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Real-world effectiveness of casirivimab and imdevimab among patients diagnosed with COVID-19 in the ambulatory setting: a retrospective cohort study using a large claims database

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ABSTRACT

Objective To assess the real-world effectiveness of casirivimab and imdevimab (CAS+IMD) versus no COVID-19 antibody treatment among patients diagnosed with COVID-19 in the ambulatory setting, including patients diagnosed during the Delta-dominant period prior to Omicron emergence.

Design Retrospective cohort study.

Setting Komodo Health closed claims database.

Participants 13 273 128 patients diagnosed with COVID-19 (December 2020 through September 2021) were treated with CAS+IMD or untreated but treatment eligible under the Emergency Use Authorization (EUA). Each treated patient was exact and propensity score matched without replacement to up to five untreated EUA-eligible patients.

Interventions CAS+IMD.

Primary and secondary outcome measures Composite endpoint of 30-day all-cause mortality or COVID-19-related hospitalisation. Kaplan-Meier estimators were used to calculate outcome risks overall and across subgroups: age, COVID-19 vaccination status, immunocompromised status, and timing of diagnosis (December 2020 to June 2021, and July to September 2021). Cox proportional hazards models were used to estimate adjusted HRs (aHRs) and 95% CIs.

Results Among 75 159 CAS+IMD-treated and 1 670 338 EUA-eligible untreated patients, 73 759 treated patients were matched to 310 688 untreated patients; matched patients were ~50 years, ~60% were women and generally well balanced across risk factors. The 30-day risk of the composite outcome was 2.1% and 5.2% in the CAS+IMD-treated and CAS+IMD-untreated patients, respectively; equivalent to a 60% lower risk (aHR 0.40; 95% CI, 0.38 to 0.42). The effect of CAS+IMD was consistent across subgroups, including those who received a COVID-19 vaccine (aHR 0.48, 95% CI, 0.41 to 0.56), and those diagnosed during the Delta-dominant period (aHR 0.40, 95% CI, 0.38 to 0.42).

Conclusions The real-world effectiveness of CAS+IMD is consistent with the efficacy for reducing all-cause mortality or COVID-19-related hospitalisation reported in clinical trials. Effectiveness is maintained across patient subgroups, including those prone to breakthrough infections, and was effective against susceptible variants including Delta.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This retrospective cohort study assessed the real-world effectiveness of casirivimab and imdevimab (CAS+IMD) versus no COVID-19 antibody treatment among patients diagnosed with COVID-19 in the ambulatory setting, including patients diagnosed during the Delta-dominant period prior to Omicron emergence.
⇒ Claims data did not distinguish between subcutaneous and intravenous administration of CAS+IMD.
⇒ Potential confounding variables such as viral load and symptoms, which may predict severe COVID-19, as well as body mass index and COVID-19 vaccination status are not well captured in claims data.
⇒ The study did not overlap with emergence of the Omicron variant.

INTRODUCTION

Clinical studies have identified neutralising monoclonal antibodies (mAbs) as efficacious agents of passive immunotherapy for early treatment of patients diagnosed with COVID-19 in the ambulatory setting.[1–4] These mAbs, which include casirivimab and imdevimab (CAS+IMD; Regeneron, Inc.), bamlanivimab with etesevimab (Eli Lilly), sotrovimab (GlaxoSmithKline) and bebtelovimab (Eli Lilly), have received Emergency Use Authorization (EUA) from the US Food and Drug Administration for treatment of non-hospitalised patients ≥12 years old who have mild-to-moderate COVID-19 and are at high risk of progressing to severe disease, including hospitalisation or death.[5–7]

While mAbs demonstrated efficacy in COVID-19 patients, the emergence of additional variants of concern (VOCs) after the completion of clinical trials highlights the need for continued evaluation of mAbs in the real world. Delta (B.1.617.2) and Delta plus (AY.4.2) are VOCs that are associated with higher infection rates[8 9] as well as increased hospitalisation and mortality compared with the Alpha (B.1.1.7) variant.[10–12] In vitro studies suggested that CAS+IMD retains neutralisation activity against most VOCs, including Delta but with the exception of Omicron (B.1.1.529).[5 13–17] Most real-world studies assessing the effectiveness of CAS+IMD for treating COVID-19[18–30] were conducted prior to Delta, and those that did overlap with the emergence of the Delta variant were single centre and of small sample size.[19 30 31] Furthermore, with the introduction of COVID-19 vaccines, an improved understanding of patients most vulnerable to poor COVID-19 outcomes (ie, older patients, patients with multiple comorbidities and patients who are immunocompromised) and the emergence of the Delta variant, it became important to evaluate the effectiveness of CAS+IMD across these patient subgroups. Therefore, the objective of this study was to assess the effectiveness of CAS+IMD compared with no COVID-19 antibody treatment on 30-day all-cause mortality or COVID-19-related hospitalisation among patients diagnosed with COVID-19 in the ambulatory setting overall and among patient subgroups, including among patients diagnosed with COVID-19 during the Delta-dominant period.

METHODS

Study design and patient population

Based on a protocol in which we prespecified the study design and analyses, we conducted a retrospective cohort study using the closed administrative claims data from the Komodo Health claims database; the closed claims dataset contains complete medical and prescription claims information from 150 payers across all geographic regions of the USA.[32] As of 30 September 2021, approximately 98 000 patients in the dataset who had a COVID-19 diagnosis (International Classification of Diseases, Tenth Edition, Clinical Modification (ICD-10-CM) code U07.1) received intravenous or subcutaneous CAS+IMD.

Among patients diagnosed with COVID-19 in the outpatient setting between 1 December 2020 and 30 September 2021, we identified patients treated with CAS+IMD, and patients who were eligible to be treated with CAS+IMD under the EUA but were untreated. Among treated patients, the index date was the date of CAS+IMD administration. For untreated patients, the index date was an assigned date matching the distribution of days from COVID-19 diagnosis to treatment for the CAS+IMD-treated patients. Additional inclusion criteria were continuous enrolment for ≥6 months pre index (ie, baseline); age ≥12 years at index; a COVID-19 diagnosis within 10 days prior to (days 0 to −10) or on the index (day 0) but no diagnosis in the prior 30-day period (days −11 to −40); and a valid date of death. Patients were excluded if they were treated with other COVID-19 mAbs over the baseline period or on the index date, or received CAS+IMD during baseline.

Outcomes

The study outcome was the composite of 30-day all-cause mortality or COVID-19-related hospitalisation. Sources used by Komodo to identify mortality included Social Security Administration data, a private obituary data source and a private claims mortality dataset. COVID-19-related hospitalisation was defined as a COVID-19 diagnosis as the primary or admitting diagnosis. Patients were followed from the index date until the occurrence of the outcome or a censoring event, which included receipt of another COVID-19 mAb, the end of the 30-day risk period, healthcare plan disenrollment, or study end date (30 September 2021).

Study variables

Baseline demographic variables included age (as a continuous variable and categorised as 12–17, 18–54, 55–64 and ≥65 years), sex and geographic region. COVID-19-related variables included location of diagnosis (emergency room/urgent care vs other), the number of days from diagnosis to index date, the index month and vaccinated against COVID-19 (ie, receipt of ≥1 dose). The Charlson Comorbidity Index (CCI) Score was derived using the presence of comorbidities over the baseline period.[33] Body mass index (BMI) was categorised as normal, overweight or obese based on ICD-10-CM diagnosis codes over the baseline period (including index date). The occurrence of ≥1 all-cause hospitalisations and ≥1 all-cause emergency room/urgent care visits during the baseline period was also captured. Specific risk factors for the use of CAS+IMD under the EUA were identified during the baseline period. These risk factors included the following: age≥65 years on index date; age 12–17 years on index date with BMI ≥85th percentile for age and sex based on Centers for Disease Control and Prevention growth charts[34]; BMI>25 kg/m^2; pregnancy; diabetes; chronic lung disease; immunosuppressive disease; history of immunosuppressive treatment; cardiovascular disease, hypertension or congenital heart disease; sickle cell disease; and neurodevelopmental disorders. The following EUA risk factors were evaluated over the baseline period only and did not include the index date since COVID-19 could result in these conditions: chronic kidney disease; cardiovascular disease or hypertension; and use of medical-related technological dependence.

Subgroups

Subgroups of interest included age groups of 12–17, 18–54, 55–64 and ≥65 years; elevated risk defined as age ≥65 years or 55–64 years with BMI ≥35 kg/m^2, type 2 diabetes, chronic obstructive pulmonary disease or chronic kidney disease; immunocompromised status, ie, B-cell deficiencies, both overall and by type of deficiency

(primary, secondary and drug-induced as defined in online supplemental table 1; vaccinated against COVID-19; and timing of COVID-19 diagnosis (December 2020 to June 2021 in which Epsilon, Alpha, Iota and Gamma were dominant variants vs July 2021 onward, which is the month the Delta variant became the dominant variant in the USA).[35] A post-hoc analysis was also conducted among vaccinated patients who were also at elevated risk based on the above definition.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Statistical analysis

Matching

Propensity scores (PSs), derived using logistic regression, predicted the probability of CAS+IMD treatment versus no treatment given age, sex, index month, 3-digit zip code, days between COVID-19 diagnosis and the index date, individual EUA criteria, BMI category, CCI Score, COVID-19 vaccination status and baseline healthcare resource utilisation. CAS+IMD-treated patients were then matched using a calliper of 0.2 of the SD of the logit of the estimated PS[36] and exact matched to up to five untreated EUA-eligible patients without replacement on the index month, 3-digit zip code and days from COVID-19 diagnosis to the index date. Covariates with missing data (eg, BMI) were included in the PS model using the missing-indicator method.[37–39] Balance between groups was measured by standardised mean differences (SMDs), with a value ≥0.1 indicating imbalance.[40]

Primary analysis

Baseline characteristics, including means, SDs, medians and IQRs for continuous variables, and frequency and percent for categorical variables, are reported among treated and untreated matched patients. Kaplan-Meier estimators were used to estimate the 30-day risk of the composite outcome among the matched patients,[41] with 95% confidence bands across the entire Kaplan-Meier survival curves constructed using the Hall-Wellner method.[42] Log-ranks tests were used to compare survival distributions.

Adjusted HRs (aHRs) with 95% CIs were derived using Cox proportional hazards models that fit the model to the matched pairs, and used sandwich variance estimators to account for clustering within matched sets.[43] The adjusted models included only an indicator variable for treatment, and the aHRs were derived by exponentiating the coefficient from the model.

Subgroup analyses

The 30-day outcome risk for each subgroup was derived using Kaplan-Meier estimators. Cox proportional hazards models were used to estimate the effectiveness of CAS+IMD across subgroups using interaction terms between treatment and the subgroup in the model; results are presented as the aHR with its 95% CI. These estimates were derived from the same matched set of patients as the

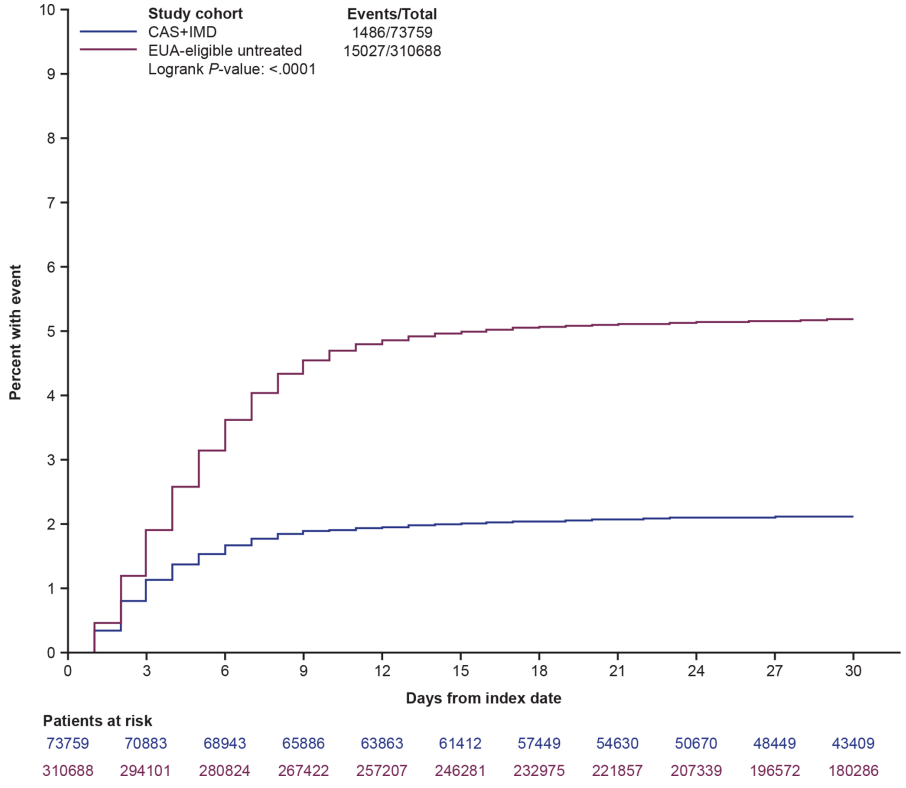

Figure 1 Kaplan-Meier curve for 30-day all-cause mortality or COVID-19-related hospitalisation among patients diagnosed with COVID-19 in the outpatient setting who were treated with CAS+IMD or who were EUA-eligible but untreated. CAS+IMD, casirivimab and imdevimab; EUA, Emergency Use Authorization.

primary analysis and accounted for clustering of patients without adjustment for multiplicity of testing.

Sensitivity analyses

Sensitivity analyses included modifying the definition of COVID-19-related hospitalisation to having a COVID-19 diagnosis in the primary position, requiring that only the untreated patients meet EUA criteria, shortening the time window between diagnosis and treatment to 5 days from 10 days and using 3 months pre index continuous enrolment instead of 6 months.

The analytic file was created, and all analyses were conducted, using SAS software V.9.4.

RESULTS

Patient populations

Among 13 273 128 patients who had a COVID-19 diagnosis during the study period in the closed claims Komodo dataset, 75 159 who received CAS+IMD and 1 670 338 who were untreated met study criteria and were eligible for matching. Prior to matching, the groups were imbalanced on several variables (online supplemental table 2).

Among treated patients, 73 759 were successfully matched to 310 688 patients who were EUA eligible but untreated (online supplemental figure 1). After matching, the SMDs indicated no imbalance between treated and matched EUA-eligible untreated patients on any of the baseline variables (online supplemental table 3). Treated and EUA-eligible untreated patients were primarily female (~60%), with a mean age~50 years, with greatest representation from the South (65%–67%). The mean (SD) and median (IQR) number of days from diagnosis to index date in the CAS+IMD-treated cohort was 1.6 (2.1) and 1 (3), respectively, and the timing was comparable for the assigned index dates for the EUA-eligible untreated patients. Among the individual EUA criteria, the combination of cardiovascular disease, hypertension and congenital heart disease had the highest prevalence (53%–55%) followed by neurodevelopmental disorders (~37%) and being overweight (34%–36%) (online supplemental table 3).

Primary analysis

The 30-day risk of all-cause mortality or COVID-19-related hospitalisations was 2.1% (95% CI, 2.0% to 2.2%) in the CAS+IMD-treated cohort and 5.2% (95% CI, 5.1% to 5.3%) in the EUA-eligible untreated cohort (figure 1), representing 1486 and 15 027 events, respectively. Most of the events in both cohorts occurred within the first 10 days post index. In adjusted models, CAS+IMD was associated with a 60% lower risk of the composite outcome compared with the untreated EUA eligible patients (aHR 0.40; 95% CI, 0.38 to 0.42) (figure 2). The 30-day mortality risk in the treated cohort was 0.1% (95% CI, 0.06% to 0.11%, representing 51 deaths) and 0.6% (95% CI, 0.56% to 0.62%, representing 1491 deaths) in the untreated cohort. Multiple sensitivity analyses showed results that were consistent with the primary analysis (figure 2).

Subgroup analyses

The 30-day outcome risk among untreated EUA-eligible patients was highest for patients in the oldest age groups, and among those at elevated risk or who are immunocompromised (B-cell deficient) (figure 3). After matching, the effectiveness of treatment with CAS+IMD was consistent across patient subgroups defined by age, COVID-19 vaccination status, elevated risk and immunocompromised status (figure 3); there was a greater risk reduction among those with primary or secondary B-cell deficiency,

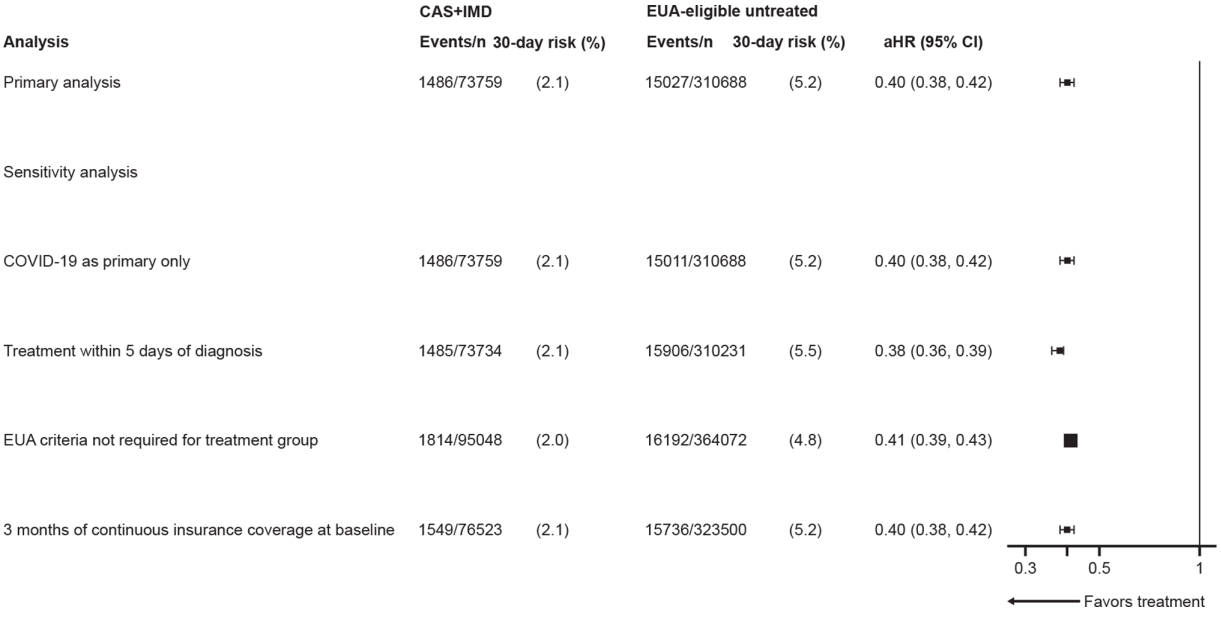

Figure 2 Primary and sensitivity analyses of 30-day all-cause mortality or COVID-19-related hospitalisation among patients diagnosed with COVID-19 in the outpatient setting. aHR, adjusted HR; CAS+IMD, casirivimab and imdevimab; EUA, Emergency Use Authorization.

Analysis	CAS+IMD Events/n	CAS+IMD 30-day risk (%)	EUA-eligible untreated Events/n	EUA-eligible untreated 30-day risk (%)	aHR (95% CI)
Age group, year					
12-17	4/1651	(0.3)	60/8515	(0.8)	0.32 (0.13, 0.75)
18-54	674/41087	(1.7)	6500/172818	(4.0)	0.42 (0.39, 0.46)
55-64	454/19245	(2.5)	4618/73742	(6.7)	0.36 (0.33. 0.39)
≥ 65	354/11776	(3.2)	3849/55613	(7.6)	0.42 (0.38. 0.47)
Vaccination status					
Vaccinated	172/12983	(1.4)	1305/52681	(2.7)	0.48 (0.41, 0.56)
Unvaccinated	1314/60776	(2.3)	13722/258007	(5.7)	0.39 (0.37, 0.41)
Elevated risk[a]					
Yes	634/22796	(2.9)	6768/95028	(7.7)	0.37 (0.34, 0.40)
No	852/50963	(1.8)	8259/215660	(4.1)	0.43 (0.40, 0.45)
B-cell deficiency					
Yes	146/4483	(3.5)	972/14185	(7.4)	0.44 (0.37, 0.52)
No	1340/69276	(2.0)	14055/296503	(5.1)	0.39 (0.37. 0.42)
Types of B-cell deficiency					
Primary	0/15	(0.0)	3/33	(9.2)	N/A
Secondary	2/183	(1.2)	60/560	(1.2)	0.12 (0.03. 0.50)
Drug-induced	144/4285	(3.6)	909/13592	(7.2)	0.46 (0.39, 0.55)
No	1340/69276	(2.0)	14055/296503	(5.1)	0.39 (0.37, 0.42)
Time period of COVID-19 diagnosis					
December 2020 to June 2021	176/7116	(2.5)	1610/32675	(5.0)	0.50 (0.43, 0.58)
July 2021 to end of study	1310/66643	(2.1)	13417/278013	(5.2)	0.40 (0.38, 0.42)

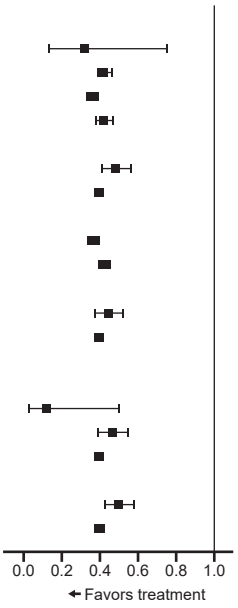

Figure 3 Subgroup analyses of 30-day risk of all-cause mortality or COVID-19-related hospitalisation among patients diagnosed with COVID-19 in the outpatient setting. aHR, adjusted HR; CAS+IMD, casirivimab and imdevimab; EUA, Emergency Use Authorization. [a]Defined as age≥65 years or 55–64 years with body mass index≥35 kg/m^2, type 2 diabetes, chronic obstructive pulmonary disease or chronic kidney disease.

although the numbers were small. Post-hoc analysis also showed that the treatment was associated with a 60% reduction in risk among vaccinated patients who were also at elevated risk (aHR 0.40; 95% CI, 0.28 to 0.57).

Regardless of whether they were treated during the Delta-dominant period or not, patients who received CAS+IMD had a lower risk than EUA-eligible non-treated patients (figure 4). Treatment with CAS+IMD was associated with a 50% lower risk (aHR 0.50; 95% CI, 0.43 to 0.58) during the earlier period, and a 60% lower risk (aHR 0.40; 95% CI, 0.38 to 0.42) during Delta-dominant period (figure 4).

DISCUSSION

This observational cohort study confirms and extends the evidence from clinical trials and other smaller real-world studies that patients with COVID-19 in the outpatient setting benefit from treatment with CAS+IMD. Among patients treated with CAS+IMD, there was a 60% reduction in the risk of 30-day all-cause mortality or COVID-19-related hospitalisation compared with the EUA-eligible untreated patients. The benefit of treatment was observed across all patient subgroups. Notably, we found that the effectiveness of CAS+IMD was maintained during the Delta-dominant period and among patients receiving ≥1 dose of the COVID-19 vaccine.

In the primary analysis, the 60% reduction in risk was within the range of 50%–90% lower risk of hospitalisations relative to untreated patients that was suggested by published real-world studies,[18 19 22 23 44] although most of those studies used more broadly defined endpoints such as all-cause hospitalisations.[18 23 44] Moreover, the risk reduction observed in this study is comparable to the 60% risk reduction of the same composite endpoint that was observed with CAS+IMD treatment compared with untreated EUA-eligible patients in a real-world study based on data from two large claims databases in the pre-Delta period.[45] Our results are also consistent with those of the clinical trial demonstrating the efficacy of CAS+IMD for the treatment of COVID-19,[2] and suggest that the benefits of CAS+IMD extend beyond the clinical trial setting. The subgroup analyses demonstrate that CAS+IMD is effective in EUA-eligible patients regardless of age, COVID-19 vaccination or being immunocompromised.

An important finding of this study was that the effectiveness of CAS+IMD was maintained when Delta was the dominant SARS-CoV-2 variant in the USA. The Delta variant was of special concern because of its greater virulence in addition to its high transmissibility, which quickly made it the predominant variant.[8–12] In the adjusted model, the aHRs showed that the magnitude of the treatment effect was slightly higher during the Delta-dominant period than the pre-Delta period (60% and 50% lower risk, respectively, relative to EUA-eligible untreated patients). While the observed difference may have been driven by lower accessibility and stricter patient selection in the pre-Delta period, our results demonstrate that CAS+IMD retains activity against the Delta variant. Such activity was previously suggested by in vitro studies[5 13–16] and smaller real-world studies that reported its effectiveness for reducing all-cause hospitalisation or mortality.[30 31]

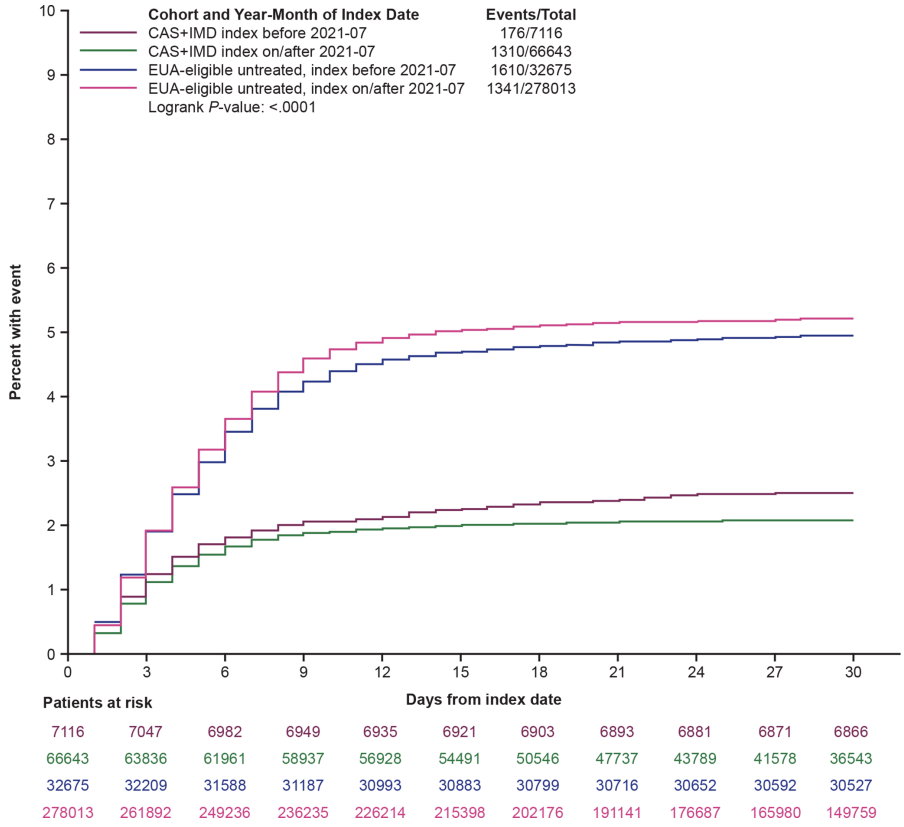

Figure 4 Kaplan-Meier curve for composite endpoint of 30-day all-cause mortality or COVID-19-related hospitalisation among patients diagnosed with COVID-19 in the outpatient setting, stratified by treatment received and timing of COVID-19 diagnosis. CAS+IMD, casirivimab and imdevimab; EUA, Emergency Use Authorization.

An additional consequence of the emergence of variants such as Delta that are characterised by increased virulence is the occurrence of breakthrough infections among vaccinated individuals.[46–48] Limited evidence has suggested that breakthrough infections in fully vaccinated patients are amenable to treatment with CAS+IMD.[19 31] In the current analysis, the 52% reduction in risk among vaccinated patients suggests that patients vaccinated against COVID-19 who experience breakthrough infections due to waning immunity or lack of effectiveness of vaccines can benefit from treatment.[19] In addition, the reduction in outcome risk among patients treated with CAS+IMD was slightly greater (61%) among unvaccinated than vaccinated patients, likely resulting from a greater risk of severe COVID-19 among those who are not vaccinated. While these results support the benefits of treatment among those who cannot be or are unwilling to be vaccinated, they also suggest that vaccinated individuals who contract COVID-19 and are eligible for treatment under the EUA can also benefit from treatment with CAS+IMD.

The findings of this study also suggest that immunocompromised patients (ie, those who are B-cell deficient) can benefit from treatment with CAS+IMD. This is relevant because these patients have been shown to be at higher risk of being infected with COVID-19, and of progressing to more severe disease with poorer outcomes.[49 50] Furthermore, patients with primary immunodeficiencies have a low likelihood of benefitting from vaccination,[51] which makes them a group with a large unmet need.

Limitations

Limitations of this study include that information on viral load and symptoms, variables that may predict severe COVID-19,[52–54] are not captured in claims data. Moreover, a reason that at least some EUA-eligible patients were untreated may be that they had less severe disease, although social and cultural factors such as race and ethnicity, which were not available in the database, have also been reported to influence the decision to be treated with mAbs[55] and have also been associated with a higher risk of poor COVID-19 outcomes.[56] Another limitation is that several important variables such as BMI and COVID-19 vaccination status are not well captured in claims data; when this study was conducted, approximately 70% of the population had received one dose and 60% had received two doses. Residual confounding is therefore likely, which could result in either an underestimation or overestimation of the treatment benefit as the mechanism of missingness is unknown. We were also not able to distinguish between the subcutaneous and intravenous administration of CAS+IMD. Additionally, it is possible that some deaths were not captured and that the 30-day risk of all-cause mortality may have been underestimated. Finally, the study period did not overlap with emergence of the Omicron variant, although CAS+IMD

is not expected to be active against Omicron,[57] as in vitro data indicate that CAS+IMD has markedly reduced neutralisation activity against this variant.[58 59]

CONCLUSIONS

This study suggests that, in susceptible variants, treatment with CAS+IMD is effective against COVID-19 and that its effectiveness is maintained across various patient subgroups. Among patients diagnosed with COVID-19 in the ambulatory setting, treatment with CAS+IMD was associated with a 60% reduction in risk of 30-day all-cause mortality or COVID-19-related hospitalisation relative to matched untreated EUA-eligible patients that was maintained even after the emergence of the Delta variant and across a number of high-risk patient populations. While breakthrough infections are likely, especially in patients with risk factors and after emergence of VOCs with reduced susceptibility to vaccines or with waning immunity, early treatment of these patients with CAS+IMD reduced the risk of disease progression that would require hospitalisation or result in death. Evaluation of COVID-19 treatments and outcomes needs to remain ongoing as new VOCs emerge so that risk factors that can further improve COVID-19 management strategies can be identified.

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Contributors Mohamed Hussein accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MH, WW, VM, RJS, DJM, DMW and JJJ contributed to the research conception and design. MH, WW and JJJ drafted the manuscript. Data were acquired, analysed and interpreted by MH, WW, VM, RJS, DW, DJM, BH, DMW and JJJ. Statistical analysis was performed by DW and WW. DW provided administrative, technical or material support. All authors critically reviewed the manuscript for important intellectual content.

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Competing interests All authors are employees and stockholders of Regeneron Pharmaceuticals, Inc.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was conducted as secondary research using deidentified data licensed from a third party, Komodo, in compliance with 45 CFR 164.514(a)–(c). The data had identifying patient information removed and were coded in such a way that they could not be linked back to subjects from whom they were originally collected prior to the authors gaining access. This research did not require institutional review board or ethics review, as analyses of these data do not meet the definition of 'research involving human subjects' as defined within 45 CFR 46.102(f), which stipulates human subjects as living individuals about whom an investigator obtains identifiable private information for research purposes.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. All data generated or analysed during this study are included in this published article.

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