.029
Yes	113	15.1%	121	16.1%	234	15.6%	
ACH: present (within 6 months pre-index)							0.010
Yes	13	1.7%	14	1.9%	27	1.8%	
ACH: past (>6 months pre-index)							0.006
Yes	36	4.8%	35	4.7%	71	4.7%	
Theophylline: present (within 6 months pre-index)							0.052
Yes	1	0.1%	0	0.0%	1	0.1%	
Theophylline: past (>6 months pre-index)							0.000
Yes	2	0.3%	2	0.3%	4	0.3%	
CAR T-cell therapy							
Present (within 6 months pre-index)							0.052
Yes	1	0.1%	0	0.0%	1	0.1%	
Past (>6 months pre-index)							0.073
Yes	2	0.3%	0	0.0%	2	0.1%	
Convalescent plasma							
Present (within 6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	
Past (>6 months pre-index)							0.052
Yes	0	0.0%	1	0.1%	1	0.1%	
Abatacept							
Present (within 6 months pre-index)							0.090
Yes	3	0.4%	0	0.0%	3	0.2%	
Past (>6 months pre-index)							0.069
Yes	4	0.5%	1	0.1%	5	0.3%	
Anakinra							
Present (within 6 months pre-index)							0.000
Yes	0	0.0%	0	0.0%	0	0.0%	

Pharmacotherapy variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Past (>6 months pre-index)							0.052
Yes	0	0.0%	1	0.1%	1	0.1%	
Tocilizumab							
Present (within 6 months pre-index)							0.000
Yes	1	0.1%	1	0.1%	2	0.1%	
Past (>6 months pre-index)							0.052
Yes	0	0.0%	1	0.1%	1	0.1%	
Immunosuppressive therapy							
Cyclosporine, everolimus, sirolimus, tacrolimus: present (within 6 months pre-index)							0.038
Yes	21	2.8%	26	3.5%	47	3.1%	
Cyclosporine, everolimus, sirolimus, tacrolimus: past (>6 months pre-index)							0.011
Yes	48	6.4%	46	6.1%	94	6.3%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: present (within 6 months pre-index)							0.029
Yes	28	3.7%	24	3.2%	52	3.5%	
Cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate, mycophenolate mofetil, sulfasalazine: past (>6 months pre-index)							0.011
Yes	52	6.9%	50	6.7%	102	6.8%	
Leukotrienes							
Present (within 6 months pre-index)							0.010
Yes	60	8.0%	62	8.3%	122	8.1%	
Past (>6 months pre-index)							0.028
Yes	134	17.9%	142	18.9%	276	18.4%	
Lipid-lowering							
Present (within 6 months pre-index)							0.006
Yes	236	31.5%	238	31.7%	474	31.6%	
Past (>6 months pre-index)							0.038
Yes	301	40.1%	315	42.0%	616	41.1%	

Pharmacotherapy variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
PDLs							
Present (within 6 months pre-index)							0.052
Yes	1	0.1%	0	0.0%	1	0.1%	
Past (>6 months pre-index)							0.030
Yes	1	0.1%	2	0.3%	3	0.2%	
TNFXs							
Present (within 6 months pre-index)							0.084
Yes	20	2.7%	11	1.5%	31	2.1%	
Past (>6 months pre-index)							0.023
Yes	24	3.2%	21	2.8%	45	3.0%	
Other Biologics							
Present (within 6 months pre-index)							0.038
Yes	7	0.9%	10	1.3%	17	1.1%	
Past (>6 months pre-index)							0.011
Yes	11	1.5%	12	1.6%	23	1.5%	
Procedure related variables							**ASD**
Radiation therapy							0.014
Yes	31	4.1%	29	3.9%	60	4.0%	
Transplant							
Organ							0.131
Yes	1	0.1%	9	1.2%	10	0.7%	
Hematopoietic							0.052
Yes	1	0.1%	0	0.0%	1	0.1%	

Abbreviations: ACH = anticholinergic; ASD = absolute standardized difference; BEB = bebtelovimab; CAR-T = chimeric antigen receptor-modified T cell; LABA = long-acting beta-agonist; PAX = paxlovid; SABA = short-acting beta-agonist; TNFX = tumor necrosis factor inhibitor.

Table.A2.12. Baseline Healthcare Utilization Variables for Supplemental Analyses in the Matched Cohorts

Healthcare utilization variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
Inpatient encounter: 31-365 days pre-index							0.024
Yes	143	19.1%	150	20.0%	293	19.5%	
Number inpatient encounters: 31-365 days pre-index							0.002
0	607	80.9%	600	80.0%	1,207	80.5%	
1-2	59	7.9%	69	9.2%	128	8.5%	
3-5	33	4.4%	35	4.7%	68	4.5%	
6+	51	6.8%	46	6.1%	97	6.5%	
ED encounter: 8-365 days pre-index							0.024
Yes	314	41.9%	323	43.1%	637	42.5%	
Number ED encounters: 8-365 days pre-index							0.011
0	436	58.1%	427	56.9%	863	57.5%	
1-2	208	27.7%	220	29.3%	428	28.5%	
3-5	74	9.9%	70	9.3%	144	9.6%	
6+	32	4.3%	33	4.4%	65	4.3%	
Outpatient encounter: 8-365 days pre-index							0.025
Yes	732	97.6%	729	97.2%	1,461	97.4%	
Number outpatient encounters: 8-365 days pre-index							0.006
0	18	2.4%	21	2.8%	39	2.6%	
1-5	121	16.1%	124	16.5%	245	16.3%	
6-11	170	22.7%	161	21.5%	331	22.1%	
12-23	218	29.1%	210	28.0%	428	28.5%	
24+	223	29.7%	234	31.2%	457	30.5%	
Outpatient encounter: 7 days pre-index							0.048
Yes	589	78.5%	574	76.5%	1,163	77.5%	
Number outpatient encounters: 7 days pre-index							0.011
0	161	21.5%	176	23.5%	337	22.5%	

Healthcare utilization variables							ASD
	PAX N=750		BEB N=750		Total N=1,500		
	Frequency	%	Frequency	%	Frequency	%	
1-2	511	68.1%	488	65.1%	999	66.6%	
3-5	74	9.9%	80	10.7%	154	10.3%	
6+	4	0.5%	6	0.8%	10	0.7%	

Abbreviations: ASD = absolute standardized difference; BEB = bebtelovimab; ED = early discontinuation; PAX = Paxlovid.

16.4.3 A2.4.3. Outcome Data

16.4.3.1 A2.4.3.1. COVID-19 Treatments and Insurance Disenrollment During Follow-up

Administration of COVID-19 treatments within 30 days after the index date was uncommon in both the unmatched and matched cohorts (Table.A2.13). A subsequent BEB dose was administered in 12.4% and 10.4% of BEB-exposed patients in the unmatched and matched cohorts, respectively. A subsequent PAX dose was dispensed in 6.7% and 8.3% of PAX-exposed patients in the unmatched and matched cohorts, respectively. These frequencies are higher than observed in the cohorts formed using EHR data alone, in which 4.46% of matched BEB-exposed patients had an additional BEB administration documented and 2.09% of PAX-exposed patients filled an additional PAX prescription. Insurance disenrollment during follow-up was uncommon in both the unmatched and matched cohorts.

Table.A2.13. COVID-19 Treatment Administration and Insurance Disenrollment during Follow-up for Supplemental Analyses in the Unmatched and Matched Cohorts

	Unmatched Cohorts						Matched Cohorts					
	PAX N = 3,301		BEB N = 1,998		Total N = 5,299		PAX N = 750		BEB N = 750		Total N = 1,500	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
COVID-19 treatment												
Convalescent plasma	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Bamlanivimab/ etesevimab	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Bebtelovimab	9	0.3%	248	12.4%	257	4.8%	2	0.3%	78	10.4%	80	5.3%
Casirivimab/ imdevimab	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Sotrovimab	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Tixagevimab/ cilgavimab	3	0.1%	2	0.1%	5	0.1%	0	0.0%	1	0.1%	1	0.1%
Tocilizumab	0	0.0%	1	0.1%	1	0.0%	0	0.0%	0	0.0%	0	0.0%
Hydroxychloro-quine	3	0.1%	6	0.3%	9	0.2%	1	0.1%	1	0.1%	2	0.1%
Ivermectin	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Molnupiravir	4	0.1%	4	0.2%	8	0.2%	0	0.0%	0	0.0%	0	0.0%
Nirmatrelvir/ ritonavir	63	1.9%	0	0.0%	63	1.2%	14	1.9%	0	0.0%	14	0.9%
Nirmatrelvir	220	6.7%	21	1.1%	241	4.5%	62	8.3%	5	0.7%	67	4.5%
Ritonavir	64	1.9%	0	0.0%	64	1.2%	14	1.9%	0	0.0%	14	0.9%
Remdesivir	14	0.4%	9	0.5%	23	0.4%	4	0.5%	1	0.1%	5	0.3%
Insurance disenrollment	36	1.1%	11	0.6%	47	0.9%	9	1.2%	4	0.5%	12	0.9%

Abbreviations: BEB = bebtelovimab; COVID-19 = coronavirus disease-2019; PAX = paxlovid.

16.4.3.2 A2.4.3.2 Number of Events and Cumulative Incidence for Primary and Secondary Outcomes

In the unmatched cohorts, the cumulative incidence of hospitalization or death was 5.91% (95% CI: 4.91%, 7.03%) among BEB-treated patients and 3.06% (95% CI: 2.50%, 3.71%) among PAX-treated patients (Table.A2.14). For secondary outcomes, the cumulative incidence of hospitalizations was 5.91% (95% CI: 4.91%, 7.03%) and 3.03% (95% CI: 2.47%, 3.67%) for BEB and PAX, respectively. The cumulative incidence of ED visits was 11.56% (95% CI: 10.19%, 13.05%) and 6.60% (95% CI: 5.78%, 7.51%) for BEB and PAX, respectively. The cumulative incidence of death was 0.100% (95% CI: 0.012%, 0.361%) and 0.061% (95% CI: 0.007%, 0.219%) in BEB and PAX, respectively.

In the matched cohorts, the cumulative incidence of hospitalization or death was 2.80% (95% CI: 1.74%, 4.25%) and 3.60% (95% CI: 2.39%, 5.19%) in BEB and PAX, respectively. Among secondary outcomes, the cumulative incidence of hospitalizations was 2.80% (95% CI: 1.74%, 4.25%) and 3.60% (95% CI: 2.39%, 5.19%) for BEB and PAX, respectively. The cumulative incidence of ED visits among BEB and PAX-treated patients was 8.40% (95% CI: 6.51%, 10.62%) and 8.27% (95% CI: 6.40%, 10.47%), respectively. The cumulative incidence of death was 0.133% (95% CI: 0.003%, 0.741%) and 0.000% (95% CI: 0.000%, 0.491%) for BEB and PAX, respectively. Compared to the matched cohorts in the TriNetX Dataworks USA Network (without linked claims), the cumulative incidence of all outcomes increased except for death.

Table.A2.14. Cumulative Incidence for Primary and Secondary Outcomes for Supplemental Analyses in the Unmatched and Matched Cohorts

Outcome	Exposure	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL
Unmatched cohorts						
Primary analysis						
Hospitalization OR Death	BEB	1,998	118	5.91%	4.91%	7.03%
	PAX	3,301	101	3.06%	2.50%	3.71%
Secondary analyses						
Hospitalization	BEB	1,998	118	5.91%	4.91%	7.03%
	PAX	3,301	100	3.03%	2.47%	3.67%
ED visit	BEB	1,998	231	11.56%	10.19%	13.05%
	PAX	3,301	218	6.60%	5.78%	7.51%
Death	BEB	1,998	2	0.100%	0.012%	0.361%
	PAX	3,301	2	0.061%	0.007%	0.219%
Matched cohorts						
Primary analysis						
Hospitalization OR Death	BEB	750	21	2.80%	1.74%	4.25%
	PAX	750	27	3.60%	2.39%	5.19%
Secondary analyses						
Hospitalization	BEB	750	21	2.80%	1.74%	4.25%
	PAX	750	27	3.60%	2.39%	5.19%

ED visit	BEB	750	63	8.40%	6.51%	10.62%
	PAX	750	62	8.27%	6.40%	10.47%
Death	BEB	750	1	0.133%	0.003%	0.741%
	PAX	750	0	0.000%	0.000%	0.491%

Abbreviations: 95% LCL=95% confidence interval lower confidence limit; 95% UCL=95% confidence interval upper confidence limit; BEB=bebtelovimab; PAX=Paxlovid.

16.4.4 A2.4.4. Main Results

RDs for primary and secondary outcomes in the unmatched and matched cohorts are presented in Table.A2.15. In the matched cohorts, BEB (compared to PAX) was not associated with an increased risk of hospitalization or death; the RD was -0.80% (95% LCL -2.58%, 95% UCL 0.98%). Additionally, BEB (compared to PAX) was not associated with increased risks of hospitalization (RD -0.80%; 95% LCL -2.58%, 95% UCL 0.98%), an ED visit (RD 0.13%; 95% LCL -2.66%, 95% UCL 2.93%), or death (RD 0.133%; 95% LCL -0.128%, 95% UCL 0.394%).

Table.A2.15. Risk differences for primary and secondary outcomes for supplemental analyses in the unmatched and matched cohorts

Outcome	Exposure	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
Unmatched cohorts				
Primary analysis				
Hospitalization OR Death	BEB	2.85%	1.66%	4.04%
	PAX			
Secondary analyses				
Hospitalization	BEB	2.88%	1.69%	4.06%
	PAX			
ED visit	BEB	4.96%	3.32%	6.60%
	PAX			
Death	BEB	0.040%	-0.123%	0.202%
	PAX			
Matched cohorts				
Primary analysis				
Hospitalization OR Death	BEB	-0.80%	-2.58%	0.98%
	PAX			
Secondary analyses				
Hospitalization	BEB	-0.80%	-2.58%	0.98%
	PAX			
ED visit	BEB	0.13%	-2.66%	2.93%
	PAX			
Death	BEB	0.133%	-0.128%	0.394%
	PAX			

Outcome	Exposure	Risk Difference (RD, PAX = reference)		
		RD	95% LCL	95% UCL

Abbreviations: 95% LCL=95% confidence interval lower confidence limit; 95% UCL=95% confidence interval upper confidence limit; BEB=bebtelovimab; PAX=Paxlovid.
Note: For the Risk Difference analyses, PAX is the reference category.

16.4.5 A2.4.5. Other Analyses

16.4.5.1 A2.4.5.1. Subgroup Analyses

Results from subgroup analyses for the matched cohorts are displayed in Table.A2.16. There was no evidence of effect modification by subgroups for age ≥ 65 years, immunocompromised status, COVID-19 vaccine, or ED visit within 7 days pre-index. There was an increased risk of an ED visit with BEB compared to PAX in the age ≥ 65 years subgroup, however the low number of events (10 in BEB and one in PAX) and wide 95% confidence interval of the effect estimate (RD 6.72%; 95% LCL 2.03%, 95% UCL 11.40%) indicate limited precision.

Table.A2.16. Results from Subgroup Analyses in the Matched Cohorts for Supplemental Analyses

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
Subgroup: Age ≥ 65 years (yes/no)										
Primary analysis										
Hospitalization OR Death	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	134	4	2.99%	0.82%	7.47%	-5.22%	-10.69%	0.24%
	PAX		134	11	8.21%	4.17%	14.21%			
	BEB	Condition Absent	616	17	2.76%	1.62%	4.38%	0.16%	-1.64%	1.97%
	PAX		616	16	2.60%	1.49%	4.18%			
Secondary analyses										
Hospitalization	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	134	4	2.99%	0.82%	7.47%	-5.22%	-10.69%	0.24%
	PAX		134	11	8.21%	4.17%	14.21%			
	BEB	Condition Absent	616	17	2.76%	1.62%	4.38%	0.16%	-1.64%	1.97%
	PAX		616	16	2.60%	1.49%	4.18%			
ED visit	BEB	All	750	63	8.40%	6.51%	10.62%	0.13%	-2.66%	2.93%
	PAX		750	62	8.27%	6.40%	10.47%			
	BEB	Condition Present	134	10	7.46%	3.64%	13.30%	6.72%	2.03%	11.40%
	PAX		134	1	0.75%	0.02%	4.09%			
	BEB	Condition Absent	616	53	8.60%	6.51%	11.10%	-1.30%	-4.53%	1.94%
	PAX		616	61	9.90%	7.66%	12.54%			
Death	BEB	All	750	1	0.13%	0.00%	0.74%	0.133%	-0.128%	0.394%
	PAX		750	0	0.00%	0.00%	0.49%			
	BEB	Condition Present	134	0	0.00%	0.00%	2.72%	0.000%	0.000%	0.000%
	PAX		134	0	0.00%	0.00%	2.72%			
	BEB		616	1	0.16%	0.00%	0.90%	0.162%	-0.156%	0.480%

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
	PAX	Condition Absent	616	0	0.00%	0.00%	0.60%			
Subgroup: Immunocompromised (yes/no)										
Primary analysis										
Hospitalization OR Death	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	384	18	4.69%	2.80%	7.31%	0.52%	-2.39%	3.43%
	PAX		384	16	4.17%	2.40%	6.68%			
	BEB	Condition Absent	366	3	0.82%	0.17%	2.38%	-2.19%	-4.16%	-0.21%
	PAX		366	11	3.01%	1.51%	5.31%			
Secondary analyses										
Hospitalization	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	384	18	4.69%	2.80%	7.31%	0.52%	-2.39%	3.43%
	PAX		384	16	4.17%	2.40%	6.68%			
	BEB	Condition Absent	366	3	0.82%	0.17%	2.38%	-2.19%	-4.16%	-0.21%
	PAX		366	11	3.01%	1.51%	5.31%			
ED visit	BEB	All	750	63	8.40%	6.51%	10.62%	0.13%	-2.66%	2.93%
	PAX		750	62	8.27%	6.40%	10.47%			
	BEB	Condition Present	384	28	7.29%	4.90%	10.37%	-0.26%	-3.97%	3.45%
	PAX		384	29	7.55%	5.12%	10.67%			
	BEB	Condition Absent	366	35	9.56%	6.75%	13.05%	0.55%	-3.66%	4.75%
	PAX		366	33	9.02%	6.29%	12.43%			
Death	BEB	All	750	1	0.13%	0.00%	0.74%	0.133%	-0.128%	0.394%
	PAX		750	0	0.00%	0.00%	0.49%			
	BEB	Condition Present	384	1	0.26%	0.01%	1.44%	0.260%	-0.249%	0.770%
	PAX		384	0	0.00%	0.00%	0.96%			

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
	BEB	Condition Absent	366	0	0.00%	0.00%	1.00%	0.000%	0.000%	0.000%
	PAX		366	0	0.00%	0.00%	1.00%			
Subgroup: COVID-19 vaccine (yes/undetermined)										
Primary analysis										
Hospitalization OR Death	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	259	9	3.47%	1.60%	6.49%	0.77%	-2.21%	3.75%
	PAX		259	7	2.70%	1.09%	5.49%			
	BEB	Condition Absent	491	12	2.44%	1.27%	4.23%	-1.63%	-3.85%	0.59%
	PAX		491	20	4.07%	2.51%	6.22%			
Secondary analyses										
Hospitalization	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	259	9	3.47%	1.60%	6.49%	0.77%	-2.21%	3.75%
	PAX		259	7	2.70%	1.09%	5.49%			
	BEB	Condition Absent	491	12	2.44%	1.27%	4.23%	-1.63%	-3.85%	0.59%
	PAX		491	20	4.07%	2.51%	6.22%			
ED visit	BEB	All	750	63	8.40%	6.51%	10.62%	0.13%	-2.66%	2.93%
	PAX		750	62	8.27%	6.40%	10.47%			
	BEB	Condition Present	259	10	3.86%	1.87%	6.99%	-0.77%	-4.24%	2.70%
	PAX		259	12	4.63%	2.42%	7.95%			
	BEB	Condition Absent	491	53	10.79%	8.19%	13.88%	0.61%	-3.22%	4.44%
	PAX		491	50	10.18%	7.65%	13.20%			
Death	BEB	All	750	1	0.13%	0.00%	0.74%	0.133%	-0.128%	0.394%
	PAX		750	0	0.00%	0.00%	0.49%			
	BEB	Condition Present	259	1	0.39%	0.01%	2.13%	0.386%	-0.369%	1.141%
	PAX		259	0	0.00%	0.00%	1.41%			

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
	BEB	Condition Absent	491	0	0.00%	0.00%	0.75%	0.000%	0.000%	0.000%
	PAX		491	0	0.00%	0.00%	0.75%			
Subgroup: Emergency department visit within 7 days pre-index (yes/no)										
Primary analysis										
Hospitalization OR Death	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	197	5	2.54%	0.83%	5.82%	-2.03%	-5.68%	1.62%
	PAX		197	9	4.57%	2.11%	8.50%			
	BEB	Condition Absent	553	16	2.89%	1.66%	4.66%	-0.36%	-2.40%	1.67%
	PAX		553	18	3.25%	1.94%	5.10%			
Secondary analyses										
Hospitalization	BEB	All	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
	PAX		750	27	3.60%	2.39%	5.19%			
	BEB	Condition Present	197	5	2.54%	0.83%	5.82%	-2.03%	-5.68%	1.62%
	PAX		197	9	4.57%	2.11%	8.50%			
	BEB	Condition Absent	553	16	2.89%	1.66%	4.66%	-0.36%	-2.40%	1.67%
	PAX		553	18	3.25%	1.94%	5.10%			
ED visit	BEB	All	750	63	8.40%	6.51%	10.62%	0.13%	-2.66%	2.93%
	PAX		750	62	8.27%	6.40%	10.47%			
	BEB	Condition Present	197	41	20.81%	15.37%	27.16%	4.06%	-3.64%	11.76%
	PAX		197	33	16.75%	11.82%	22.71%			
	BEB	Condition Absent	553	22	3.98%	2.51%	5.96%	-1.27%	-3.74%	1.21%
	PAX		553	29	5.24%	3.54%	7.44%			
Death	BEB	All	750	1	0.13%	0.00%	0.74%	0.133%	-0.128%	0.394%
	PAX		750	0	0.00%	0.00%	0.49%			
	BEB	Condition Present	197	0	0.00%	0.00%	1.86%	0.000%	0.000%	0.000%
	PAX		197	0	0.00%	0.00%	1.86%			

Outcome	Exposure	Matched Pairs Analyzed	Number of Patients Analyzed	Number of Patients with Event	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference)		
								RD	95% LCL	95% UCL
	BEB	Condition Absent	553	1	0.18%	0.00%	1.00%	0.181%	-0.173%	0.535%
	PAX		553	0	0.00%	0.00%	0.66%			

Abbreviations: 95% LCL=95% confidence interval lower confidence limit; 95% UCL=95% confidence interval upper confidence limit; BEB=bebtelovimab; PAX=Paxlovid.

16.4.5.2 A2.4.5.2. Sensitivity Analyses

16.4.5.2.1 A2.4.5.2.1. Results of Sensitivity Analyses to Mitigate Potential Channeling Bias

In these sensitivity analyses, outcomes that occurred on the first day of follow-up were excluded. Results for the matched cohorts are presented in Table.A2.17. For convenience, the table includes results using the primary analytic approach and results pertaining to this sensitivity analysis.

For the primary outcome (hospitalization or death within 30 days post-index), two events occurred on the first day of follow-up (i.e., Day 1) for patients treated with BEB (number of Day 1 events=1) and PAX (number of Day 1 events =1). While this resulted in a small reduction in the cumulative incidence of the primary outcome in both groups, the RD (and 95% CI) was essentially unchanged compared to the RD (95% CI) using the primary methodology.

The results for the hospitalization outcome followed the same pattern as the primary composite outcome. This occurred because there was only one death in the TriNetX Linked Network cohorts; the patient who died was hospitalized prior to death. For the ED outcome, we did not observe differential exclusion of events on Day 1. For BEB- and PAX-exposed patients, seven and six ED events occurred on the first day of follow-up, respectively. These events were excluded. This resulted in a small reduction in the cumulative incidence in both groups; however, the RD (and 95% CI) was essentially unchanged compared to the RD (95% CI) using the primary methodology. Zero death events occurred on the first day of follow-up. Therefore, the death outcome results did not change.

Table.A2.17. Results from Sensitivity Analyses to Mitigate Potential Channeling Bias for Supplemental Analyses

Outcome	Methodology	Exposure	Number of Patients Analyzed	Number of Patients with Events	Cumulative Incidence	95% LCL	95% UCL	Risk Difference (RD, PAX = reference) RD	95% LCL	95% UCL
Primary analysis										
Hospitalization OR Death	**Primary**	BEB	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
		PAX	750	27	3.60%	2.39%	5.19%			
Hospitalization OR Death	**Excluding Events on Day 1**	BEB	750	20	2.67%	1.64%	4.09%	-0.80%	-2.54%	0.94%
		PAX	750	26	3.47%	2.28%	5.04%			
Secondary analyses										
Hospitalization	**Primary**	BEB	750	21	2.80%	1.74%	4.25%	-0.80%	-2.58%	0.98%
		PAX	750	27	3.60%	2.39%	5.19%			
Hospitalization	**Excluding Events on Day 1**	BEB	750	20	2.67%	1.64%	4.09%	-0.80%	-2.54%	0.94%
		PAX	750	26	3.47%	2.28%	5.04%			
ED visit	**Primary**	BEB	750	63	8.40%	6.51%	10.62%	0.13%	-2.66%	2.93%
		PAX	750	62	8.27%	6.40%	10.47%			
ED visit	**Excluding Events on Day 1**	BEB	750	56	7.47%	5.69%	9.59%	0.00%	-2.66%	2.66%
		PAX	750	56	7.47%	5.69%	9.59%			
Death	**Primary**	BEB	750	1	0.133%	0.003%	0.741%	0.133%	-0.128%	0.394%
		PAX	750	0	0.000%	0.000%	0.491%			
Death	**Excluding Events on Day 1**	BEB	750	1	0.133%	0.003%	0.741%	0.133%	-0.128%	0.394%
		PAX	750	0	0.000%	0.000%	0.491%			

Abbreviations: 95% LCL=95% confidence interval lower confidence limit; 95% UCL=95% confidence interval upper confidence limit; BEB=bebtelovimab; PAX=Paxlovid.

Note: For the Risk Difference analyses, PAX is the reference category.

16.4.5.2.2 A2.4.5.2.2. Results of Sensitivity Analyses to Assess the Impact of Unmeasured Confounding

The E-value results for the assessment of unmeasured confounding are presented in Table.A2.18. The table includes E-value results pertaining to both the RD (i.e., the primary effect estimate) and the RR. E-value results on the RR scale are intended to augment interpretation regarding the magnitude of unmeasured confounding that would be needed to modify the observed RR to a different RR value.

For the primary outcome of hospitalization or death within 30 days post-index, considering the confounders included in the propensity score generating model, unmeasured confounding with a magnitude of at least 1.89 (i.e., E-value=1.89) would be required to fully attenuate (i.e., RD=0.0) the observed RD (-0.08% [95% CI -2.58%, 0.98%]). On the RR scale, unmeasured confounding with a magnitude of at least 2.49 would be required to change the observed RR (0.78 [95% CI 0.44, 1.36]) to a RR of 0.5. Unmeasured confounding with a magnitude of >3.0 and >4.0 would be required to change the observed RR to RRs of 1.5 and 2.0, respectively. Note that an RR >1.0 signifies a greater risk of the outcome for BEB versus PAX.

The minimum magnitude of unmeasured confounding required to nullify (RD=0.0%) the observed treatment effect for hospitalization is the same as the primary composite outcome (i.e., E-value=1.89). For the ED outcome, unmeasured confounding of at least 1.14 (i.e., E-Value=1.14) would be required to nullify (RD=0.0%) the observed RD (i.e., RD=0.13% [-2.66%, 2.93%]). For the death outcome, given the small number of observed deaths, the observed treatment effect (RD=0.13% [-0.13%, 0.39%]) had an insufficient number of events to assess unmeasured confounding.

Table.A2.18. Results of Sensitivity Analyses to Assess the Impact of Unmeasured Confounding for Supplemental Analyses

Outcome	Unmeasured Confounding Required to Nullify the Observed Treatment Effect: Risk Difference Scale		Unmeasured Confounding Required to Change the Observed Treatment Effect: Risk Ratio Scale					
	Observed RD 95% CI	E-Value RD=0.0	Observed RR 95% CI	E-Value True RR=0.5	E-Value True RR=1.0	E-Value True RR=Observed RR	E-Value True RR=1.5	E-Value True RR=2.0
Primary analysis								
Hospitalization OR Death	-0.008 (0.026-0.009)	1.89	0.78 (0.44-1.36)	2.49	1.89	1.00	3.27	4.58
Secondary analyses								
Hospitalization	-0.008 (0.026-0.009)	1.89	0.78 (0.44-1.36)	2.49	1.89	1.00	3.27	4.58
ED visit	0.001 (-0.027-0.029)	1.14	1.02 (0.73-1.42)	3.48	1.14	1.00	2.32	3.35
Death	*Insufficient number of events to assess unmeasured confounding*							

Abbreviations: 95% CI=95% Confidence Interval; RD=Risk Difference; RR=Risk Ratio

16.4.5.2.3 A2.4.5.2.3. Results of Sensitivity Analyses to Assess the Impact of Missing Baseline Covariate Data

No baseline covariates met the pre-specified criteria of missingness >0% and <30% to assess the potential bias of missing baseline data using multiple imputation before matching—the missingness for BMI, eGFR, and blood pressure was 54%, 32%, and 87%, respectively. Therefore, sensitivity analyses to assess the potential impact of missing baseline covariate data were not conducted.

16.5 A2.5. Discussion

16.5.1 A2.5.1. Key Results

These supplemental analyses in the TriNetX Linked Network were conducted to assess the robustness of findings from the cohort study in the TriNetX Dataworks USA Network which evaluated the effectiveness of BEB compared to PAX in patients with COVID-19. The same primary (30-day all-cause hospitalization OR death) and secondary (all-cause hospitalization, all-cause death, and all-cause ED encounter) outcomes assessed in the TriNetX Dataworks USA Network study were assessed in the supplemental analyses. Subgroup and sensitivity analyses were conducted as well to assess potential effect modification and bias.

While the overall risk of the primary outcome in the matched cohorts was higher compared to that of the matched cohorts in the TriNetX Dataworks USA Network (without linked claims), the risk difference (-0.80% [-2.58%, 0.98%]) suggested that BEB was not associated with an increased risk of 30-day all-cause hospitalization or death compared to PAX. Similarly, secondary outcome risks (except for death) were higher compared to the matched cohorts in the TriNetX Dataworks USA Network. However, BEB was not associated with increased risks of hospitalization, ED encounter, or death compared to PAX. Subgroup analyses were overall consistent with the primary and secondary analyses, suggesting no evidence of effect modification by age, immunocompromised status, COVID-19 vaccination status, or baseline ED visit. While there was an increased risk of an ED visit with BEB compared to PAX in the age ≥ 65 years subgroup, the low number of events and limited precision of the effect estimate may indicate a chance finding rather than effect modification. The results from sensitivity analyses to assess the potential impact of channeling bias were consistent with those from the primary and secondary analyses, suggesting the observed findings were not substantially impacted by channeling bias. Likewise, sensitivity analyses pertaining to unmeasured confounding showed a considerable magnitude of unmeasured confounding (1.9 on RD scale and 1.9 – 4.5 on the RR scale) would be needed to substantially change the observed results. These subgroup and sensitivity analysis results depict robustness of the study findings in the TriNetX Linked Network and corroborate findings from the study conducted in the TriNetX Dataworks USA Network, providing further evidence of BEB's effectiveness for patients with COVID-19 during the period of high prevalence of Omicron BA.4 and BA.5 subvariants in the US.

Findings from these supplemental, linked analyses were consistent with the main analyses using the TriNetX Dataworks USA Network (i.e., EHR data without linked claims) despite potential

differences in data completeness and underlying populations between the two data sources. Use of the TriNetX Linked Network allowed augmentation of EHR data with insurance claims data, providing additional information on healthcare services given by HCOs outside of those contributing to the TriNetX Dataworks USA Network. These may include diagnoses, procedures, treatments, and other acute and non-acute medical services that were not captured in the EHR database alone. Further, mortality information was derived from additional data sources (Social Security Death Index, obituary feed data) for patients in the TriNetX Linked Network, allowing for more complete ascertainment of death outcomes compared to the EHR data alone. There were also notable differences in baseline characteristics between data sources. Patients in the TriNetX Linked Network were younger but generally had higher proportions of comorbidities, pharmacotherapy use, and healthcare resource utilization compared to patients in the TriNetX Dataworks USA Network. This may be due to the additional capture of insurance claims which identified comorbidities, pharmacotherapy use, and other healthcare services that were not identified in the EHR data. This could also reflect a different underlying population in the supplemental, linked analyses compared to the main analyses, as patients in the TriNetX Linked Network are the subset of those in TriNetX Dataworks USA Network who had health insurance claims data available for linkage to the EHR data. Patients in this subset may differ with regards to demographics and other characteristics. For example, patients in the TriNetX Linked Network primarily represent patients with commercial, Managed Medicaid, and Medicare Advantage insurance plans rather than traditional Medicare.

A few recent studies related to BEB or PAX real-world effectiveness have been published since the time of initiating the supplemental analyses. One study described adverse events, including hospitalization and death, in 849 patients treated with BEB in a suburban medical center. The study found a low proportion of hospitalizations (0.1%) and no deaths among BEB-treated patients (Knopp et al. 2023). Two studies reported a lack of real-world effectiveness in BEB-treated patients in a large healthcare system, however neither study utilized an active comparator group (i.e., they compared BEB-treated to untreated patients) (Sridhara et al. 2023 and Wang et al. 2023). Although propensity score techniques can reduce bias due to baseline differences between treated and untreated groups, an active comparator is generally more preferred over an untreated comparator to better address residual confounding. Furthermore, the Wang et al. study included time during which BQ.1/BQ.1.1 subvariants were growing. These variants are known to be resistant to BEB and do not reflect the circulating variants at the time of this analysis. Both studies found a low risk of hospitalization or death in BEB-treated patients (0.1 – 2.2%). Last, a study conducted in a large healthcare system, including periods in which the BQ.1, BQ.1.1, XBB, and XBB.1.5 subvariants were present, reported a decreased hazard of hospitalization or death among nirmatrelvir-treated vs. untreated patients (Lin et al. 2023).

16.5.2 A2.5.2. Limitations

While confounding bias is a potential limitation of this and all observational studies, confounding control was achieved in this study by using an active comparator rather than an untreated comparison group, CEM on highly selected and *a priori* defined baseline covariates, and PS matching on a broader set of pre-specified and HDPS-identified baseline covariates.

Moreover, use of the TriNetX Linked Network allowed for the ascertainment of baseline diagnoses recorded, procedures given, and medications dispensed from HCOs outside of the TriNetX Dataworks USA Network, further mitigating potential confounding bias.

Similar to the study conducted in TriNetX Dataworks USA, exposure misclassification may occur. For PAX-treated patients, prescriptions and dispensings do not confirm adherence to the prescribed dosing regimen. However, given the potential severity and global awareness of SARS-CoV-2 infection, adherence may have improved and therefore mitigated exposure misclassification to some degree. Furthermore, we observed that the utilization of the opposite treatment during follow-up (i.e., PAX in BEB-treated or BEB in PAX-treated patients) was rare.

Leveraging the closed insurance claims data from the TriNetX Linked Network improved mitigation of outcome misclassification, as it allowed for the capture of hospitalizations and ED visits that occurred outside of the EHR network but were recorded in the insurance claims. Further, the additional linked mortality data from the Social Security Death Index and obituary feeds potentially reduced misclassification of death outcomes.

It is unclear if differences in baseline characteristics between patients in the TriNetX Linked Network (i.e., patients with EHR data and linked insurance claims) and patients in the TriNetX Dataworks USA Network (i.e., patients with EHR data alone) were due to the additional capture of diagnoses, pharmacotherapy, and other healthcare services via the linked claims or due to true underlying differences between patients with EHR data and linked claims and patients with EHR data alone.

Given that the TriNetX Linked Network represents a subset of patients within the TriNetX Dataworks USA Network, the study sample size was reduced compared to the study conducted in the latter database. This reduced treatment effect precision—especially among subgroup analyses, in which the ability to detect effect modification was limited compared to the study conducted in the TriNetX Dataworks USA Network. This also impacts generalizability, as patients in the TriNetX Linked Network are primarily commercially insured rather than federally insured (e.g., traditional Medicare), as mentioned below in Section 16.5.4 (A2.5.4).

16.5.3 A2.5.3. Interpretation

Results of these supplemental analyses in the TriNetX Linked Network suggest that BEB was not associated with an increased risk of the 30-day hospitalization or death, nor was it associated with an increased risk of the secondary outcomes compared to PAX. These findings corroborate those of the study conducted in the TriNetX Dataworks USA Network.

16.5.4 A2.5.4. Generalisability

While patients in the larger TriNetX Dataworks USA Network have been shown to be broadly representative of patients who receive medical care in the US, patients within the TriNetX Linked Network may be more representative of patients with health insurance, particularly those who are commercially-insured. Thus, results of this study may be more generalizable to a commercially-insured population compared to a federally-insured population (e.g., Medicare or Medicaid).

16.6 A2.6. Conclusions

These supplemental analyses in the TriNetX Linked Network suggest that BEB was not associated with an increased risk of hospitalization or death, nor was it associated with an increased risk of secondary outcomes (hospitalization, ED visit, death) compared to PAX in patients with COVID-19 during the period of high prevalence of the Omicron BA.4 and BA.5 subvariants. These findings support those of the initial study conducted in the TriNetX Dataworks USA Network that concluded BEB was non-inferior to PAX, strengthening the evidence base on the real-world effectiveness of BEB. Though BEB was de-authorized in November 2022, these studies demonstrate an example of how real-world evidence can inform regulatory decision-making when a public health crisis, such as the COVID-19 pandemic, demands a robust assessment of the real-world use and effectiveness of new, emerging therapeutics.

16.7 A2.7. References

[FDA] Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes new monoclonal antibody for treatment of COVID-19 that retains activity against omicron variant 2022. 2022. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains.

Knopp BW, Weiss HZ, Fahmy S, et al. A comparison of the adverse effects and utility of different monoclonal antibodies for SARS-CoV-2: a retrospective cohort study. *Cureus*. 2023;15(8):e43094.

Lin D, Abi Fadel F, Huang S, et al. Nirmatrelvir or molnupiravir use and severe outcomes from omicron infections. *JAMA Network Open*. 2023;6(9):e2335077.

Sridhara S, Gungor AB, Erol HK, et al. Lack of effectiveness of bebtelovimab monoclonal antibody among high-risk patients with SARS-CoV-2 omicron during BA.2, BA2.12.1 and BA.5 subvariants dominated era. *PLoS ONE*. 2023;18(4):e0279326.

Wang X, Abi Fadel F, Huang S, et al. Effectiveness of bebtelovimab against hospitalization and death from the omicron Ba.4/BA.5 and BQ.1/BQ.1.1 subvariants. *Chest*. 2023;164(4):872-74.