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## Impact of early versus late administration of bamlanivimab on readmissions in patients with high-risk COVID-19

James D. Melton III, MD<sup>a</sup>, Kayla Wilson, PharmD, MS<sup>a,\*</sup>, Fred Blind, MD<sup>a</sup>, Andrew Barbera, MD<sup>a</sup>, Donna Bhisitkul, MD<sup>b</sup>, Shannon Hasara, PharmD<sup>a</sup>, Karen Homa, PhD<sup>c</sup>, Juliana Karp, MD<sup>a</sup>, Hal Escowitz, MD<sup>a</sup>, Todd Haber, MD<sup>a</sup>, Diana DeGroot, DNP, RN<sup>a</sup>, Jonathan Anderson, MD<sup>a</sup>, Jason DeLeon, MD<sup>a</sup>, Jesse De Los Santos, MD<sup>a</sup>, Donna Faviere, DNP, RN<sup>a</sup>, Joanne Fuell, MN, RN<sup>a</sup>, Rita Gillespie, DO<sup>a</sup>, Jesse Glueck, MD<sup>a</sup>, Cliff Reeber, MD<sup>a</sup>, David J. Rhodes, MD<sup>b</sup>, Vashun Rodriguez, MD<sup>a</sup>

<sup>a</sup> Department of Emergency Medicine, Lakeland Regional Health, Lakeland, FL, USA

<sup>b</sup> Department of Pediatric Emergency Medicine, Lakeland Regional Health, Lakeland, FL, USA

<sup>c</sup> Department of Research and Sponsored Studies, Lakeland Regional Health, Lakeland, FL, USA

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### ABSTRACT

**Background:** Recombinant monoclonal antibody therapies have been utilized under emergency use authorization (EUA) for the prevention of clinical decompensation in high-risk COVID-19 positive patients for up to 10 days from symptom onset. The purpose of this study was to determine the impact of the timing of the monoclonal antibody, bamlanivimab, on clinical outcomes in high-risk COVID-19 positive patients.

**Methods:** This was an IRB-approved, retrospective evaluation of adult patients who received bamlanivimab per EUA criteria in the emergency department (ED). Patients were dichotomized into two groups– 3 days of symptoms or less (*early*) versus 4 to 10 days (*late*). The primary outcome was hospitalization for COVID-related illness at 28 days (or treatment failure). Secondary outcomes were COVID-related ED visits at 28 days, hospital and intensive care unit (ICU) length of stay (LOS), and in-hospital mortality at 28 days.

**Results:** A total of 839 patients were included in the analysis. There was no difference observed in COVID-related hospitalization rates within 28 days between the early and late bamlanivimab administration groups (7.5% vs. 8.2%,  $p = 0.71$ ). There was no difference in COVID-related ED visits within 28 days with 13% of patients returning to the ED.

**Conclusions:** In conclusion, there were no differences in the rates of hospitalization at 28 days when bamlanivimab was administered in the first 3 days of illness versus days 4 to 10. Future prospective studies are warranted to expand upon the characteristics of patients that may or may not benefit from monoclonal antibody therapy.

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## 1. Introduction

### 1.1. Background

Since the discovery of the novel coronavirus, SARS-CoV-2, in December 2019, Coronavirus disease 2019 (COVID-19) has developed into a global pandemic responsible for over 3.3 million deaths and over 163 million infected individuals [1]. Infection with COVID-19 can cause a wide variety and range of symptoms with older adults and those with underlying medical conditions at higher risk for severe complications.

Multiple therapeutic agents have been developed and tested with the goal of reducing morbidity and mortality in COVID-19 illness. Bamlanivimab, a recombinant neutralizing monoclonal antibody directed against the spike protein of SARS-CoV-2, emerged as a promising therapy to block viral entry into host cells. On November 9, 2020, bamlanivimab received emergency use authorization (EUA) by the Food and Drug Administration (FDA) [2]. Monoclonal antibody therapy is authorized for adults and children over the age of 12 with mild to moderate COVID-19 illness who are at high risk of clinical decompensation and severe disease. The findings from Chen et al. in the BLAZE-1 study supported the authorization decision by the FDA [3]. Though the study failed to determine a difference in its primary outcome, change from baseline in viral load at day 11, a difference was observed in a secondary endpoint, reduction in hospitalizations at day 29. Further analysis discovered a greater reduction in hospitalization in bamlanivimab-treated

\* Corresponding author at: Lakeland Regional Health, 1324 Lakeland Hills Blvd, Lakeland, FL 33805, USA.

E-mail address: [Kayla.Wilson@mylrh.org](mailto:Kayla.Wilson@mylrh.org) (K. Wilson).

patients who were aged 65 years or older and those with a body mass index (BMI) of at least 35 kg/m<sup>2</sup> or more.

### 1.2. Importance

During this study time period, National Institutes of Health (NIH) guidelines cited insufficient data to recommend either for or against the use of bamlanivimab for treatment of outpatients with mild to moderate COVID-19 [4]. The Infectious Diseases Society of America (IDSA) echoed these recommendations and suggested *against* the routine use of bamlanivimab, citing a low certainty of evidence and imprecision of the data, as few hospitalizations were recorded in BLAZE-1 [5]. At the time of this writing, the NIH guidelines have been updated to recommend *for* the use of bamlanivimab in combination with an additional antibody, etesevimab. The panel cites the emergence of new data suggesting that bamlanivimab as monotherapy is less effective against circulating variants. This decision was published in April 2021, after this study period had ended. However, there is still a need for continued research to identify the time point at which bamlanivimab, or any monoclonal therapy, would be most efficacious during COVID-19 illness. The authors hypothesize that bamlanivimab, when administered early in illness (within 3 days of symptom onset), will be more efficacious than later administration, as pro-inflammatory markers increase and the window closes for preventing viral entry into host cells.

### 1.3. Goals of this investigation

The purpose of this study was to determine the impact of the timing of bamlanivimab administration on clinical outcomes in high-risk COVID-19 positive patients at a community hospital. Additional study goals were to describe patient characteristics of the high-risk cohort, to report clinical outcomes, and to determine factors associated with hospitalization at 28 days.

## 2. Methods

### 2.1. Study design

This was an institutional review board-approved, retrospective, observational study of high-risk COVID-19 positive patients who received bamlanivimab therapy in the emergency department (ED). The study was conducted in a 165-bed ED with a pre-pandemic volume of more than 210,000 annual visits. The study institution was designated as a bamlanivimab treatment site by the Department of Health on November 16, 2020. The ED was selected as the most suitable setting to identify at-risk patients eligible for therapy and is readily equipped to handle any infusion-related reactions. A multidisciplinary team was quickly assembled to operationalize monoclonal antibody therapy, and the first infusion was administered within 24 h of receipt of the medication. From November 16, 2020 to March 31, 2021, the study institution administered over 1000 doses of bamlanivimab to outpatient, high-risk COVID-19 positive patients. An analytics report identified all adult patients aged 18 years or older with mild to moderate COVID-19 that received bamlanivimab administrations in the ED between November 19, 2020 and February 18, 2021. COVID-19 diagnosis was determined either by positive Reverse – Transcription Polymerase Chain Reaction (RT-PCR) at the study institution, or verification of outpatient clinic positive RT-PCR result. During the study period, the NIH guidelines recommended offering pregnant patients monoclonal antibody therapy, and the institution followed these guidelines during the patient selection process. No power calculation was performed as no similar studies exist in the literature to determine an appropriate effect size.

### 2.2. Selection of participants

A study team consisting of 20 members (15 ED physicians, 3 ED nurse administrators, 2 ED clinical pharmacists) reviewed the electronic medical record and collected baseline demographics and outcome data. If a patient experienced an infusion-related event and did not complete the full therapy, the event was documented as part of the safety analysis, however no other information was obtained. For all other study patients, baseline demographics and outcome data was obtained through electronic medical record review. Patient demographics included age, gender, BMI, comorbidities, severity of illness, days of symptoms, COVID-19 vaccine history, and corticosteroid therapy in the previous 7 days. Clinical indicators included oxygen saturation at presentation and radiographic evidence of COVID-19 infection (chest x-ray or computed tomography (CT)). To evaluate the accuracy of the entered data, an inter-rater blinded to the study objectives was assigned a randomly selected 10% study sample. A reliability goal of at least 90% agreement was deemed acceptable.

Severity of illness definitions were acquired from the BLAZE-1 study. [3] Severity was defined as *moderate* if shortness of breath was present, or if the respiration rate was at least 20 breaths per minute and the heart rate was at least 95 beats per minute. Severity was defined as *mild* if the criteria for moderate illness was not met. Patients were dichotomized into two groups based on the number of days of symptoms at the time of bamlanivimab administration – 3 days or less (*early*) versus 4 to 10 days (*late*). Oxygen saturation was dichotomized into less than or equal to 94% and greater than 94%, and BMI into less than 30 kg/m<sup>2</sup> (underweight, normal, and overweight) and greater than or equal to 30 kg/m<sup>2</sup> (obese). Patient age was also dichotomized into four separate groups: 18–54 years, 55–64 years, 65–79 years, and 80 years and older.

### 2.3. Outcomes

The primary outcome was hospitalization for COVID-related illness at 28 days (or treatment failure). The secondary outcomes of this study were COVID-related ED visits at 28 days, hospital and intensive care unit (ICU) length of stay (LOS), and in-hospital mortality at 28 days. Additionally, a descriptive safety analysis of infusion-related events was performed.

### 2.4. Statistical analysis

Descriptive statistics were reported as medians and interquartile ranges (IQR) for continuous variables, and frequencies and percentages for categorical variables. Baseline patient characteristics, clinical indicators, and outcomes were compared between early and late groups using Chi-square (or Fisher exact when case counts were less than 5) for categorical variables and Mann-Whitney U for continuous variables. A multivariate logistic regression analysis assessed the association between hospitalization within 28 days, and patient characteristic and clinical variables. All variables were selected a priori with the final model containing significant variables and adjusted for patient characteristics (age and gender). As BMI was not recorded on all study patients, only the significant logistic model variables were tested for these patients, which included BMI. Model results were reported using odds ratios and 95% confidence intervals (CI). A two-tailed *p*-value of <0.05 was considered significant for all analyses. All statistical analysis was performed using IBM SPSS Statistics 27.

## 3. Results

### 3.1. Characteristics of study subjects

A total of 839 patients were identified for inclusion during the study time period (Fig. 1). Three patients were excluded from the efficacy analysis as they experienced an infusion-related event in the first few

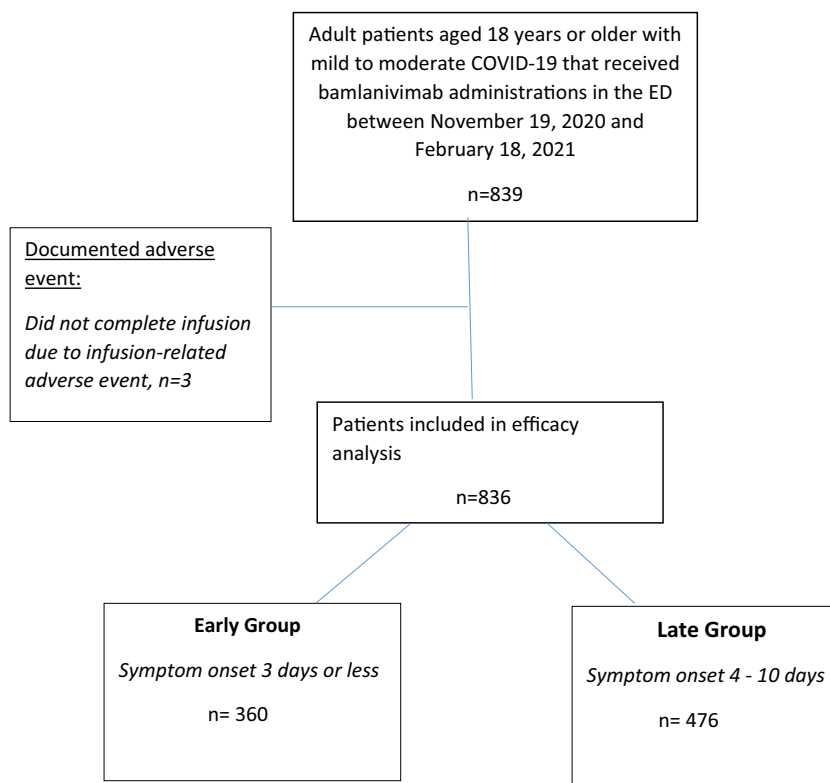


Fig. 1. Patient selection.

minutes of therapy administration and did not complete therapy. For the remaining 836 patients, the median age was 65 years (IQR 56–73) and 55% of patients were female. Table 1 summarizes the patient characteristics and clinical indicators for both the early and late bamlanivimab administration groups. Patient characteristics and most clinical indicators were similar between groups. The median BMI was 31 kg/m<sup>2</sup> and 57% of the patients were obese. Patients in both groups had similar comorbidities with 66% of patients having hypertension and 33% having diabetes. Overall, 17% of patients experienced moderate illness at the time of bamlanivimab administration. More patients in the late group presented with oxygen saturation readings of 94% or less (7% in the early group vs. 11% in the late group;  $p = 0.049$ ). Additionally, there were more patients in late group with radiographic findings of COVID-19 (8% in the early group vs. 13% in the late group;  $p = 0.024$ ).

### 3.2. Main results

There was no difference observed in COVID-related hospitalization rates within 28 days between the early and late bamlanivimab administration groups (7.5% vs. 8.2%;  $p = 0.71$ ) (Table 2). The inter-rater reliability agreement was 96% for the primary outcome. Among the patients who required hospitalization, lengths of stay and in-hospital mortality were similar between the two groups. There was no difference in COVID-related ED visits within 28 days with 13% of patients returning to the ED during the follow up time period. Table 3 summarizes the adverse events with four patients reporting difficulty breathing.

Table 4 lists the multivariate logistic analysis results. Four variables predicted hospitalization with odds ratios of 2 or greater: oxygen saturation, illness severity, radiographic evidence, and age. Patients with oxygen saturation less than or equal to 94% were 2.3 times more likely to require admission while those with moderate illness had a 2.6-fold increased risk of hospitalization compared to those with mild illness. Patients with radiographic evidence of COVID-19 were 2.9 times more likely to require admission. Patients 65 years and older had an increase

in odds of hospitalization compared to patients under 65 years of age in which 65 to 79 year old group were twice as likely to be hospitalized and those 80 and older had a 5.5-fold increased odds of hospitalization. There were 666 patients with a recorded BMI, which did not attenuate the model and also was not a predictor of hospitalization. Additionally, the number of days of illness did not attenuate the model and was not a predictor of hospitalization.

### 4. Discussion

There was no difference in the rate of hospitalizations at 28 days between the early and late bamlanivimab administration groups with an overall rate of 7.9% observed. These results support the EUA treatment window of 10 days from symptom onset, which remains a treatment requirement of all available monoclonal antibody therapies, including bamlanivimab-etesevimab and casirivimab-imdevimab. The hospitalization rates in this study were higher than previously reported in the BLAZE-1 study across all patients (1.6%), and in the high-risk post hoc cohort (4.2%) [3]. However, the entire study sample received bamlanivimab using existing high-risk EUA criteria and may represent real-world usage.

The primary outcome of hospitalization at 28 days was selected as a patient-centered, clinical endpoint. The authors felt that hospitalization rates were a more appropriate indicator of clinical efficacy than what has been reported in previous studies, particularly due to its correlation with mortality [6,7]. Additionally, hospitalizations and ED visits were analyzed separately as many patients may return to the ED for continued symptoms after bamlanivimab administration, but may not have been ill enough to require admission and be counted as a treatment failure. In this study, there was no difference observed in ED visits or hospitalization rates at 28 days.

The safety profile was similar between both groups. There were eight infusion-related reactions during the course of the study time period with two patients requiring admission for observation. One patient developed angioedema several hours after the infusion;

**Table 1**  
Patient characteristics and clinical indicators by timing of bamlanivimab administration.

	Early administration n = 360	Late administration n = 476	Total n = 836	p-value
Age (years)				
Median (IQR)	65 (55–72)	66 (56–74)	65 (56–73)	0.177
Groups				0.255
18–54	86 (24)	106 (22)	192 (23)	
55–64	94 (26)	103 (22)	197 (24)	
65–79	137 (38)	212 (45)	349 (42)	
80 and older	43 (12)	55 (12)	98 (12)	
Gender				
Female	200 (56)	257 (54)	457 (55)	0.653
Male	160 (44)	219 (46)	349 (45)	
Body-mass index (kg/m <sup>2</sup> )				
Median (IQR)	31 (26–38)	31 (26–38)	31 (26–38)	
< 30	121/290 (42)	162/376 (43)	283/666 (42)	0.992
≥ 30	169/290 (58)	214/376 (57)	383/666 (58)	0.725
Medical history				
Asthma	33 (9.2)	42 (8.8)	75 (9)	0.864
Cardiovascular Disease	55 (15)	75 (16)	130 (16)	0.850
Chronic Kidney Disease	13 (3.6)	20 (4.2)	33 (3.9)	0.664
COPD	21 (5.8)	27 (5.7)	48 (5.7)	0.850
Diabetes	121 (34)	159 (33)	280 (33)	1.000
Hypertension	231 (64)	324 (68)	555 (66)	0.237
Immunosuppressive Disease	28 (7.8)	37 (7.8)	65 (7.8)	1.000
Immunosuppressive Therapy	14 (3.9)	24 (5)	38 (4.5)	0.428
Severity of illness				
Mild	298 (83)	393 (83)	691 (83)	1.000
Moderate	62 (17)	83 (17)	145 (17)	
Days of symptoms				
0–1	82 (2)	*	82 (9.8)	
2–3	278 (77)	*	278 (33)	
4–6	*	289 (61)	289 (35)	
7–10	*	187 (39)	187 (22)	
Oxygen saturation at presentation				
≤ 94%	25 (6.9)	54 (11)	79 (9.4)	0.049
> 94%	335 (93)	422 (89)	757 (91)	
Radiographic evidence of COVID-19				<0.001
Present	28 (7.8)	60 (13)	88 (11)	0.024
Absent	97 (27)	76 (16)	173 (21)	<0.001
Unable to obtain	235 (65)	340 (71)	575 (69)	0.057
Corticosteroid therapy in previous 7 days				0.900
Yes	23 (6.4)	34 (7.1)	57 (6.8)	
No	317 (88)	417 (88)	734 (88)	
Unable to obtain	20 (5.6)	25 (5.3)	45 (5.4)	
Prior receipt of COVID vaccine				1.000
Yes	5 (1.4)	7 (1.5)	12 (1.4)	
No	355 (99)	469 (99)	824 (99)	

Results reported as n (%) unless otherwise noted.  
COVID-19 = Coronavirus disease 2019, LOS = length of stay, ICU = intensive care unit, IQR = interquartile range, COPD = chronic obstructive pulmonary disease.

however, this patient was also on lisinopril therapy and it is unknown if that contributed to their presentation. Of the eight events that occurred, three patients experienced symptoms within the first five minutes of the infusion. The majority of symptoms were mild in severity and included chills, fever, shortness of breath, and chest pain. Patients received supportive care including diphenhydramine, methylprednisolone, and famotidine. No patients required the use of epinephrine. Although the ED was identified as the setting to administer monoclonal therapies at this institution, the low incidence of infusion-related reactions and mild severity may permit its use in outpatient areas

**Table 2**  
Clinical outcomes.

	Early administration n = 360	Late administration n = 476	p-value
COVID-related hospitalization at 28 days	27 (7.5)	39 (8.2)	0.713
Hospital LOS (days), median (IQR)	3 (2–5)	4 (2–7)	0.27
ICU admission	0	2	0.509
In-hospital mortality*	0	3	0.264
COVID-related ED visit at 28 days	46 (13)	60 (13)	1.000

Results reported as n (%) unless otherwise noted; \*2 patients admitted to ICU died.

**Table 3**  
Safety outcomes.\*

	Early administration n = 360	Late administration n = 476
Infusion Reaction, n (%)	4 (1.1)	4 (0.8)
Altered mental status	0	0
Arrhythmia	0	0
Chest pain	1	1
Chills	1	0
Difficulty Breathing	1	3
Fever	0	1
Hypoxia	1	0
Nausea	0	0
Weakness	0	0

\* Eight patients experienced an infusion-related reaction; however, three patients were removed from the efficacy outcomes analysis due to receiving less than 5 min of the infusion.

**Table 4**  
Treatment failures: multivariate logistics regression analysis (adjusted by gender).

	Odds Ratio (95% CI)	p-value
Oxygen saturation at presentation ≤ 94%	2.3 (1.1–4.5)	0.022
Severity of illness, moderate	2.6 (1.4–4.7)	0.002
Radiographic evidence of COVID-19 present	2.9 (1.5–5.4)	0.001
Age*		
65–79 years	2.0 (1.1–3.7)	0.033
≥ 80 years	5.5 (2.7–11.3)	0

\* age < 65 years reference; CI = confidence interval; COVID-19 = Coronavirus disease 2019.

outside of the ED with trained staff and emergency medical equipment available.

Interestingly, if evidence of COVID-19 pneumonia was present on CT or X-ray prior to bamlanivimab administration, patients were greater than 2 times more likely to fail therapy. This finding is hypothesis-generating and has not been evaluated previously in the literature. These findings suggest that if a patient has already developed infiltrates on chest radiograph or presents with shortness of breath with tachypnea and tachycardia, treatment with bamlanivimab has a higher likelihood of being ineffective at preventing clinical decompensation.

Although it seems reasonable to extrapolate these findings to other monoclonal therapies that are currently available, future studies exploring these indicators with other products are warranted. The results of this analysis and others may guide institutions faced with formulary decisions on the indications for use of monoclonal products as manufacturers seek to receive FDA approval and move away from existing availability through the EUA process.

#### 4.1. Limitations

There are several important limitations to this study. This was a retrospective chart review, which relied heavily on the validity of the



documentation in the electronic medical record. Due to the retrospective nature of this study, the ability to demonstrate a causal relationship between the timing of bamlanivimab administration during the course of COVID-19 illness and clinical outcomes is lacking. The study also did not include a control group of patients who met high-risk criteria and did not receive bamlanivimab therapy, limiting the ability to discern the treatment effect of this therapy compared to standard of care. This study was conducted at a single-site ED during the COVID-19 pandemic, which may limit generalizability to institutions with throughput processes and procedures dissimilar to this community hospital. Additionally, clinical outcomes data was only available for patients that were admitted to this institution, therefore, the study was unable to account for study patients that were admitted to another institution.

## 5. Conclusion

In conclusion, there were no differences in the rates of hospitalization at 28 days when bamlanivimab was administered in the first 3 days of illness versus days 4 to 10. There was no difference in the rates of ED visits at 28 days and a small number of infusion-related reactions were observed. Future prospective studies are warranted to expand upon the characteristics of patients that may or may not benefit from monoclonal antibody therapy.

## Author contributions

JM, KW, FB, AB, DB, and SH conceived the study and designed the trial. All listed individuals with the exception of KH participated in data collection. MH was responsible for quality control of the data. KH provided statistical advice on the study design and analyzed the data.

JM, KW and SH drafted the manuscript, and all authors contributed substantially to its revision. JM and KW take responsibility for the paper as a whole.

## Declaration of Competing Interest

Nothing to disclose.

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