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BRIEF REPORT

# Effect of Bamlanivimab as Monotherapy or in Combination with Etesevimab or Sotrovimab on Persistently High Viral Load in Patients with Mild-to-Moderate COVID-19: A Randomized, Phase 2 BLAZE-4 Trial

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## ABSTRACT

***Introduction***: Treatment with monoclonal antibodies provides rapid, passive immunity and may stop COVID-19 disease progression. The study evaluated the effect of bamlanivimab (BAM) or BAM + etesevimab (ETE)/sotrovimab compared to placebo on SARS-CoV-2 viral load in patients with COVID-19.

***Methods***: The phase 2, randomized, single-dose study included patients aged between ≥ 18 and < 65 years, not hospitalized at the time of randomization, and had ≥ 1 mild or moderate COVID-19 symptoms. Study included arms 1–6 (placebo, BAM 175 mg + ETE 350 mg, BAM 700 mg + ETE 1400 mg, BAM 2800 mg + ETE 2800 mg, BAM 700 mg alone, and BAM 350 mg + ETE 700 mg, respectively), BAM 700 mg + ETE 700 mg unintentional dosing; and arms 7 and 8 (BAM 700 mg + sotrovimab 500 mg and placebo, respectively). The primary endpoint was proportion of patients with SARS-CoV-2 log viral load > 5.27 on day 7 (persistently high viral load [PHVL]) who received BAM or BAM + (ETE or sotrovimab).

***Results***: A total of 725 patients, mean age 39.6 years (range 18–75 years), 50.2% male were randomized and infused with study drug in arms 1–6; and a total 202 patients, mean age 38 years (range 18–63 years), 53.5% female were randomized and infused with study drug in arms 7 and 8. A significantly lower proportion of patients in arms 2–6 and arm 7 experienced PHVL on day 7 compared to placebo. On day 7, patients in arms 2, 3, and 6 consistently experienced significantly greater reduction in viral load than placebo. Significant improvement was observed in time to viral load clearance and time to symptom improvement by day 29 in some arms compared to placebo. No new safety concerns were observed with drug combinations.

***Conclusion***: The study demonstrated that a significantly lower proportion of patients with mild-to-moderate COVID-19 treated with BAM or BAM + (ETE or sotrovimab) experienced a PHVL at day 7.

***Trial Registration***: ClinicalTrials.gov identifier, NCT04634409.

**Keywords:** Bamlanivimab; Etesevimab; mAb; SARS-CoV-2; Sotrovimab; Viral load

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**Key Summary Points**

***Why carry out the study?***

The COVID-19 pandemic was the most significant pandemic in the past century.

Clinical studies have demonstrated the efficacy of antibody combinations against the SARS-CoV-2 spike protein in the management of COVID-19 infection.

Bamlanivimab (BAM), etesevimab (ETE), and sotrovimab are fully human neutralizing immunoglobulin G1 monoclonal antibodies specific to the SARS-CoV-2 spike protein. This study evaluated the effect of BAM as monotherapy or in combination with ETE/sotrovimab (different doses) in minimizing the SARS-CoV-2 viral load in patients with mild-to-moderate COVID-19.

***What was learned from this study?***

The study demonstrated that a significantly lower proportion of patients with mild-to-moderate COVID-19 treated with BAM alone or BAM+ETE/sotrovimab experienced a persistently high viral load at day 7.

Also, a significant improvement was observed in viral load clearance and symptom improvement by day 29 with no new safety concerns.

## INTRODUCTION

An outbreak of severe respiratory infections caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was observed in China in late 2019 and it continues to mutate and spread globally [1]. SARS-CoV-2 had a significant impact on early patient morbidity and death and there was little information on the dynamics of the virus with a few therapeutic options available until November 2020 [2]. It is known that SARS-CoV-2 has a spike protein on its surface that attaches and enters the human cell. Hence, many monoclonal antibodies (mAbs) have been developed that can bind to the SARS-CoV-2 spike protein, which can block the virus from entering the human cell and prevent progression to severe disease [3]. Bamlanivimab (BAM) was the first mAb to receive Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients [4]. Subsequently, the FDA granted additional EUAs to mAbs, in combination and as a single antibody agent [4–6]. Clinical studies have demonstrated the efficacy of antibodies against the SARS-CoV-2 spike protein in the management of SARS-CoV-2 infection [7]. BAM and etesevimab (ETE) are fully human neutralizing immunoglobulin (Ig) G1 mAbs specific to the SARS-CoV-2 spike protein. They are neutralizing antibodies to SARS-CoV-2 that can inhibit viral attachment and neutralize the virus [8]. Sotrovimab is a fully human Fc-engineered dual-action IgG1 mAb that targets a conserved region in the spike protein of SARS-CoV-2 [7, 9].

Since rapid mutation of the COVID-19 virus was expected and could lead to resistance to single mAbs, finding an effective and safe dose of mAb combinations was of interest to minimize the risk of antibody resistance for COVID-19 treatment. Subsequently, all EUAs for the mAbs were either deauthorized or revoked as a result of non-susceptible variants in circulation. This study evaluated the effect of BAM alone and in combination with ETE or sotrovimab compared to placebo on SARS-CoV-2 viral load in patients with mild-to-moderate COVID-19.

## METHODS

### Patient Population, Study Design, and Intervention

BLAZE-4 was a phase 2, randomized, double-blind, placebo-controlled, single-dose (single dose per patient) study to evaluate the efficacy

and safety of mono and combination therapy with monoclonal antibodies conducted at 93 sites in all regions of the USA and 31 of the 50 states among patients with mild-to-moderate COVID-19 illness in an outpatient setting. The first patient visit was conducted on 29 October 2020 and the last patient visit for arms 7 and 8 was 7 January 2021.

The study included patients aged between $\geq 18$ and $< 65$ years, not hospitalized at the time of randomization, having one or more mild or moderate COVID-19 symptoms [10], and their samples were collected for the first positive SARS-CoV-2 viral infection per PCR (reference PCR assay) [11] determination $\leq 3$ days prior to the start of the infusion. Patients with body mass index (BMI) $\geq 35$; suspected or proven serious; active bacterial, fungal, viral, or other infection (besides COVID-19); or who received treatment with SARS-CoV-2-specific mAbs were excluded from the study.

The study received approval from the relevant ethics committee(s) and was conducted in accordance with the Declaration of Helsinki of 1964. The sponsor complied with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRB)/ independent ethics committees (IEC), and investigators. All patients provided written informed consent for study participation.

The study included arms 1–6 that were enrolled as one cohort. Patients in each arm received different doses of drug combinations as follows: placebo (arm 1), BAM 175 mg + ETE 350 mg (arm 2), BAM 700 mg + ETE 1400 mg (arm 3), BAM 2800 mg + ETE 2800 mg (arm 4), BAM 700 mg alone (arm 5), BAM 350 mg + ETE 700 mg (arm 6), and BAM 700 mg + ETE 700 mg unintentional dosing arm. In this unintentional dosing, 20 patients from arm 2 instead of receiving BAM 175 mg + ETE 350 mg potentially received BAM 700 mg + ETE 700 mg. These 20 patients, randomly assigned at eight different sites, were identified through pharmacokinetic analyses and analyzed separately for both the efficacy and safety populations. Patients in arms 7 and 8 were enrolled as a separate cohort to receive BAM 700 mg + sotrovimab 500 mg and placebo, respectively. Treatment arm 1 was the corresponding placebo control for arms 2–6 and treatment arm 8 was the corresponding placebo control for arm 7. For all arms, the study drug was administered as a single intravenous infusion and patients were followed up for 29 days. The maximum therapeutic doses for BAM and ETE were selected on the basis of PK/PD viral dynamics modeling and has a sustained concentration above the in vitro $IC_{90}$ of viral cell-entry neutralization in the lung tissue for at least 28 days in 90% of the participant population. The dose for sotrovimab was selected on the basis of extensive nonclinical data and expected human PK extrapolated from cynomolgus monkeys.

## Endpoints

The primary endpoint was the proportion of patients with SARS-CoV-2 persistently high viral load (PHVL) in BAM alone (arm 5) and BAM + ETE (arms 2–4 and 6) or BAM + sotrovimab (arm 7) versus placebo (arms 1 and 8). PHVL was defined as a log viral load $> 5.27$, corresponding to a mean PCR cycle-threshold value of $< 27.5$ on day 7 based on prior analyses [8]. The secondary endpoints were to assess SARS-CoV-2 viral load change from baseline through day 11, time to SARS-CoV-2 clearance through day 29, time to symptom improvement through day 29, and safety (treatment-emergent adverse event [TEAE], serious adverse event [SAE], all-cause death, and adverse events [AEs] leading to drug discontinuation). The symptoms were assessed daily on days 1–11 for outpatients only (day 1, assess prior to dosing).

## Statistical Analysis

The planned sample size is approximately 100 participants per treatment arm. Since arm 6 began enrollment after arms 1–5, additional participants were enrolled in arm 1 (placebo) and arm 3 (BAM 700 mg + ETE 1400 mg) to ensure at least a 50% increase in participants concurrently enrolled with arm 6.

The sample size was determined on the basis of pairwise comparisons of each dose compared

to placebo (arms 2–6 vs. arm 1 and arm 8 vs. arm 7). An assumed sample size provides > 87% power to test the superiority of at least one dose of BAM alone, BAM + ETE, or BAM + sotrovimab versus placebo at the two-sided 0.05 alpha level, adjusted for multiplicity (for the comparisons between arms 2–6 and arm 1), on the proportion of participants with SARS-CoV-2 viral load > 5.27 at day 7 (+ 2 days). This assumes the true underlying proportion of participants meeting this endpoint is 5% in BAM alone, BAM + ETE, and BAM + sotrovimab arms and 19% in the placebo arms.

The efficacy population included all randomized patients who received study intervention and provided at least one post-baseline viral load measurement. Number of patients, mean, standard deviation, median, minimum, and maximum were used to summarize continuous measures. The number of patients and percentage were used to summarize categorical measures.

SARS-CoV-2 viral load data were evaluated using a log base 10 scale. The log viral load was calculated from the cycle threshold (Ct) values with the following considerations:

- Ct values range between 0 and 45, where negative CoV-2 tests were associated with a Ct value of 45.
- Samples with a positive CoV-2 test result (< 45) were normalized to reduce pre-analytical variability in the viral load measurements according to the following formula: Ct − (Ct value for the RNAse P (RP) mRNA target for that sample − 26.17), where 26.17 is a historical average value of RP Ct for the assay.
- The log base 10 viral load was calculated from the normalized Ct value using the following formula: $(45 - \text{Ct})/\log_2 10$, or $(45 - \text{Ct})/3.321928$.

For PHVL, missing data for day 7 SARS-CoV-2 viral load were imputed using relevance sequence imputation (RSI) as follows: imputed using the first available non-missing data for day 5, day 3, day 11, or day 1. For categorical measures, statistical hypotheses testing was conducted using logistic regression with a regression model with a Firth penalized likelihood [12]. The differences in the proportion of PHVL among the treatment groups, along with the relative risk and odds ratio, were estimated using data with RSI. For continuous measures, statistical hypotheses testing was conducted using a mixed-effects model for repeated measures. The Cox proportional hazard model and Kaplan–Meier curves were used for the assessment of time to SARS-CoV-2 clearance and time to symptom improvement.

The safety population included all randomized participants who received any amount of study intervention. Safety data were summarized descriptively. All hypothesis tests were two-sided at an alpha level of 0.05.

## RESULTS

### Patient Baseline Demographics and Clinical Characteristics

In total, 725 patients were randomized and infused with the study drug in arms 1–6 (arm 1, $N = 155$; arm 2, $N = 83$; arm 3, $N = 158$; arm 4, $N = 103$; arm 5, $N = 105$; arm 6, $N = 101$; and BAM 700 mg + ETE 700 mg unintentional dosing, $N = 20$). Patients in arms 1–6 were aged (mean) 39.6 years (range 18–75 years); (although inclusion criteria was patients aged < 65 years, five patients aged 65 years [$n = 3$], 66 years [$n = 1$], and 75 years [$n = 1$] were inadvertently enrolled by sites); gender was equally distributed (50.2% male); 87.5% were White and 5.5% were Black or African American; mean BMI was 27.2 kg/m$^2$; and 84.0% of patients had mild COVID-19, with a majority (91.9%) at low-risk of severe COVID-19. Patients with either one or all of the following characteristics were considered high-risk (low-risk patients did not have any of these characteristics): age ≥ 65 years; BMI ≥ 35.0 kg/m$^2$; have chronic kidney disease, diabetes, and immunosuppressive disease; were receiving immunosuppressive treatment; or age ≥ 55 years and have cardiovascular disease, or hypertension, or chronic obstructive pulmonary disease or other chronic respiratory disease. A total of 202 patients were randomized and infused in arm 7 ($N = 101$) and arm 8

($N = 101$). Patients in these two arms were aged (mean) 38.3 years (range 18–63 years); 53.5% were female; 84.5% were White and 10.3% were Black or African American, with a mean BMI of 26.9 kg/m$^2$; and approximately 85% of patients had mild COVID-19 with a majority (95.5%) at low risk of severe COVID-19. Details are presented in Table S1 in the electronic supplementary material.

## Primary Outcome

### *SARS-CoV-2 Persistently High Viral Load on Day 7*

A significantly lower proportion of patients treated with BAM alone and BAM + ETE (arms 2–6) experienced PHVL on day 7 compared to those treated with placebo (arm 1) (difference − 15.5% [95% confidence interval (CI) − 25.5, − 5.6], $P = 0.009$ for BAM 175 mg + ETE 350 mg [arm 2]; − 16.9% [95% CI − 25.5, − 8.4], $P < 0.001$ for BAM 700 mg + ETE 1400 mg [arm 3]; − 20.0% [95% CI − 28.7, − 11.2], $P < 0.001$ for BAM 2800 mg + ETE 2800 mg [arm 4]; − 13.5% [95% CI − 23.2, − 3.7], $P = 0.013$ for 700 mg BAM alone [arm 5]; − 19.8% [95% CI − 28.6, − 11.0], $P < 0.001$ for BAM 350 mg + ETE 700 mg [arm 6]; and − 17.7% [95% CI − 32.7, − 2.8], $P = 0.141$ for BAM 700 mg + ETE 700 mg unintentional dosing).

Similarly, a significantly lower proportion of patients treated with BAM + sotrovimab (arm 7) experienced PHVL on day 7 compared to placebo (arm 8) (difference − 19.8% [95% CI − 30.4, − 9.2], $P < 0.001$ for 700 mg + 500 mg BAM + sotrovimab) (Table 1).

## Secondary Outcomes

### *SARS-CoV-2 Viral Load Change from Baseline*

Through day 7, patients treated with BAM 175 mg + ETE 350 mg (arm 2), BAM 700 mg + ETE 1400 mg (arm 3), and BAM 350 mg + ETE 700 mg (arm 6) consistently showed a significantly greater reduction in viral load compared to placebo (arm 1). However, on day 11, as time progressed, no clinically meaningful differences were observed between patients in the placebo arm compared to patients in any intervention arms (arms 2–6). Patients treated with BAM + sotrovimab (arm 7) demonstrated a statistically significant greater reduction in viral load compared to placebo (arm 8) on days 5, 7, and 11 (Fig. 1).

### *Time to SARS-CoV-2 Clearance*

Patients treated with BAM 700 mg + ETE 1400 mg (arm 3) (78%) and BAM 350 mg + ETE 700 mg (arm 6) (74%) showed a statistically significant increase in the likelihood of achieving viral load clearance through day 29 compared to placebo (arm 1). Patients treated with BAM + sotrovimab (arm 7) were 36% more likely to achieve viral clearance through day 29 compared to placebo. However, the difference was not statistically significant (Fig. 2).

### *Time to Symptom Improvement*

Patients treated with BAM 175 mg + ETE 350 mg (arm 2) (31%), BAM 700 mg + ETE 1400 mg (arm 3) (33%), BAM 2800 mg + ETE 2800 mg (arm 4) (34%), and BAM 700 mg + ETE 700 mg unintentional dosing (83%) showed faster median time and a statistically significant increase in likelihood of achieving symptom improvement by day 29 compared to placebo (arm 1). In patients treated with BAM + sotrovimab (arm 7), no statistically significant differences were observed by day 29 compared to placebo (arm 8) in time to symptom improvement (Fig. 3).

### *Safety*

BAM alone and BAM + ETE did not show an increase in TEAEs compared with placebo. Most of the TEAEs reported were mild to moderate in severity. Infusion-related reaction (an adverse drug reaction of BAM alone and BAM + ETE) was reported in < 2% of patients. There were no events of anaphylaxis and no deaths were reported. By day 85, one patient treated with the placebo (arm 1) experienced a COVID-19-related hospitalization. A total of four patients experienced COVID-19-related emergency room visits (placebo [arm 1]: two patients; BAM 700 mg + ETE 700 mg unintentional dosing:

**Table 1** SARS-CoV-2 persistent high viral load (viral load with relevance sequence imputation > 5.27) at Day 7 in efficacy population—Treatment Arms 1–8

| | **BAM or BAM + ETE** | | | | | | | **BAM + sotrovimab** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Placebo *N* = 155 (Arm 1)** | **BAM 175 mg + ETE 350 mg *N* = 82 (Arm 2)** | **BAM 350 mg + ETE 700 mg *N* = 101 (Arm 6)** | **BAM 700 mg + ETE 1400 mg *N* = 157 (Arm 3)** | **BAM 2800 mg + ETE 2800 mg *N* = 103 (Arm 4)** | **BAM alone 700 mg *N* = 105 (Arm 5)** | **BAM 700 mg + ETE 700 mg unintentional dosing[a] *N* = 20** | **Total *N* = 723** | **Placebo *N* = 101 (Arm 8)** | **BAM 700 mg + sotrovimab 500 mg *N* = 101 (Arm 7)** | **Total *N* = 202** |
| Day 7 (observed) | | | | | | | | | | | |
| Nx | 138 | 78 | 86 | 144 | 94 | 96 | 17 | 653 | 96 | 96 | 192 |
| Response, *n* (%)[b] | 36 (26.1) | 7 (9.0) | 4 (4.7) | 14 (9.7) | 5 (5.3) | 12 (12.5) | 2 (11.8) | 80 (12.3) | 28 (29.2) | 8 (8.3) | 36 (18.8) |
| 95% CI[c] | (18.8, 33.4) | (2.6, 15.3) | (0.2, 9.1) | (4.9, 14.6) | (0.8, 9.9) | (5.9, 19.1) | (0.0, 27.1) | (9.7, 14.8) | (20.1, 38.3) | (2.8, 13.9) | (13.2, 24.3) |
| Day 7 (observed) | | | | | | | | | | | |
| Response, *n* (%) | 43 (27.7) | 10 (12.2) | 8 (7.9) | 17 (10.8) | 8 (7.8) | 15 (14.3) | 2 (10.0) | 103 (14.2) | 30 (29.7) | 10 (9.9) | 40 (19.8) |
| 95% CI[c] | (20.7, 34.8) | (5.1, 19.3) | (2.7, 13.2) | (6.0, 15.7) | (2.6, 12.9) | | | | | | |
| Difference (95% CI) vs. placebo | – | − 15.5 (− 25.5, − 5.6) | − 19.8 (− 28.6, − 11.0) | − 16.9 (− 25.5, − 8.4) | − 20.0 (− 28.7, − 11.2) | | | | | | |
| Relative risk (95% CI) vs. placebo | – | 0.44 (0.23, 0.83) | 0.29 (0.14, 0.58) | 0.39 (0.23, 0.65) | 0.28(0.14, 0.57) | | | | | | |
| Odds ratio (95% CI) vs. placebo[d] | – | 0.37 (0.18, 0.78) | 0.24 (0.11, 0.52) | 0.32 (0.18, 0.59) | 0.23 (0.10, 0.51) | | | | | | |
| *P* value vs. placebo | – | 0.009 | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | | | | | | |

**Table 1** continued

| BAM or BAM + ETE | | | BAM + sotrovimab | | |
|---|---|---|---|---|---|
| **BAM alone 700 mg *N* = 105 (Arm 5)** | **BAM 700 mg + ETE 700 mg unintentional dosing[a] *N* = 20** | **Total *N* = 723** | **Placebo *N* = 101 (Arm 8)** | **BAM 700 mg + sotrovimab 500 mg *N* = 101 (Arm 7)** | **Total *N* = 202** |
| (7.6, 21.0) | (0.0, 23.1) | (11.7, 16.8) | (20.8, 38.6) | (4.1, 15.7) | (14.3, 25.3) |
| − 13.5 (− 23.2, − 3.7) | − 17.7 (− 32.7, − 2.8) | – | – | − 19.8 (− 30.4, − 9.2) | – |
| 0.51 (0.30, 0.88) | 0.36 (0.09, 1.38) | – | – | 0.33 (0.17, 0.65) | – |
| 0.44 (0.23, 0.84) | 0.35 (0.09, 1.41) | – | – | 0.27 (0.12, 0.58) | – |
| 0.013 | 0.141 | – | – | $P < 0.001$ | – |

*BAM*, bamlanivimab, *CI* confidence interval, *ETE* etesevimab, *N* number of patients in the efficacy population, *n* number of participants in the specified category, *PK* pharmacokinetic(s), *RSI* relevance sequence imputation, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

[a]In the unintentional dosing arm, 20 patients from arm 2 instead of receiving BAM 175 mg + ETE 350 mg potentially received BAM 700 mg + ETE 700 mg. These 20 patients, randomly assigned at 8 different sites, were identified through PK analyses, and were analyzed separately for both the efficacy and safety populations

[b]Percentage of response is calculated by $n/Nx \times 100\%$

[c]Confidence intervals are constructed using the asymptotic method, without continuity correction (normal approximation to the binomial distribution)

[d]Logistic regression analysis with treatment as factors

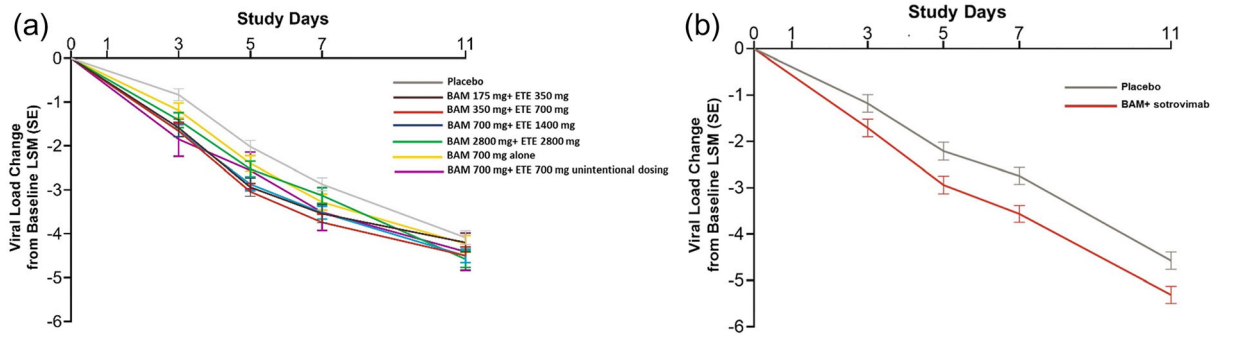


**Fig. 1** SARS-CoV-2 viral load change from baseline: treatment arms 1–6, and BAM 700 mg + ETE 700 mg unintentional dosing (**a**); arms 7 and 8 (**b**). In the unintentional dosing arm, 20 patients from arm 2 instead of receiving BAM 175 mg + ETE 350 mg potentially received BAM 700 mg + ETE 700 mg. These 20 patients, randomly assigned at 8 different sites, were identified through PK analyses, and were analyzed separately for both the efficacy and safety populations. *BAM* bamlanivimab, *ETE* etesevimab, *LSM* least square mean, *PK* pharmacokinetic(s), *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SE* standard error

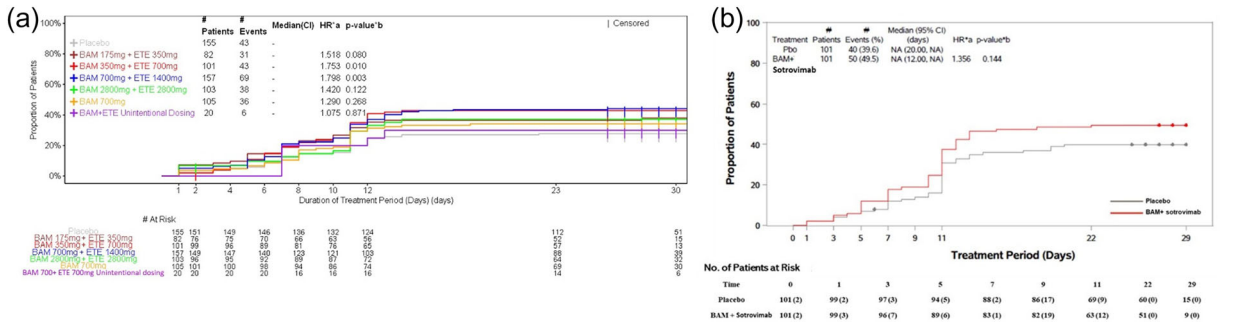


**Fig. 2** Time to SARS-CoV-2 viral load clearance, Kaplan–Meier product limit curve: treatment arms 1–6, and BAM 700 mg + ETE 700 mg unintentional dosing (**a**); arms 7 and 8 (**b**).[a]HR unstratified. [b]*P* value (2-sided)—log-rank for comparison with placebo. In the unintentional dosing arm, 20 patients from arm 2 instead of receiving BAM 175 mg + ETE 350 mg potentially received BAM 700 mg + ETE 700 mg. These 20 patients, randomly assigned at 8 different sites, were identified through PK analyses, and were analyzed separately for both the efficacy and safety populations. *BAM* bamlanivimab, *CI* confidence interval, *ETE* etesevimab, *HR* hazard ratio, *NA* not applicable, *No.* number, *PK* pharmacokinetic(s), *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

one patient [two different visits]; 700 mg BAM alone [arm 5]: one patient). Among the patients in arms 7 and 8, a total of 6 (5.9%) patients in arm 7 and 10 (9.9%) patients in arm 8 reported at least one TEAE. There were no SAEs, discontinuations due to AEs, or deaths reported. One high-risk patient treated with BAM + sotrovimab (two different visits) experienced COVID-19-related emergency room visits. Details are presented in Table S2 in the electronic supplementary material.

## DISCUSSION

In this phase 2 portion of the BLAZE-4 trial, the efficacy of BAM monotherapy, BAM + ETE, and BAM + sotrovimab were evaluated in patients with mild-to-moderate COVID-19. With the

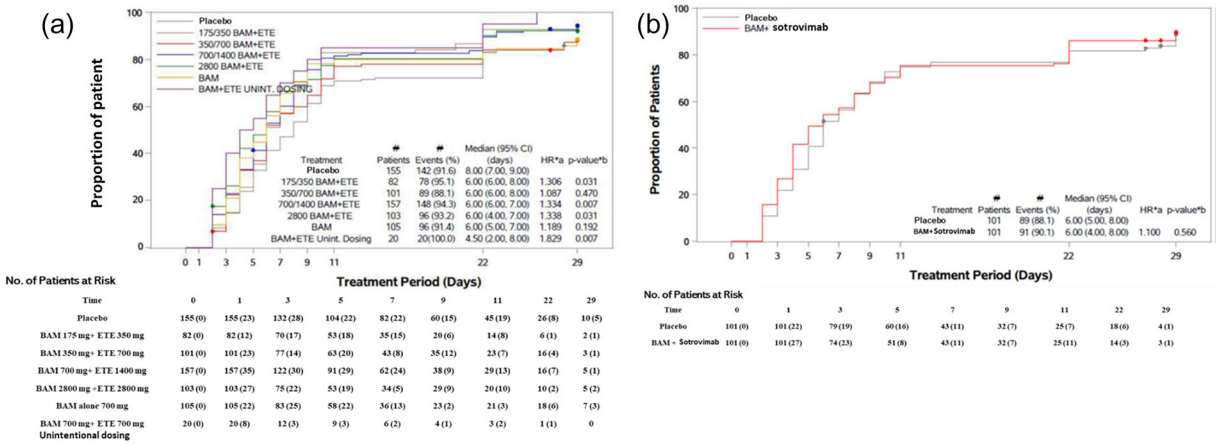


**Fig. 3** Time to symptom improvement, Kaplan–Meier product limit curve: treatment arms 1–6, and BAM 700 mg + ETE 700 mg unintentional dosing (**a**); arms 7 and 8 (**b**). [a]HR unstratified. [b]*P* value (2-sided)—log-rank for comparison with placebo. In the unintentional dosing arm, 20 patients from arm 2 instead of receiving BAM 175 mg + ETE 350 mg potentially received BAM 700 mg + ETE 700 mg. These 20 patients, randomly assigned at 8 different sites, were identified through PK analyses, and were analyzed separately for both the efficacy and safety populations. *BAM* bamlanivimab, *CI* confidence interval, *ETE* etesevimab, *HR* hazard ratio, *No.* number, *PK* pharmacokinetic(s)

first patient enrolled in October 2020, randomization occurred when the original Wuhan strain was dominant and subsequently when the Alpha variant was gaining prominence.

Patients were well balanced in baseline demographics and disease characteristics across all the treatment arms. Patients generally had mild COVID-19 across all treatment arms. A significantly lower proportion of patients in the BAM + ETE treatment arms showed PHVL on day 7 compared to placebo. Also, a statistically significant improvement in viral load reduction from baseline up to day 7 was observed in patients treated with BAM 175 mg + ETE 350 mg (arm 2), BAM 700 mg + ETE 1400 mg (arm 3), and BAM 350 mg + ETE 700 mg (arm 6), which is consistent with the previously published report where fewer patients in the BAM + ETE arms than in the placebo arm had a log viral load > 5.27 [8]. Similarly, a significantly lower proportion of patients treated with BAM + sotrovimab showed PHVL on day 7 compared to placebo, and a significant reduction in viral load from baseline was observed from baseline to day 7 (Fig. 1) [8].

The safety data for treatment arms 1–8 was consistent with the previous report [8]. No deaths were reported and administration of BAM alone and BAM + (ETE or sotrovimab) did not lead to an increase in TEAEs compared to placebo. Most of the TEAEs reported were mild to moderate in severity. No new safety concerns were observed with the drug combination.

### Limitations

The study was performed during the time of the original Wuhan strain and the subsequent Alpha variant, but the results of the treatments from this study may not be generalizable in other patient populations carrying different viral mutants or current strains of COVID-19 because of differences in viral susceptibility. Moreover, this study does not assess the virologic effect or clinical benefit of treatment with BAM alone or BAM + (ETE or sotrovimab) in high-risk patients with COVID-19.

## CONCLUSION

The study demonstrates that BAM alone or when co-administered with other neutralizing antibodies ETE or sotrovimab results in a

significant reduction in viral load in early treatment of patients with mild-to-moderate COVID-19. Safety data showed that the frequencies of TEAEs and SAEs for patients who received BAM alone and BAM + (ETE or sotrovimab) were similar to placebo.

## ACKNOWLEDGEMENTS

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***Author Contributions.*** Russell M. Nichols: was involved in manuscript drafting and critical revision. Lisa Macpherson: contributed to data analysis, data interpretation, and manuscript drafting. Dipak Patel: was involved in the study design, data acquisition, data interpretation, and critical revision of the manuscript for important intellectual content. Wendy W. Yeh: was involved in study design, data analysis, data interpretation, manuscript drafting, and critical revision of the manuscript for important intellectual content. Amanda Peppercorn: contributed to the conceptualization of the work, study design, data analysis, data interpretation, and critical revision of the manuscript.

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***Data Availability.*** The data that support the findings of this study are available from Eli Lilly and Company but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Eli Lilly and Company.

### *Declarations*

***Conflict of Interest.*** Russell M. Nichols, Lisa Macpherson, and Dipak Patel are employees and shareholders of Eli Lilly and Company. Wendy W. Yeh is an employee and shareholder of Vir Biotechnology. Amanda Peppercorn is an employee and shareholder of GSK.

***Ethical Approval.*** The study received approval from the relevant ethics committee(s) and was conducted in accordance with the Declaration of Helsinki of 1964. Detailed information about the ethical review board is provided as supplemental information. All patients provided written informed consent for study participation.



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