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MAJOR ARTICLE

# Effectiveness of Severe Acute Respiratory Syndrome Coronavirus 2 Monoclonal Antibody Infusions in High-Risk Outpatients

**Nicholas Piccicacco,[1] Kristen Zeitler,[1] Jose Montero,[2] Ambuj Kumar,[3,4] Seetha Lakshmi,[2] Kami Kim,[2] David Wein,[5] Tiffany Vasey,[5] Matthew Vasey,[5] and Asa Oxner[3]**

[1]Department of Pharmacy, Tampa General Hospital, Tampa, Florida, USA, [2]Division of Infectious Diseases, Department of Internal Medicine, University of South Florida Morsani College of Medicine, Tampa, Florida, USA, [3]Division of General Medicine, Department of Internal Medicine, University of South Florida Morsani College of Medicine, Tampa, Florida, USA, [4]Office of Research Methodology and Biostatistics Core, University of South Florida Morsani College of Medicine, Tampa, Florida, USA, and [5]Department of Emergency Medicine, Tampa General Hospital, Tampa, Florida, USA

***Background.*** Coronavirus disease 2019 (COVID-19) continues to stress the health care system. Neutralizing monoclonal antibodies (mAbs) were effective in reducing COVID-19–related hospitalizations and emergency department (ED) visits in their respective clinical trials. However, these results have yet to be reproduced in a practical setting following implementation of current US Food and Drug Administration (FDA) guidance.

***Methods.*** This retrospective cohort study included outpatients with confirmed COVID-19 infection, who had mild/moderate symptoms for 10 days or less, and who were deemed high-risk for severe COVID-19 under FDA's Emergency Use Authorization for mAbs. Patients who received either bamlanivimab or casirivimab/imdevimab from 18 November 2020 through 5 January 2021 were included (n = 200). This was compared against a control cohort of randomly selected high-risk COVID-19 outpatients who declined or were not referred for mAb treatment during the same period (n = 200). The primary outcome was a composite of 29-day COVID-19–related hospitalizations and/or ED visits. Prespecified secondary outcomes included the individual components of the primary endpoint, 29-day all-cause mortality, and serious adverse drug events.

***Results.*** Patients treated with mAbs were significantly less likely to be hospitalized or visit the ED compared with patients not treated with mAb (13.5% vs 40.5%; odds ratio, 0.23 [95% confidence interval, .14–.38]; $P < .001$). The mortality rate was 0% in the mAb group compared with 3.5% in the control group ($P = .02$). Only 2 patients receiving mAb experienced a serious adverse event requiring treatment.

***Conclusions.*** Among high-risk COVID-19 outpatients with mild/moderate symptoms, early administration of mAbs can potentially reduce the strain on the health care system during the current pandemic.

**Keywords.** bamlanivimab; casirivimab/imdevimab; COVID-19; SARS-CoV-2; monoclonal antibodies.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), emerged in December 2019 and has had a sustained global impact. The spectrum of illness for COVID-19 can range from asymptomatic to severe disease or even death. Patients at highest risk for poor outcomes include elderly patients; those with morbid obesity, diabetes, or chronic lung conditions; immunocompromised patients; and those with multiple comorbidities [1, 2]. As of March 2021, remdesivir is the only US Food and Drug Administration (FDA)–approved medication for COVID-19; however, FDA has also granted emergency use authorizations (EUA) to baricitinib, convalescent plasma, and 3 SARS-CoV-2 anti-spike neutralizing monoclonal antibody (mAb) agents.

SARS-CoV-2 mAb infusions were developed to promote passive immunity and reduce overall viral load. Both bamlanivimab and casirivimab/imdevimab initially demonstrated the ability to reduce SARS-CoV-2 viral load, more than their respective placebo groups. In the interim analysis of bamlanivimab's phase 2 trial, this medication caused a 10.4% absolute reduction in hospitalizations and emergency department (ED) visits for high-risk COVID-19 patients (age ≥65 years or with a body mass index [BMI] of ≥35 kg/m$^2$) [3]. Additionally, the casirivimab/imdevimab study (REGN-COV2) exhibited a 9% absolute reduction in hospitalizations and ED visits for serum antibody–negative patients [4]. Due to limited therapeutic options for COVID-19, both mAbs were granted FDA EUAs based on these data. Since these EUA approvals, additional data have shown casirivimab/imdevimab to reduce hospitalizations by 70% compared to

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Correspondence: Nicholas Piccicacco, PharmD, BCIDP, AAHIVP, Tampa General Hospital, 1 Tampa General Circle, Tampa, FL 33606, USA (npiccicacco@tgh.org).

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placebo [5]. Furthermore, a new monoclonal antibody cocktail of bamlanivimab combined with etesevimab was also granted FDA EUA approval; available data have highlighted this agent's clinical benefit through a relative risk reduction in COVID-19–related hospitalizations and deaths by 87% [6].

The purpose of this study is to evaluate the pragmatic effectiveness of SARS-CoV-2 mAbs, specifically bamlanivimab and casirivimab/imdevimab, in preventing COVID-19–related hospitalizations and ED visits. Both medications were given EUAs based on limited clinical outcomes data; therefore, their true utility in a nontrial setting is still unknown.

## METHODS

### Study Design

This is a single-center, retrospective cohort study that included outpatients with confirmed COVID-19 infection, who had mild to moderate symptoms without an increasing need for oxygen compared to their baseline, and were deemed high risk for progression to severe COVID-19 under the FDA's EUA for mAbs. The study protocol was reviewed and approved by the University of South Florida (USF) institutional review board.

### Patients

All patients had confirmed COVID-19 infection (either by antigen or polymerase chain reaction testing that was performed at our hospital or associated ambulatory clinics), were >12 years of age, and weighed at least 40 kg. In addition, all patients were classified as having mild to moderate symptoms for 10 days or less at the time of inclusion and as being at high risk for progression to severe COVID-19 as detailed in FDA EUA documents (Table 1) [7, 8].

**Table 1. High-Risk Coronavirus Disease 2019 Patient Criteria per the Food and Drug Administration Emergency Use Authorization Fact Sheets for Bamlanivimab and Casirivimab/Imdevimab**

| |
|---|
| Age ≥65 y |
| BMI ≥35 kg/m$^2$ |
| Diabetes |
| Chronic kidney disease |
| Immunosuppressant disease or treatment |
| Age ≥55 y AND have 1 of the following: |
| • Hypertension |
| • Chronic respiratory disease/chronic obstructive pulmonary disease |
| • Cardiovascular disease |
| Age 12–17 y AND have 1 of the following: |
| • BMI ≥85th percentile for age and gender |
| • Sickle cell disease |
| • Congenital or acquired heart disease |
| • Neurodevelopmental disorder, eg, cerebral palsy |
| • Medical-related technological dependence, eg, tracheostomy, gastrostomy, or positive-pressure ventilations (not related to COVID-19) |
| • Asthma, reactive airway, or other chronic respiratory disease that requires daily medication control |

Source: Food and Drug Administration [7, 8].

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019.

At our institution, patients with confirmed COVID-19 infection in the ambulatory or hospital setting are referred to the COVID-19 Confirmed (CoCo) Clinic for follow-up and at-home monitoring. This telehealth clinic, which documents clinic notes in the electronic medical record (EMR), allowed for thorough follow-up of both cohorts. Because of this, patients were excluded from our study if there was no documentation from this clinic after initial diagnosis or mAb administration.

Outpatients who received a single infusion of either bamlanivimab 700 mg or casirivimab/imdevimab 2400 mg from 18 November 2020 through 5 January 2021 were included in the mAb cohort (n = 200). The decision to administer one mAb or the other was dependent on weekly drug inventory and allocation, room temperature stability concerns when transporting drug to our initial off-campus infusion clinic location, and ease of compounding to accommodate high infusion clinic volumes. These patients represent the initial 200 mAb infusions since the program's inception. As of 15 April 2021, our institution's custom operations map has administered >700 mAbs in a single hospital-based ambulatory clinic. This clinic utilizes emergency medicine advanced practice providers as well as emergency medicine physicians for collaborative purposes.

The control cohort consisted of randomly selected high-risk COVID-19 outpatients who did not receive mAb during the same period (n = 200). These patients were either offered mAb and declined or were never referred for mAb and missed their candidacy window. The list of control patients was generated in our EMR (Epic Systems Corporation, Verona, Wisconsin), using filters matching the high-risk criteria in the mAb group as detailed in FDA EUA documents (Table 1). After this list was produced, it was uploaded into a spreadsheet where each patient was assigned a number via a random number generator and then sorted from lowest to highest. Patients were excluded from the control group if they received a mAb dose, had >10 days of symptoms before their initial positive SARS-CoV-2 test, or were immediately hospitalized at the time of their initial COVID-19 diagnosis. During chart review, it was manually confirmed that these patients truly met EUA criteria by age, past medical history, and symptom onset timing. To make a fair comparison with the exposure cohort, we also excluded patients who did not have a theoretical window of 48 hours or more from COVID-19 diagnosis for mAb administration in the outpatient setting.

### Primary and Secondary Outcomes

The primary outcome was a composite of COVID-19–related hospitalizations and ED visits within 29 days post-mAb infusion or 29 days from initial COVID-19 diagnosis in the control cohort. Hospitalizations were denoted as ≥24 hours of an acute care stay. Of note, if a patient's initial COVID-19 diagnosis

was made in the ED, that did not count toward an ED visit in either cohort.

Prespecified secondary outcomes included the incidence of each component of the primary endpoint, 29-day all-cause mortality, as well as serious adverse drug events in the mAb cohort. Adverse drug events were counted if an FDA MedWatch form was submitted. We also sought to examine whether any comorbidity was independently associated with the primary outcome and the optimal day for mAb administration after symptom onset.

### Sample Size

To determine sample size, the bamlanivimab BLAZE-1 trial's post hoc analyses of high-risk patients, which included ≥65 years and/or BMI of ≥35 kg/m$^2$, were utilized. Chen and colleagues observed an 10.4% absolute reduction in COVID-19–related hospitalizations and ED visits [3]. Group sample sizes of 185 per group achieves 90% power to detect a difference between groups of 15% for the primary composite endpoint. The expected composite outcome event rate in mAb group is assumed to be 20% under the null hypothesis and 35% under the alternative hypothesis. The proportion in the control group is estimated to be 20%. The test statistic used is the 2-sided $Z$ test with pooled variance with a significance level of 5%.

### Statistical Analyses

Descriptive statistics were used to summarize patient and disease characteristics where continuous variables are summarized as mean and standard deviation and rates for categorical variables. The difference in continuous variables among COVID-19 subjects receiving vs not receiving mAb was assessed using the nonparametric Kruskal-Wallis test and $\chi^2$ test for categorical variables. The adjusted and unadjusted associations between categorical variables and compared groups was assessed using binary logistic regression and summarized as odds ratio (OR) along with 95% confidence interval (CI).

The optimal day for administration of mAb after symptom onset was assessed using the receiver operating curve (ROC) analysis and summarized as area under the curve (AUC) along with 95% CI. The α level was set at .05 for all analyses. All data analyses were performed using SPSS version 26 statistical analysis software (IBM Corporation, Armonk, New York).

## RESULTS

### Patient Demographics and Characteristics

As shown in Table 2, the 2 groups were relatively comparable. Patients in the mAb arm had numerically a smaller number of risk factors (mean of 2.1 ± 1.1 vs 2.3 ± 1.2; $P$ = .02). A significantly higher proportion of patients in the mAb arm were immunocompromised (17% vs 7.5%; $P$ = .01), which included patients with solid organ transplants, HIV/AIDS, active cancer on chemotherapy, and humoral immunity deficits (either inherited or due to immunosuppressive therapy). However, the control arm had significantly more patients aged ≥55 years with hypertension (60% vs 46.5%; $P$ = .01) or chronic lung disease (16% vs 8%; $P$ = .02). Patients in the mAb arm received either bamlanivimab (76%) or casirivimab/imdevimab (24%). The mean duration of symptoms prior to receipt of mAb was 5.1 ± 2.2 days.

### Primary Outcome

Patients treated with mAb were significantly less likely to be hospitalized or visit the ED compared with control patients (13.5% vs 40.5%), resulting in an OR of 0.23 (95% CI, .14–.38; $P$ < .001) (Table 3). This significant reduction represents a number needed to treat (NNT) of 4 (95% CI, 2.8–5.3). The results remained unchanged when adjusted for immunocompromise, age ≥55 with hypertension or lung disease, and number of risk factors (adjusted OR, 0.22 [95% CI, .13–.37]; $P$ < .001).

These results remained significant when comparing the individual mAbs against the control cohort as well. Patients who received bamlanivimab (n = 152) were less likely to be hospitalized or visit the ED compared with control patients (14.5% vs 40.5%), resulting in an OR of 0.25 (95% CI, .15–.42; $P$ < .001). Also, patients who received casirivimab/imdevimab (n = 48) when compared with control patients demonstrated a lower likelihood of the composite primary endpoint (10.4% vs 40.5%), resulting in an OR of 0.17 (95% CI, .06–.45; $P$ < .001).

### Secondary Outcomes

Patients treated with mAb were significantly less likely to be hospitalized compared with the control cohort (7.5% vs 30%), resulting in an OR of 0.19 (95% CI, .1–.35; $P$ < .001) and NNT of 4 (95% CI, 3.4–6.6). The results remained unchanged when adjusted for the previously mentioned risk factors (adjusted OR, 0.18 [95% CI, .1–.35]; $P$ < .001).

Patients treated with mAb were significantly less likely to visit the ED (6% vs 13%), resulting in an OR of 0.43 (95% CI, .21–.87; $P$ = .02) and NNT of 14 (95% CI, 7.9–77.3). The results remained unchanged when adjusted for the previously mentioned risk factors (adjusted OR, 0.43 [95% CI, .2–.89]; $P$ = .023).

All-cause mortality in the mAb group was 0% vs 3.5% in the control group ($P$ = .02). Two mAb patients experienced an adverse event requiring intervention. One patient developed rectal bleeding after the infusion, which required hospital admission; a second patient developed an allergic reaction within a few hours of infusion, resulting in an ED visit. The patient experienced diffuse redness and rash, which resolved with diphenhydramine.

**Table 2. Patient Demographics and Baseline Clinical Characteristics**

| Characteristic | mAb (n = 200) | Control (n = 200) | *P* Value |
|---|---|---|---|
| Age, y, mean ± SD | 62.5 ± 14.8 | 63.9 ± 13.4 | .52 |
| Gender, female, No. (%) | 98 (49) | 109 (54.5) | .32 |
| Race, No. (%) | | | |
| White | 123 (61.5) | 110 (55) | .19 |
| African American | 25 (12.5) | 42 (21) | |
| Hispanic | 22 (11) | 23 (11.5) | |
| Asian | 6 (3) | 3 (1.5) | |
| Other/unknown | 24 (12) | 22 (11) | |
| BMI, kg/m$^2$, mean ± SD | 31.7 ± 7.6 | 31.3 ± 7.3 | .75 |
| Risk factors for severe COVID-19, No. (%) | | | |
| Age ≥65 y | 100 (50) | 105 (52.5) | .69 |
| BMI ≥35 kg/m$^2$ | 59 (29.5) | 57 (28.5) | .91 |
| Diabetes | 67 (33.5) | 85 (42.5) | .08 |
| CKD/ESRD | 13 (6.5) | 17 (8.5) | .57 |
| Immunocompromised[a] | 34 (17) | 15 (7.5) | **.01** |
| Age 55 y + hypertension | 93 (46.5) | 120 (60) | **.01** |
| Age 55 y + chronic lung disease | 16 (8) | 32 (16) | **.02** |
| Age 55 y + CVD | 21 (10.5) | 29 (14.5) | .29 |
| Multiple high-risk factors | 122 (61) | 141 (70.5) | .06 |
| No. of risk factors, mean ± SD | 2.1 ± 1.1 | 2.3 ± 1.2 | **.02** |
| COVID-19 symptom onset | | | |
| Days of symptoms prior to positive SARS-CoV-2 test, mean ± SD | 2.7 ± 2 | 2.9 ± 2.4 | .62 |
| Days of symptoms prior to mAb infusion, mean ± SD | 5.1 ± 2.2 | … | |
| mAb administered, No. (%) | | | |
| Bamlanivimab | 152 (76) | … | |
| Casirivimab/imdevimab | 48 (24) | … | |

Bold *P* Values denote statistical significance ($P < .05$).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; ESRD, end-stage renal disease; mAb, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

[a]Included solid organ transplant, HIV/AIDS, active cancer on chemotherapy, and humoral immunity deficit (either inherit or due to immunosuppressive therapy) patients.

Administering mAb within 6 days of symptom onset was associated with the highest efficacy with a sensitivity and specificity of 67% and 56%, respectively, for preventing either hospitalizations or ED visits within 29 days (Table 4). The AUC was 0.66 (95% CI, .54–.76). Administering mAb within 7 days was associated with the highest efficacy with a sensitivity and specificity of 74% and 75%, respectively, for preventing hospitalizations within 29 days with AUC of 0.76 (95% CI, .64–.85). Administering mAb within 6 days was associated with the highest efficacy, with a sensitivity and specificity of 50% and

**Table 3. Primary and Secondary Outcomes**

| Outcome | mAb (n = 200) | Control (n = 200) | NNT | *P* Value |
|---|---|---|---|---|
| Primary outcome | | | | |
| Day 29 COVID-19 hospitalization and/or ED visit, No. (%) | 27 (13.5) | 81[a] (40.5) | 4 | |
| Unadjusted OR (95% CI) | 0.23 (.14–.38) | | … | **<.001** |
| Adjusted OR (95% CI) | 0.22 (.13–.37) | | … | **<.001** |
| Secondary outcomes | | | | |
| Day 29 COVID-19 hospitalization, No. (%) | 15 (7.5) | 60 (30) | 4 | |
| Unadjusted OR (95% CI) | 0.19 (.1–.35) | | … | **<.001** |
| Adjusted OR (95% CI) | 0.18 (.1–.35) | | … | **<.001** |
| Day 29 COVID-19 ED visit, No. (%) | 12 (6) | 26 (13) | 14 | |
| Unadjusted OR (95% CI) | 0.43 (.21–.87) | | … | **.02** |
| Adjusted OR (95% CI) | 0.43 (.2–.89) | | … | **.02** |
| Day 29 all-cause mortality, No. (%) | 0 (0) | 7 (3.5) | 14 | **.01** |

Bold *P* Values denote statistical significance ($P < .05$).

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ED, emergency department; mAb, monoclonal antibody; NNT, number needed to treat; OR, odds ratio.

[a]Five patients during the 29-day follow-up period had both an ED visit as well as hospitalization

53%, respectively, for preventing ED visits within 29 days with AUC of 0.53 (95% CI, .31–.69).

Patients treated with mAb within 6 days were significantly less likely to be hospitalized or visit the ED compared with patients treated with mAb after 6 days (7.7% vs 28.1%), resulting in an OR of 0.21 (95% CI, .09–.5; $P < .001$) (Table 4). This significant reduction represents an NNT of 5 (95% CI, 3.0–12.6). The results remained unchanged when adjusted for immunocompromised, age ≥55 years with hypertension or lung disease, and number of risk factors (adjusted OR, 0.22 [95% CI, .09–.53]; $P < .001$).

## DISCUSSION

The results from our observational study show that mAbs are an effective intervention for reducing the risk of hospitalization and/or ED visits in high-risk COVID-19 outpatients. We instead focused on relevant patient-oriented clinical outcomes. Importantly, we observed 77% reduced odds of 29-day hospitalizations and ED visits with an absolute difference in this composite endpoint of 27%, compared to 4.7% in the BLAZE-1 trial; when examining those aged ≥65 years and patients with BMI ≥35 kg/m$^2$ in BLAZE-1, this endpoint value increased to 9% [3]. It should be noted that our data were powered to detect a difference between our groups. Our dataset also demonstrated a benefit over the REGN-COV2 trial, which showed a 9% absolute reduction in their composite endpoint [4]. Individually, we noted 81% reduced odds of hospitalizations and 57% reduced odds of ED visits with mAb infusions. Our data are in line with more recently available data on casirivimab/imdevimab and bamlanivimab/etesevimab, which have shown a relative risk reduction in hospitalizations and deaths by 70% and 87%, respectively [5, 6]. This is one of the first publications to show the effectiveness of mAbs for high-risk COVID-19 outpatients in preventing utilization of ED and hospital visits.

The COVID-19 pandemic has put a significant strain on fiscal and personnel resources across all health systems. During the summer of 2020, the Florida Hospital Association estimated that total losses due to COVID-19 (after accounting for federal relief) through the first 4 months of COVID-19 were $3.8 billion, with this number estimated to increase to $7.4 billion by the end of August [9]. These staggering costs are due to lost procedural revenue, increase in hospitalizations especially for critically ill patients, changes in hospital bed utilization to promote safe distancing, and use of new therapeutics without reimbursed costs. Patients in high-risk populations, which are the target for mAbs under EUA guidance, have the potential to further overwhelm the health care system due to a strain on health care personnel and the need for high quantities of resources. We believe our unique interdisciplinary program for mAb infusions and telehealth clinic (CoCo) providing continuity of care for our COVID-19 patients allowed us to demonstrate the benefit of this therapy for high-risk patients as evidenced in the primary endpoint. Our data demonstrate the potential impact of mAbs to keep high-risk COVID-19 patients out of the hospital and reduce the negative impact on the health care system.

In comparing our 2 groups, we saw a numerical difference in mortality (0% vs 3.5%). We were not powered, nor did we seek to show a mortality benefit with mAb infusions. Deaths in the control arm can be explained by the natural progression of COVID-19, which to date has caused 545 751 deaths in the US through the week of 10 April 2021 [10]. As these high-risk patients are prone to hospitalizations, mechanical ventilation, and other complications including death from COVID-19, it is even more vital to evaluate the clinical effectiveness of mAbs and consider these high-risk patients for mAb. Additionally, health care providers and the public should be educated to seek mAb candidacy at the earliest onset of COVID-19 symptoms.

Overall, patients receiving mAbs tolerated both agents well. We reported only 2 serious adverse events. In published trials, no patients were noted to have developed serious adverse events with bamlanivimab; the most common side effects included nausea (3.9%), dizziness (3.2%), and diarrhea (3.2%) [3]. Casirivimab/imdevimab was similarly well tolerated, with

**Table 4. Receiver Operating Curve Analysis: Optimal Time for mAb Administration After Symptom Onset**

| Outcome | AUC (95% CI) | Sensitivity | Specificity | |
|---|---|---|---|---|
| Day 29 COVID-19 hospitalization and/or ED visit | 0.66 (.54–.76) | 67% | 56% | |
| Day 29 COVID-19 hospitalization | 0.76 (.64–.85) | 74% | 75% | |
| Day 29 COVID-19 ED visit | 0.53 (.31–.69) | 50% | 53% | |
| **Impact of mAb Earlier vs. Later than 6 Days from Symptom Onset** | | | | |
| | mAb Administered ≤ 6 d of Symptoms (n = 143) | mAb Administered > 6 d of Symptoms (n = 57) | NNT | *P* value |
| Day 29 COVID-19 hospitalization and/or ED visit, No. (%) | 11 (7.7) | 16 (28.1) | 5 | |
| Unadjusted OR (95% CI) | 0.21 (.09–.5) | | | **<.001** |
| Adjusted OR (95% CI) | 0.22 (.09–.53) | | | **<.001** |

Bold *P* Values denote statistical significance ($P < .05$).

Abbreviations: AUC, area under the curve; CI, confidence interval; COVID-19, coronavirus disease 2019; ED, emergency department; mAb, monoclonal antibody; NNT, number needed to treat; OR, odds ratio.

1 serious adverse event reported [4]. Our experience with both agents is comparable to previously published studies and reinforces their safety profiles.

Using ROC analyses, we investigated if there was an optimal window when receipt of mAb would reduce the risk for subsequent hospitalization and/or ED visit within 29 days of infusion. Our data showed that the benefit with mAb is best served when given within 6 days of initial symptoms to reduce the risk for ED visits and within 7 days for hospitalizations. Of note, those patients in our study who required an ED visit or were hospitalized generally presented early in their postinfusion course; only 1 patient required an ED visit >14 days after receipt of mAb. In their corresponding trials, patients were randomized to bamlanivimab within a median of 3 days of symptoms and within 4 days with casirivimab/imdevimab [3, 4]. Our data support early administration of mAbs to reduce subsequent hospital or ED visits. Reflecting on our findings, it would be prudent to consider decreasing the FDA eligibility window for mAbs to within 7 days of symptom onset. These medications are a relatively scarce resource and it would be practical to administer them to patients who are likely to see the most benefit.

It is important to note that in BLAZE-1, most patients requiring an ED visit were subsequently admitted to the hospital, so they refer to their composite as hospitalizations [3]. Our study differs since ED visits documented patients who visited the ED but were subsequently sent home, indicating that these patients did not require additional health care resources. Additionally, REGN-COV2 included any patients with telehealth and urgent care visits in their composite analysis [4]. Our standard patient workflow for all individuals diagnosed with COVID-19 included subsequent telehealth follow-up. Since all patients were contacted in the initial days post-mAb infusion, we did not include telehealth in the numerator of our primary outcome.

Our study has several limitations. Due to its retrospective nature, this study may have been affected by confounding variables that a placebo-controlled, randomized clinical trial design would have eliminated. Since both mAbs had already shown promising data on reducing health care exposure and received FDA EUAs, it was not ethical to withhold treatment and conduct a placebo-controlled study. Although we did assess whether specific comorbidities were independently associated with the primary outcome, the sample size of each comorbidity was small. Additional data after larger numbers of patients are treated may address whether specific subgroups of at-risk patients benefit more from mAb treatment.

Due to the data being collected at a single center, patients who were hospitalized or visited an ED at another institution could have been missed in the primary endpoint; however, both mAb and control groups were at the same risk for this limitation. This was also minimized due to routine follow-up by our telehealth clinic, which documented when patients were admitted to an outside hospital. Since our study was conducted at a single center in Tampa, Florida, the external validity to other health care systems and geographical areas is unknown. Due to Florida's high elderly population per capita and surge during the holiday season when this study was conducted, our control cohort may have had higher rates of hospitalizations in comparison to other areas during that same period and the previous clinical trials for mAbs. Finally, we may have introduced selection bias into our control group since this randomized patient list was created at an academic medical center and its associated clinics that see higher-acuity patients than a community health care system. Therefore, the rate of hospitalizations and ED visits in the control group may be an overestimation of the true community incidence in the entire high-risk patient population.

Given that our study was conducted during the initial weeks after FDA EUA approval for both bamlanivimab and casirivimab/imdevimab, there may be residual confounding differences in both cohorts that a retrospective study cannot explore. For example, we were unable to decipher why patients declined or were not offered mAbs in the control cohort even though they were at high risk for severe COVID-19 progression. We can surmise that because these medications were newly EUA approved, patients and health care providers were less familiar with the benefits and side effects of mAbs and therefore, less likely to prescribe or accept referral for these medications. We also cannot comment on structural barriers to mAb care, including health literacy and ethnic differences in medical acceptance. Additionally, there were more immunocompromised patients in our exposure cohort, which was predominately driven by high rates of solid organ transplant recipients. Our hospital is one of the top 10 solid organ transplant institutes by volume in the US and these providers and clinics were early adopters to the benefits of mAb therapy, which led to high referral and acceptance rates in these patients.

Another limitation to our study is the large percentage of bamlanivimab monotherapy patients and recent revocation of its EUA approval due to in vitro activity concerns with COVID-19 variants. However, based on internal data from our hospital's esoteric and USF molecular laboratories that are sequencing SARS-CoV-2 genomes, we know there was a low percentage (<2%) of circulating variants in the Tampa Bay region in January 2021. Additionally, the most predominant variant at that time was B.1.1.7 (UK origin), which does not affect bamlanivimab's in vitro activity based on pseudovirus neutralization data [7]. Therefore, our data showing significant benefit are likely to be readily extrapolated to predict effectiveness for the currently EUA-approved mAbs bamlanivimab/etesevimab and casirivimab/imdevimab.

Last, we only noted 2 serious adverse drug events, which could have overestimated the safety profile of mAbs. Based on chart review, it would have been difficult to ascertain between mAb non–serious adverse events vs COVID-19 progression of symptoms, which is why it was decided to only collect on serious adverse drug events that could be clearly linked to mAb administration.

## CONCLUSIONS

Several advisory groups, including the Infectious Diseases Society of America and the National Institutes of Health, recommend use of bamlanivimab/etesevimab or casirivimab/imdevimab in high-risk ambulatory patients, albeit based on low strength of clinical trial evidence [11, 12]. Our study demonstrates that outpatients with risk factors for severe COVID-19 have reduced odds of hospitalizations and ED visits when mAbs are administered early in disease. Recently, additional data for both bamlanivimab/etesevimab and casirivimab/imdevimab have shown in yet to be published phase 3 trials that these medications can significantly reduce hospitalizations and death, which mirrors our study findings [5, 6]. Our results further strengthen the clinical utility of mAbs and FDA's EUA criteria for use in high-risk outpatients. Even though vaccination is rightfully receiving heavy attention at this time, education to the public and health care providers on targeting the use of mAbs in this patient population can help minimize stress on hospitals and health care systems during this pandemic.

### Notes

***Author contributions.*** N. P. and K. Z. had full access to the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. N. P. and K. Z. made equal contributions for authorship. Concept and design: N. P., K. Z., A. O., J. M. Acquisition, analysis, or interpretation of data: N. P., K. Z., A. O., J. M., S. L., T. V. Drafting of manuscript: N. P., K. Z.. Critical revision of the manuscript for important intellectual content: T. V., M. V., A. K., D. W., S. L., K. K., A. O., J. M. Statistical analysis: A. K., K. Z., N. P.

***Patient consent statement.*** The institutional review board at the University of South Florida approved this study design as minimal risk and waived patient consent requirements.

***Potential conflicts of interest.*** K. K. is a site investigator for several Regeneron Pharmaceuticals, Inc, clinical trials in COVID-19 and currently sits on the editorial board for the *Sanford Guide*. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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