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MAJOR ARTICLE

Bamlanivimab Efficacy in Older and High-BMI Outpatients With COVID-19 Selected for Treatment in a Lottery-Based Allocation Process

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Background. Given the challenges associated with timely delivery of monoclonal antibody (mAb) therapy to outpatients with coronavirus disease 2019 (COVID-19) who are most likely to benefit, it is critical to understand the effectiveness of such therapy outside the context of clinical trials.

Methods. This was a case–control study of 1257 adult outpatients with COVID-19, ≥65 years of age or with body mass index (BMI) ≥35, who were entered into a lottery for mAb therapy.

Results. Patients who were called to be offered mAb therapy had a statistically significant 44% reduction in the odds of hospitalization within 30 days of a positive severe acute respiratory syndrome coronavirus 2 test compared with those who were not called (odds ratio [OR], 0.56; 95% CI, 0.36–0.89; $P = .01$). Patients who actually received bamlanivimab had a statistically significant 68% reduction in the odds of hospitalization compared with those who did not receive bamlanivimab (OR, 0.32; 95% CI, 0.11–0.93; $P = .04$).

Conclusions. This study supports the effectiveness of bamlanivimab in reducing COVID-19-related hospitalizations in patients ≥65 or with BMI ≥35.

Keywords. COVID-19; monoclonal antibodies.

In fall 2020, the US Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUAs) for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reactive monoclonal antibodies bamlanivimab [1] and casirivimab together with imdevimab [2] to treat outpatients with coronavirus disease 2019 (COVID-19) and mild to moderate symptoms who are at high risk of progression to severe disease due to age, body mass index (BMI), and/or other specified clinical characteristics. The EUAs were initially based on phase II clinical trial data that demonstrated an accelerated decline in viral load in patients treated with the monoclonal antibodies (mAbs) and suggested a reduction in COVID-19-related hospitalizations, emergency department visits, or other medical visits in the treatment groups [3, 4]. In February 2021, the FDA issued another EUA for bamlanivimab together with etesevimab [5].

Preliminary analysis of a phase II trial of bamlanivimab showed that 1.6% of treated patients were hospitalized or visited the emergency department within 29 days compared with 6.3% of those who received placebo. In a post hoc analysis restricted to high-risk participants, 4.2% of those who received bamlanivimab were hospitalized or visited the emergency department compared with 14.6% of those who received placebo [3]. The pharmaceutical companies that manufacture the mAbs subsequently released phase III data that showed significantly fewer hospitalizations and deaths in participants treated with bamlanivimab together with etesevimab [6] and casirivimab together with imdevimab [7] compared with placebo.

On November 27, 2020, the Commonwealth of Massachusetts issued guidance to promote equitable allocation of mAbs in the event of scarcity. The guidance specified that if demand exceeded infusion capacity, health care systems should allocate mAbs using a lottery system with a percentage of lottery spots reserved for socially vulnerable patients [8]. Consistent with this guidance, in December 2020 the Mass General Brigham (MGB) health system implemented a centralized system for the allocation of mAbs to outpatients with COVID-19 [9]. Given the logistical challenges inherent in distributing mAbs to high-risk patients with COVID-19—including the need to quickly

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identify eligible patients and get them to infusion centers within the time window during which therapy was likely to be beneficial—it was conceivable that the efficacy of mAb therapy demonstrated in clinical trials would not be replicated under real-world conditions.

We conducted a retrospective case–control study to analyze the effect of bamlanivimab administration outside of trial conditions on the rate of hospitalizations and deaths related to COVID-19 among adult patients with BMI ≥35 or age ≥65.

METHODS

Description of Allocation Process

Based on the Massachusetts guidance and available evidence regarding which COVID-19 patients would likely benefit most from mAb therapy, MGB initially limited distribution of mAbs to adult patients with a BMI ≥35 or age ≥65. MGB required infusion within 4 days of a positive SARS-CoV-2 test being performed and within 10 days of symptom onset. The 4-day requirement was based on the fact that patients in the initial bamlanivimab trial and the casirivimab together with imdevimab trial had been infused ≤3 days [3] or ≤72 hours [4] following a positive SARS-CoV-2 test being performed [3, 4], in addition to evidence suggesting that the magnitude of benefit from mAbs is greater the earlier treatment is given [4]. Between December 2020 and February 25, 2021, all infused patients received bamlanivimab.

Beginning on December 9, 2020, referrals for mAbs were generated automatically for all adult outpatients with a positive SARS-CoV-2 test in the MGB system who had been designated as symptomatic on their test order and were ≥65 years of age or had a BMI of ≥35 recorded in the electronic medical record. The referrals were screened to determine whether the patient's time window for therapy would still be open on the date of the next available infusion and to eliminate patients who were not eligible based on chart review (eg, those who were known to already have been hospitalized with COVID-19).

On days where the number of eligible patients exceeded MGB's infusion capacity for the following day, eligible patients whose time window for mAb based on symptom onset and date of test performance would still be open were entered into a lottery for available infusion appointments. Eighty percent of the lottery spots were open to all eligible patients and assigned by lottery number. Once those spots were filled, the remaining 20% of the lottery spots ("reserve spots") were assigned by lottery number, with absolute priority going to patients who lived in a zip code with an average Centers for Disease Control Social Vulnerability Index (SVI) in the top quartile for the Commonwealth of Massachusetts and/or lived in a town in the highest quartile of COVID-19 incidence for the Commonwealth. The SVI is a composite measure that incorporates 15 individual metrics across 4 themes of disadvantage, compiled at the level of census tracts, and ranging from 0 (lowest vulnerability) to 1 (highest vulnerability) [10].

If there were not enough patients with those characteristics to fill the reserve spots, the reserve spots were offered to other patients by lottery number. Not all patients identified in the lottery to be called received bamlanivimab. Many could not be reached, declined therapy, or had severe symptoms by the time they were called.

On January 4, 2021, in the setting of high rates of eligible patients declining mAb therapy once offered, the referral process was changed to allow clinicians to enter referrals for their own patients once they had spoken to the patients about the therapy and established patient interest ("manual referrals"). From January 4, 2021, through January 27, 2021, both automatic and manual referrals were entered into the lottery. During that period, manual referrals took priority over automatic referrals in order to optimize use of available infusion capacity. Starting January 28, 2021, only manual referrals were entered into the lottery.

Study Design

We conducted a retrospective case–control study. The analysis included all patients who were entered into the lottery for mAb therapy at MGB between December 9, 2020, and February 25, 2021, with the exception of patients who were entered into the lottery but were subsequently found to not meet age or BMI criteria, were known to have received mAb therapy elsewhere, or were hospitalized on the same day their COVID-19 test was performed. Patients who were never entered into the lottery because of an expired time window for therapy or a determination that they did not meet age or BMI criteria were not included in the analysis.

Two independent reviewers reviewed the electronic medical record of each referred patient to determine whether the patient was hospitalized within 30 days of COVID-19 diagnosis and/or died of COVID-19 at any time point. The reviewers were not told before their review whether an individual patient had been called and/or received an infusion; however, they were not formally blinded. Where there was discordance between the 2 reviewers, a third reviewer reviewed the medical record and consensus was reached. The records of all patients who were identified as having been hospitalized or having died of COVID-19 were reviewed by 2 additional independent physician reviewers who reached agreement on all cases. All hospitalizations that were clearly or potentially related to COVID-19 were included as outcomes. Only those deaths that appeared to have COVID-19 as a proximate cause were included as outcomes.

We conducted our analysis using 2 different case–control definitions. The first defined cases as those who were called to be offered infusion (regardless of whether the patient was reached on the phone or accepted the treatment if reached) and controls as those who were entered into the lottery but were not called.

The second defined cases as those who received bamlanivimab infusion and controls as those who were entered into the lottery but did not receive an infusion (regardless of whether they were called). The rates of hospitalization within 30 days of a positive test being sent and the rates of death at any time point from COVID-19 were compared between cases and controls.

Although the lottery involved some randomization, treatment was not offered completely at random given the reserve for socially vulnerable patients and the preference given to those who were referred manually. In addition, a high proportion of patients who received a spot in the lottery did not end up getting treated with bamlanivimab, likely introducing confounding variables into our analysis. To address these potential confounders, logistic regression models with inverse probability of treatment weighting (IPTW) and robust sandwich error estimation were used to compare rates of hospitalization. The modeling technique created exposure probability weights for each patient, incorporating their demographic and referral characteristics. Estimation of weights was based on multivariable logistic regression for binary exposure, with age, sex, race, ethnicity, referral type, and SVI as predictors. Models for the weights were not necessarily parsimonious and included relevant factors regardless of statistical significance provided that model estimation was stable. Associations with outcomes were then estimated using weighted logistic regression models. Associations are reported as odd ratios with 95% robust confidence intervals. Patients with missing values of the covariates, predictors, and outcomes were removed from the analysis. Because there were a small number of COVID-19-related deaths and IPTW weighting can be unstable when event rates are small, we did not include weighted analysis of survival.

To mitigate risk of immortal time bias, as logistically it would be challenging for patients to be infused within 1 calendar day, a sensitivity analysis was performed excluding patients who were hospitalized within 1 day of a positive COVID-19 test being performed.

RESULTS

Figure 1 depicts the flow of patients through the system and the analyzed cohort. Of 1962 patients referred for mAb therapy during the relevant time period, 1309 were entered into the lottery. Of those, 480 were called and 829 were not called. One hundred ninety-one were infused, and 1118 were not infused. Twenty-three in the called group and 29 in the not called group were eliminated from the analysis because they did not meet age or BMI criteria, were known to have received or be planning to receive mAb infusion outside of our health system, or were hospitalized on the same day that their COVID-19 test turned positive. In the analyzed cohort, there were a total of 1257 patients: 451 in the called group, 806 in the not called group, 191 in the infused group, and 1066 in the not infused group. The mean number of days of symptoms patients had experienced by the time of infusion was 6, and the median was 6.35.

Of the 1257 patients included in the analysis, 137 (10.9%) were hospitalized within 30 days of a positive COVID-19 test for symptoms likely related to COVID-19. Forty out of 451 patients who were called (8.9%) were hospitalized within 30 days, compared with 97 of 806 patients who were not called (12.0%) (Table 1). Sixteen of 191 patients who were infused (8.4%) were hospitalized within 30 days, compared with 121 of 1066 patients who were not infused (11.4%) (Table 2). One patient was excluded from the weighted analysis due to missing SVI data. In the IPTW analysis, patients who were called to be offered infusion had a statistically significant 44% reduction in the odds of hospitalization compared with those who were not called (odds ratio [OR], 0.56; 95% CI, 0.36–0.89; $P = .01$) (Table 3). Patients who received bamlanivimab infusion had a statistically significant 68% reduction in the odds of hospitalization compared with those who did not receive bamlanivimab infusion (OR, 0.32; 95% CI, 0.11–0.93; $P = .04$) (Table 4). A sensitivity analysis comparing hospitalization rates among those who were called but not infused (12.7%) vs those who were not called at all (14.8%) showed no significant impact of having been selected to receive an offer of treatment (OR, 0.89; 95% CI, 0.59–1.34; $P = .58$).

Of the 1257 patients included in the analysis, a total of 11 died of COVID-19. Five of 451 patients who were called (1.1%) died of COVID-19, compared with 6 of 806 of patients who were not called (0.7%) (Table 1). One of 191 patients who received bamlanivimab (0.5%) died of COVID-19, compared with 10 of 1066 who did not receive bamlanivimab (0.9%) (Table 2).

When the analysis excluded patients who were hospitalized within 1 day of a positive COVID-19 test being performed (n = 9), the results were similar. In the IPTW analysis, statistically significant reductions in hospitalizations were observed in both the called group compared with the not called group (OR, 0.53; 95% CI, 0.33–0.85; $P = .01$) and the infused group compared with the not infused group (OR, 0.33; 95% CI, 0.11–0.97; $P = .04$).

DISCUSSION

Our analysis supports the effectiveness of bamlanivimab in adults ≥65 or with a BMI ≥35 outside of trial settings in reducing the incidence of hospitalization due to COVID-19 symptoms within 30 days of a positive test. It also suggests a mortality benefit, although the number of COVID-19-related deaths in the overall cohort (n = 11) was small and these results should be interpreted with caution.

In the initial all comers phase II data that constituted the foundation of the selective bamlanivimab EUA, the rates of hospitalization were 1.6% in the treatment group and 6.3% in the placebo group [3]. The subsequent phase III data for

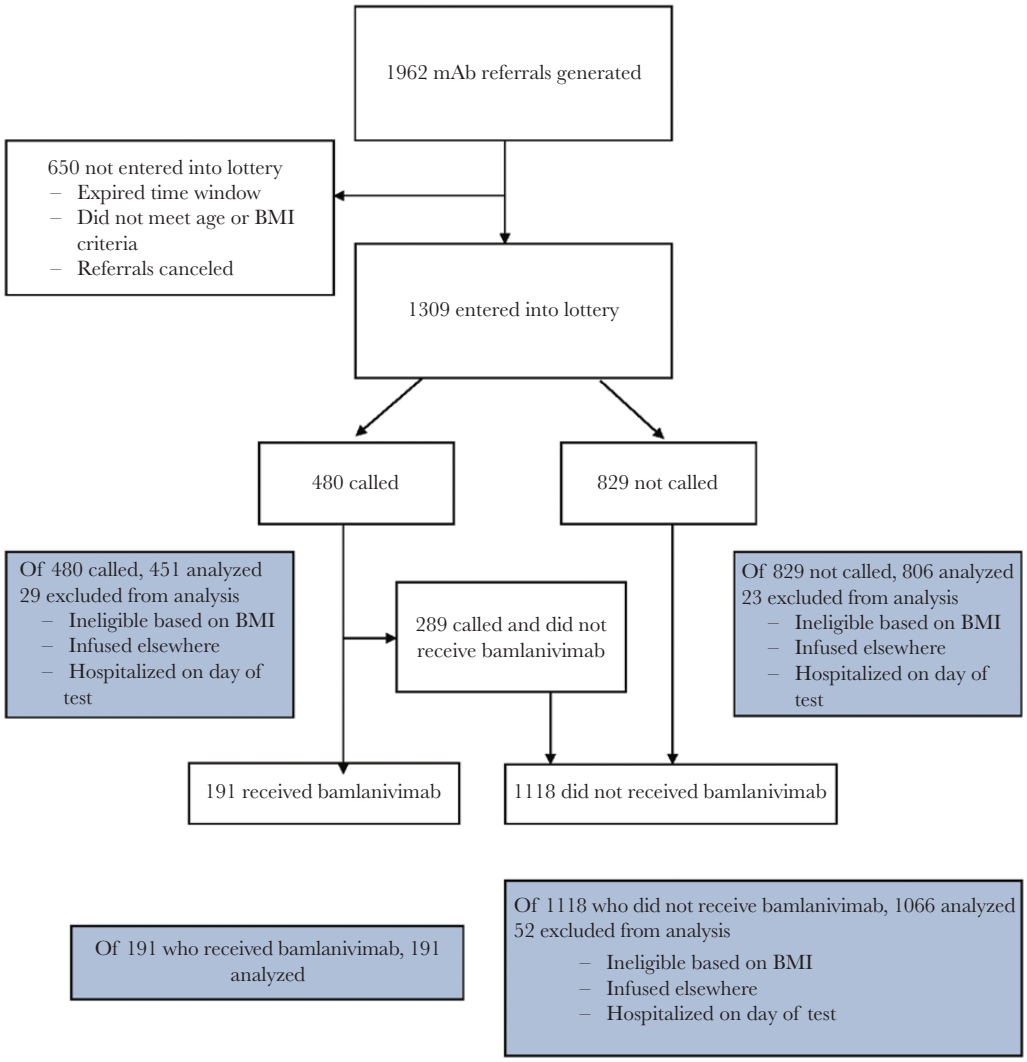

Figure 1. Flow of patients through the monoclonal antibody lottery-based allocation process. Abbreviations: BMI, body mass index; mAb, monoclonal antibody.

bamlanivimab together with etesevimab, which included only patients at high risk for progression to severe disease, demonstrated a hospitalization rate of 0.7% in the treatment group vs 5.8% in the placebo group [6]. In our study, the rates of hospitalization were 8.4% in the treatment group vs 11.4% in the untreated group. This study supports the effectiveness of mAb therapy in reducing hospitalization in what appears to be an overall sicker group of patients than the group studied in the clinical trials.

Our findings are broadly in line with those of other groups that have conducted similar studies on different populations and using different criteria for study inclusion [11–16], and they are in agreement with both the phase 2 and phase 3 results from randomized, placebo-controlled clinical trials of bamlanivimab and bamlanivimab together with etesevimab [3, 6, 17].

There are multiple strengths to the study. A large number of patients were included in the analysis. We were able to use the lottery allocation process to retrospectively identify a control group that was not offered therapy in large measure due to chance (ie, patients who were not called); the case–control analysis comparing those who were called with those who were not called supports the benefit of bamlanivimab in reducing hospitalization. This is important as there are multiple biases that are difficult to account for when comparing patients who are offered infusion and receive it with those who are offered it but do not receive it. We attempted to verify the significance of the results by additional analysis eliminating those patients who would not realistically have been able to receive the therapy under real-world conditions (ie, those who became too sick to receive treatment within 1 day of a test being sent). Finally, the use of inverse probability of treatment weighting in the regression modeling strengthens the findings.

There are multiple limitations to the study. First, although the lottery did involve significant elements of randomization, it did not entirely simulate the randomization of a clinical trial given the priority given to certain patients in the lottery

Table 1. Characteristics and Outcomes of Patients Entered Into mAb Lottery by Call Status

	Not Called (n = 806)	Called (n = 451)	Overall (n = 1257)
Age			
Mean (SD), y	64.0 (15.8)	64.6 (15.9)	64.2 (15.8)
Median [min, max], y	68.1 [18.3, 98.6]	67.9 [20.4, 93.6]	68.0 [18.3, 98.6]
Sex, No. (%)			
Female	435 (54.0)	272 (60.3)	707 (56.2)
Male	371 (46.0)	179 (39.7)	550 (43.8)
Race, No. (%)			
Asian	22 (2.7)	6 (1.3)	28 (2.2)
Black or African American	36 (4.5)	34 (7.5)	70 (5.6)
Other	36 (4.5)	31 (6.9)	67 (5.3)
Unknown	48 (6.0)	28 (6.2)	76 (6.0)
White	664 (82.4)	352 (78.0)	1016 (80.8)
Ethnicity, No. (%)			
Hispanic or Latino	53 (6.6)	38 (8.4)	91 (7.2)
Not Hispanic or Latino	553 (68.6)	277 (61.4)	830 (66.0)
Other	14 (1.7)	13 (2.9)	27 (2.1)
Unknown	186 (23.1)	123 (27.3)	309 (24.6)
Referral type, No. (%)			
Auto	767 (95.2)	304 (67.4)	1071 (85.2)
Manual	39 (4.8)	147 (32.6)	186 (14.8)
SVI			
Mean (SD)	0.327 (0.240)	0.404 (0.280)	0.354 (0.258)
Median [min, max]	0.271 [0.000400, 0.976]	0.322 [0.00140, 0.987]	0.287 [0.000400, 0.987]
Missing, No. (%)	1 (0.1)	0 (0)	1 (0.1)
Hospitalization (30 d), No. (%)			
No	709 (88.0)	411 (91.1)	1120 (89.1)
Yes	97 (12.0)	40 (8.9)	137 (10.9)
Death, No. (%)			
No	800 (99.3)	446 (98.9)	1246 (99.1)
Yes	6 (0.7)	5 (1.1)	11 (0.9)

Abbreviations: mAb, monoclonal antibody; SVI, Social Vulnerability Index.

by virtue of SVI and/or referral type. This is therefore a retrospective study, and there may be confounders that were not measured and therefore not included in the estimates of the weights. Although the estimated weights include type of referral (automatic vs manual), which could account for multiple potentially confounding factors such as underlying medical condition, tendency to seek health care, degree of connection with health care providers, and severity of illness at the time of referral, those are all factors that were not measured directly.

Second, we relied on the hospital system's electronic medical record to determine whether patients were hospitalized within 30 days of a positive COVID-19 test or died of COVID-19. Hospitalizations or deaths that were not captured in our electronic medical record would have been missed. This likely would be disproportionately true in patients who were not infused, as the group of patients who were infused might have had a closer connection with our health care system, such that that they were more likely to be manually referred and/or agree to infusion. Outcomes that were not evident in our medical record would most likely lead to underestimation of events in those who were not infused, which could in turn lead to underestimation of the effect of the therapy.

Third, our cohort included only adult patients who met age or BMI criteria but not patients who met other high-risk clinical criteria for use of mAb therapy such as immunosuppression, diabetes, chronic kidney disease, cardiovascular disease, or chronic lung disease. Our findings may not be generalizable to patients in those other high-risk groups. Fourth, the study was conducted in a single health care system, which limits its overall generalizability.

Finally, all of the patients in our cohort received bamlanivimab alone, as opposed to combination therapy with casirivimab together with imdevimab or bamlanivimab together with etesevimab. Bamlanivimab monotherapy is no longer authorized by EUA given the number of COVID-19 variants that the antibody cannot bind [18], and the circulating variants of the virus have changed significantly. This limits the generalizability of the study findings to other mAb therapies that are now in widespread use. During the time covered by this analysis, the majority of the SARS-CoV-2 infections in Massachusetts were likely with the alpha variant (B.1.1.7),

Table 2. Characteristics and Outcomes of Patients Entered Into mAb Lottery by Infusion Status

	Not Infused (n = 1066)	Infused (n = 191)	Overall (n = 1257)
Age			
Mean (SD), y	63.8 (16.1)	66.4 (13.9)	64.2 (15.8)
Median [min, max], y	68.0 [18.3, 98.6]	68.4 [21.4, 92.2]	68.0 [18.3, 98.6]
Sex, No. (%)			
Female	596 (55.9)	111 (58.1)	707 (56.2)
Male	470 (44.1)	80 (41.9)	550 (43.8)
Race, No. (%)			
Asian	25 (2.3)	3 (1.6)	28 (2.2)
Black or African American	53 (5.0)	17 (8.9)	70 (5.6)
Other	54 (5.1)	13 (6.8)	67 (5.3)
Unknown	69 (6.5)	7 (3.7)	76 (6.0)
White	865 (81.1)	151 (79.1)	1016 (80.8)
Ethnicity, No. (%)			
Hispanic or Latino	79 (7.4)	12 (6.3)	91 (7.2)
Not Hispanic or Latino	706 (66.2)	124 (64.9)	830 (66.0)
Other	20 (1.9)	7 (3.7)	27 (2.1)
Unknown	261 (24.5)	48 (25.1)	309 (24.6)
Referral type, No. (%)			
Auto	1000 (93.8)	71 (37.2)	1071 (85.2)
Manual	66 (6.2)	120 (62.8)	186 (14.8)
SVI			
Mean (SD)	0.350 (0.255)	0.376 (0.273)	0.354 (0.258)
Median [min, max]	0.288 [0.000400, 0.987]	0.282 [0.00140, 0.985]	0.287 [0.000400, 0.987]
Missing, No. (%)	1 (0.1)	0 (0)	1 (0.1)
Hospitalization (30 d), No. (%)			
No	945 (88.6)	175 (91.6)	1120 (89.1)
Yes	121 (11.4)	16 (8.4)	137 (10.9)
Death, No. (%)			
No	1056 (99.1)	190 (99.5)	1246 (99.1)
Yes	10 (0.9)	1 (0.5)	11 (0.9)

Abbreviations: mAb, monoclonal antibody; SVI, Social Vulnerability Index.

Table 3. Hospitalizations Within 30 Days of Positive SARS-CoV-2 Test by Called Status

	Hospitalized Within 30 Days of Positive SARS-CoV-2 Test, No. (%)			Weighted Logistic Regression (IPTW Weighting)	
	No (n = 1119)	Yes (n = 137)	Overall (n = 1256)	OR (95% CI)	*P* Value
Not called	708 (88.0)	97 (12.0)	805 (100)	Ref	-
Called	411 (91.1)	40 (8.9)	451 (100)	0.56 (0.36–0.89)	.01

Abbreviations: IPTW, inverse probability of treatment weighting; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 4. Hospitalizations Within 30 Days of Positive SARS-CoV-2 Test by Infusion Status

	Hospitalized Within 30 Days of Positive SARS-CoV-2 Test, No. (%)			Weighted Logistic Regression (IPTW Weighting)	
	No (n = 1119)	Yes (n = 137)	Overall (n = 1256)	OR (95% CI)	*P* Value
Not infused	944 (88.6)	121 (11.4)	1065 (100)	Ref	-
Infused	175 (91.6)	16 (8.4)	191 (100)	0.32 (0.11–0.93)	.04

Abbreviations: IPTW, inverse probability of treatment weighting; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

although we do not have specific viral genomic information in our medical record. Bamlanivimab and etesevimab are both active against the alpha variant, but animal models and in vitro testing indicate that these antibodies are not active against the beta or gamma variants, and only etesevimab has activity against delta [19, 20]. The benefits of these specific therapies

likely depend on the variants that are circulating at any given time. In addition, the relative benefit of monoclonal antibodies in vaccinated patients who develop symptomatic infections may be reduced.

Notwithstanding these limitations, the study supports the effectiveness of monoclonal antibody therapy for COVID-19 under real-world conditions in reducing the rate of hospitalization for adult patients with a BMI ≥35 or age ≥65 and suggests that there may be a mortality benefit in this population.

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Patient consent. The study was approved by the Institutional Review Board. The study does not include factors necessitating patient consent.

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