

COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

Bamlanivimab (LY-CoV555) in the Treatment of Outpatients With COVID-19: A Critical Appraisal of an Interim Analysis of the BLAZE-1 Trial

This report was published on January 12, 2021.

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

Version: 2.0
Publication Date: January 2021
Report Length: 15 Pages

Author: Lauren Bresee

Acknowledgements: Laurie Lambert, Amy Sood, Melissa Severn

Cite As: *Bamlanivimab in the treatment of outpatients with COVID-19: a critical appraisal of the BLAZE-1 trial*. Ottawa: CADTH; January 2021. (CADTH Health Technology Review).

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

AE	adverse event
CI	confidence interval
FCA	Focused Critical Appraisal
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Table of Contents

Abbreviations.....	3
Key Messages	5
Summary	5
Background	6
Trial Under Review	6
Description of the Trial Under Review.....	6
Study Objective	6
Study Characteristics and Statistical Analysis	7
Results	10
Critical Appraisal.....	15
Internal Validity	15
External Validity.....	16
Summary and Conclusions.....	16
References	18
Tables	
Table 1: Baseline Characteristics of Study Participants	11
Table 2: Mean Change in Log Viral Load and Symptoms Scores From Baseline	13
Figure	
Figure 1: Change in Symptom Score From Baseline.....	14

Key Messages

- Bamlanivimab is a monoclonal neutralizing antibody, a relatively new health technology developed from the convalescent plasma of a patient with COVID-19, that attaches to the spike protein of the receptor-binding domain of SARS-CoV-2, thereby preventing entry of SARS-CoV-2 into cells. The desired effects of a neutralizing antibody include reducing viral load and preventing worsening of symptoms and severity of illness.
- A preplanned interim analysis of an ongoing, phase II, randomized, double-blind, placebo-controlled, multi-centre trial (BLAZE-1) has been published evaluating the effect of three different bamlanivimab dosing regimens compared to placebo in patients with mild or moderate symptoms of COVID-19.
- Although the interim results suggested a potential benefit in reducing viral load and preventing worsening symptoms and severity of illness, the level of uncertainty remains high. More robust, published, peer-reviewed evidence is needed to provide clear recommendations about the potential role of bamlanivimab for the early treatment of people with mild or moderate symptoms of COVID-19.
- Bamlanivimab is administered as a one-time dose by IV infusion over a period of one hour with patient-monitoring required for up to two hours. Information about how, where, and by whom this treatment will be administered is lacking but essential.
- As the need for effective treatments in the current pandemic increases, studies may not be as robust as normally considered for decision-making. Until further evidence becomes available for patients who test positive for SARS-CoV-2 and experience mild to moderate symptoms of COVID-19, decision-makers and health care providers must consider the following: the value of potential but still-uncertain benefits of treatment with bamlanivimab, the potential risks associated with developing severe COVID-19, the potential risk of adverse reactions to the IV infusion of the drug, and the financial and other implications of access to a therapy that may or may not prove to be effective when additional evidence becomes available. We will continue to monitor the evolving evidence base for this product and other treatments for COVID-19 and their appropriate patient populations.

Summary

- The interim results of this ongoing phase II trial (BLAZE-1) found that for outpatients with mild or moderate symptoms of COVID-19, a one-time dose of bamlanivimab 2,800 mg was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11 (\pm 4 days) compared with placebo. When the three dosing regimen groups were pooled (700 mg, 2,800 mg, and 7,000 mg), a statistically significant reduction was not observed.
- For the secondary outcomes concerning symptoms and hospitalization, a post hoc analysis indicated a greater reduction in symptom severity from day 2 to day 6 in the bamlanivimab group, but most participants in both groups had fully recovered or had only mild symptoms by day 11. At day 29, fewer participants were hospitalized in the bamlanivimab group compared with the placebo group but the absolute number of hospitalizations in both groups was small and a statistical comparison was not reported.
- In terms of safety, IV administration of bamlanivimab was not associated with any serious adverse events, and the most common adverse events were diarrhea and nausea in approximately 2% to 5% of participants in both groups.
- The cost-effectiveness of bamlanivimab is unknown at this time.

- Multiple statistical tests in the analyses of the primary and secondary outcomes and the multiple treatment arms limit the interpretability of the interim results. Other limitations include the lack of detail around the clinical characteristics of the trial participants and about the number of people that were screened and subsequently excluded from the study.
- Given the limitations associated with the interim analysis, a phase III trial comparing bamlanivimab to placebo with a clinically important primary end point and adequate adjustment for multiplicity is necessary to determine whether bamlanivimab offers true benefit to outpatients with mild or moderate COVID-19.

The objective of a CADTH Focused Critical Appraisal (FCA) is to summarize and to evaluate the methodology, scientific rigour, and findings of a published study.

Background

Bamlanivimab (also known as LY-CoV555 or LY3819253) is a monoclonal neutralizing antibody that was developed from the convalescent plasma of a patient with COVID-19.¹ Bamlanivimab neutralizes severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus that causes COVID-19, by attaching to the spike protein of the receptor-binding domain of SARS-CoV-2, thereby preventing the entry of SARS-CoV-2 into cells.¹ Based on the mechanism of action, the desired effects of neutralizing antibodies include reducing viral load, preventing worsening of symptoms and severity of illness, and protecting against reinfection.²

In October 2020, the results from a preplanned interim analysis of the ongoing phase II Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) study that compared three different doses of bamlanivimab (700 mg, 2,800 mg, or 7,000 mg) to placebo were published.¹

Trial Under Review

This FCA includes a summary with critical appraisal of the interim analysis of the ongoing BLAZE-1 trial: Chen P, Nirula A, Heller B, et al. for the BLAZE-1 Investigators. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *N Engl J Med*. 2020 Oct 28 [Epub ahead of print].¹

Description of the Trial Under Review

Study Objective

The primary objective of the overall BLAZE-1 trial is to “characterize the effect of LY3819253 [bamlanivimab] compared to placebo on SARS-CoV-2 viral load and viral clearance.” The secondary objectives are to “characterize the effect of LY3819253 [bamlanivimab] compared to placebo on safety; SARS-CoV-2 viral load among participants with ≤ 8 days since symptom onset; and symptom resolution.”³

The current publication is based on a preplanned interim analysis and reports on “the effect of the neutralizing antibody on viral load, symptom scores, and clinical outcomes and also report an observed connection between a persistently high viral load and disease severity.”¹

Study Characteristics and Statistical Analysis

BLAZE-1 Study Design

The BLAZE-1 trial is an ongoing, phase II, randomized, double-blind, placebo-controlled, multi-centre trial being conducted at 41 sites in the US.³ The trial includes treatment arms for bamlanivimab, LY-CoV016 (also known as etesevimab or LY3832479), and a combination of bamlanivimab and LY-CoV016. However, this FCA only reports on the bamlanivimab interim results.¹

Patients were randomized to a single dose of bamlanivimab (700 mg, 2,800 mg, or 7,000 mg) or placebo.³ Randomization was conducted centrally using an Interactive Web Response System, and was stratified based on duration of COVID-19 symptoms at the time of randomization (either up to or before eight days of symptoms or after eight days of symptoms).³ Methods for allocation concealment were not described, nor was the process for administration of the study drug.³ It is unclear whether the study drug was administered in hospital, in an emergency department, or in an ambulatory care clinic, for example.

Patients, treating clinicians, investigators, and the sponsor study team were blinded to treatment.¹ An interim analysis was preplanned for when the last patient who was randomly assigned bamlanivimab reached day 11 of follow-up, which occurred on September 5, 2020.¹

The BLAZE-1 trial is registered on clinicaltrials.gov (NCT04427501) and is funded by Eli-Lilly.¹

Inclusion and Exclusion Criteria

Patients were eligible for the BLAZE-1 trial if they were 18 years of age and older, were not hospitalized, had a positive SARS-CoV-2 test within three days before the start of study drug infusion, and reported at least one mild or moderate symptom of COVID-19 included in the FDA's severity classification from the *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention: Guidance for Industry*.^{3,4} Mild symptoms could include "fever, cough, sore throat, malaise, headache, muscle pain, [and/or] gastrointestinal symptoms, without shortness of breath or dyspnea," and moderate symptoms were defined as "any symptom of mild illness or shortness of breath with exertion" and "clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate \geq 20 breaths per minute, saturation of oxygen (SpO₂) $>$ 93% on room air at sea level, heart rate \geq 90 beats per minute."⁴ The type of SARS-CoV-2 test used for entry into the study was not described, however, the test could have been conducted at an external testing facility.³

Patients were excluded from the study if they were pregnant or breastfeeding, had an oxygen saturation of 93% or less on room air at sea level or an arterial oxygen partial pressure to fractional inspired oxygen ratio of less than 300, a respiratory rate of 30 breaths or more per minute, or a heart rate of 125 beats or more per minute.³ Patients were also excluded if they required or had an anticipated requirement for mechanical ventilation; required the use of vasopressors for hemodynamic instability within 24 hours of randomization; had a proven or suspected serious, active viral, fungal, bacterial, or other infection besides COVID-19; or had a comorbidity that was considered life-threatening within 29 days or required surgery within seven days.³ Lastly, patients were excluded if they had a previously positive SARS-CoV-2 test before the test that made them eligible for the study or had a history of a positive SARS-CoV-2 serology test, if they received an investigational

SARS-CoV-2 vaccine or COVID-19 plasma treatment, if they received an investigational agent for SARS-CoV-2 prophylaxis within 30 days before study drug dosing, or if they participated in a trial involving an investigational intervention within the last 30 days or less than five half-lives of the investigational intervention if five half-lives exceeded 30 days.³

Interventions

Patients received bamlanivimab at a dose of 700 mg, 2,800 mg, or 7,000 mg, or placebo (0.9% sodium chloride solution), within three days of their positive SARS-CoV-2 test.¹ Bamlanivimab and placebo were administered intravenously over approximately one hour; however, the infusion rate could have been reduced if the patient experienced an infusion reaction.³ Patients were then monitored for two hours post-infusion for symptoms of an infusion reaction, and were allowed to receive acetaminophen, antihistamines, or “other appropriately indicated medications” for infusion reaction, although the other possible medications were not reported.³

It is unclear whether intervention and placebo were identical-appearing because this was not stated in the publication nor in the study protocol; however, the protocol does state: “To protect blinding, the interventions must be prepared by an unblinded site personnel qualified to prepare study interventions who are not involved in any other study-related procedures. Instructions for preparation will be provided by the sponsor.”³

Outcome Assessment

The primary outcome of the BLAZE-1 study is change from baseline to day 11 (\pm 4 days) in SARS-CoV-2 viral load for each dose of bamlanivimab compared with placebo, with baseline defined as “the last nonmissing assessment recorded on, or prior to, the date of the first study drug administration at study day 1.”³ The secondary outcomes included safety assessments (including adverse events [AEs] and serious adverse events [SAEs]); change from baseline to day 11 (\pm 4 days) in SARS-CoV-2 viral load among patients with symptoms within eight days before randomization; time to symptom resolution; proportion of patients with symptom resolution based on the symptom questionnaire responses on day seven, day 11, day 15, and day 22; change in symptom score from baseline to day 7, day 11, day 15, and day 22; time to symptom improvement; proportion of patients demonstrating symptom improvement on the symptom questionnaire on day 7, day 11, day 15, and day 22; proportion of patients who achieved SARS-CoV-2 clearance on day 7, day 11, day 15, and day 22; time to SARS-CoV-2 clearance; SARS-CoV-2 viral load area under the response time curve assessed until day 29; and proportion of patients who experienced a COVID-19–related emergency department visit, hospitalization (defined as \geq 24 hours of acute care), or death by day 29, day 60, and day 85.³

The interim analysis reported the primary outcome of change from baseline in the SARS-CoV-2 viral load at day 11 (\pm days), and the secondary outcomes of mean change in viral load from baseline to day 3 and from baseline to day 7, change in COVID-19 symptom scores from baseline, and frequency of AEs and SAEs.¹ In addition, because there were no deaths in the study and because most emergency department visits resulted in patients being admitted to hospital, the study authors reported a composite end point of emergency department visits and hospitalizations as hospitalizations.¹ Although the primary outcome and secondary outcomes of mean change in SARS-CoV-2 viral load from baseline to day 7 and the frequency of AEs and SAEs were preplanned outcomes, mean viral load change from baseline to day 3 and change in COVID-19 symptoms from baseline to before day 7 were not preplanned.³

SARS-CoV-2 viral load was measured by obtaining a nasopharyngeal swab and using a reverse transcriptase-polymerase chain reaction (RT-PCR) assay to quantify the viral load.¹ The RT-PCR assay was performed at a central laboratory for all patients.¹ It was unclear who performed the nasopharyngeal swabs and whether standardized training was received by people performing the swabs, as the protocol mentions that “visits may be conducted as a telephone call, outpatient clinic, or home visit, as long as the protocol Schedule of Activities is followed.”³

COVID-19 symptoms were captured by patients using a questionnaire that included cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, headache, loss of appetite, and changes in taste and smell.³ Each symptom was rated on a score from zero to three (0 = none or absent, 1 = mild, 2 = moderate, and 3 = severe), except for loss of appetite and changes in taste and smell, which were answered “yes” or “no.”⁵ Based on information from the publication, the symptom questionnaire was scored based on the eight symptom domains, and scores could range from zero to 24.¹ It is unclear how loss of appetite and changes in taste and smell were captured in the symptom questionnaire score.^{1,3} Symptoms were captured daily based on what the patient had experienced in the previous 24 hours for all outpatients from day 1 to day 29.³

An AE was defined as “any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered to be related to the study intervention,” and a SAE was defined as “any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, is a congenital anomaly/birth defect, or other situations.”³ Other situations included “important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.”³ Any events that occurred after the signing of the informed consent form and met the definitions above were captured as AEs or SAEs.³

Statistical Analysis

Patients who were randomized and received the study drug or placebo were included in the interim primary analysis if they had a viral load measurement at baseline and at least one measurement after the baseline measurement for the respective end point.¹ The safety analysis set included all patients who were randomized and received the study drug.³

A mixed-model repeated-measures analysis was conducted to compare the primary outcome of change in SARS-CoV-2 viral load from baseline to day 11 (± 4 days) in patients who received 700 mg, 2,800 mg, or 7,000 mg of bamlanivimab compared with placebo.¹ Statistical methods for the assessment of the secondary variables were not reported in the publication by Chen et al.¹ However, based on information from the statistical analysis plan in the study protocol, it appears that mixed-model repeated-measures analyses were also used to evaluate the secondary outcomes of change in SARS-CoV-2 viral load from baseline to day 3 and from baseline to day 7, and descriptive statistics were reported for AEs, SAEs, and hospitalizations.³ Change from baseline in COVID-19 symptom scores may have been compared between the entire bamlanivimab group and the placebo group using either a mixed-model repeated-measures analysis or an analysis of covariance, as listed in the trial protocol.³

The sample size for the BLAZE-1 trial was calculated based on the use of a simulated dynamic model to estimate change in viral load from baseline to day 11.³ Based on an assumed mean log change in SARS-CoV-2 viral load from baseline to day 11 of -4.38 for patients who received bamlanivimab and -3.48 for patients who received placebo (representing an average of an 87% viral load reduction), a sample size of 100 patients per study arm was calculated to provide approximately 91% power based on a two-sided test and an alpha of 0.05 to detect a statistical difference in change in SARS-CoV-2 viral load from baseline to day 11 (± 4 days).³

All statistical tests were two-sided, and an alpha of less than 0.05 was considered statistically significant.¹ There was no adjustment performed for the multiple bamlanivimab treatment arms or multiple statistical tests.³

Results

Patient Disposition

Randomization occurred between June 17, 2020, and August 21, 2020. A total of 467 patients were randomized: 317 patients to the bamlanivimab group and 150 patients to the placebo group.¹ A total of 452 patients were included in the primary analysis, meaning they received their dose of study medication and had a baseline and at least one follow-up measurement of SARS-CoV-2 viral load. Fifteen patients who were randomized (eight patients in the bamlanivimab group and seven patients in the placebo group) were not included in the analysis; reasons for exclusion of these patients from the analysis were not reported.¹ Of the 452 patients included in the analysis, 309 were in the bamlanivimab group and 143 patients were in the placebo group. Among the 309 patients in the bamlanivimab group, 101 patients received 700 mg, 107 patients received 2,800 mg, and 101 patients received 7,000 mg.¹

Baseline Characteristics

Baseline characteristics were reported for the bamlanivimab group as a whole and not stratified by dose received.¹ The median age was 45 years in the bamlanivimab group and 46 years in the placebo group; 10.7% of patients in the bamlanivimab group ($n = 33$) were 65 years of age or older and 14.0% of patients in the placebo group ($n = 20$) were 65 years of age or older.¹ A total of 171 patients in the bamlanivimab group (55.3%) and 78 patients in the placebo group (54.5%) were female.¹ Almost 70% of patients in the bamlanivimab group ($n = 215$) had risk factors for severe COVID-19, whereas 66.4% of patients in the placebo group ($n = 95$) had risk factors for severe COVID-19.¹ Risk factors for severe COVID-19 were defined as age 65 years or older, a body mass index of 35 kg/m² or higher, or “at least one coexisting illness in pre-specified categories”; however, coexisting conditions were not defined.^{1,3} Most patients had mild COVID-19 symptoms at baseline: 232 patients (75.1%) in the bamlanivimab group and 113 patients (79.0%) in the placebo group. The cycle threshold for mean viral load was similar in both groups: 23.9 in the bamlanivimab group and 23.8 in the placebo group.¹

Details of the baseline characteristics according to treatment group are reported in Table 1.

Table 1: Baseline Characteristics of Study Participants

Characteristic	Treatment group	
	Bamlanivimab N = 309	Placebo N = 143
Median age (range), years	45 (18 to 86)	46 (18 to 77)
≥ 65 years, n (%)	33 (10.7)	20 (14.0)
Female sex, n (%)	171 (55.3)	78 (54.5)
Race or ethnic group, n/N (%) ^a		
White	269/305 (88.2)	120/138 (87.0)
Hispanic or Latino	135/309 (43.7)	63/143 (44.1)
Black	22/305 (7.2)	7/138 (5.1)
Body mass index, kg/m ²		
Median	29.4	29.1
≥ 30 to < 40, n/N (%)	112/304 (36.8)	56/139 (40.3)
≥ 40, n/N (%)	24/304 (7.9)	9/139 (6.5)
Risk factors for severe COVID 19, n (%) ^b	215 (69.6)	95 (66.4)
Disease status, n (%) ^c		
Mild	232 (75.1)	113 (79.0)
Moderate	77 (24.9)	30 (21.0)
Median number of days since symptom onset	4.0	4.0
Mean viral load, cycle threshold value	23.9	23.8

^a Patient-reported; groups are not mutually exclusive.

^b Risk factors were defined as age 65 years or older, a body mass index of 35 kg/m² or higher, or “at least one coexisting illness in pre-specified categories.”

^c Mild symptoms were defined as fever, cough, sore throat, malaise, headache, muscle pain, and/or gastrointestinal symptoms without shortness of breath or dyspnea. Moderate symptoms were defined as “any symptom of mild illness or shortness of breath with exertion, with clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO₂) > 93% on room air at sea level, heart rate ≥ 90 beats per minute.”¹⁴

Efficacy

Primary Outcome

The total study population experienced a SARS-CoV-2 log viral load decrease of -3.81 by day 11 (baseline = 6.36; day 11 = 2.56; elimination of 99.97% viral RNA). The mean change in log viral load from baseline was -3.47 in patients who received placebo and -3.67, -4.00, and -3.38 in patients who received bamlanivimab 700 mg, 2,800 mg, and 7,000 mg, respectively. Compared with placebo, the 2,800 mg dose of bamlanivimab was associated with a SARS-CoV-2 log viral load decrease of -0.53 from baseline to day 11 (95% confidence interval [CI], -0.98 to -0.08; P = 0.02). Non-statistically significant differences were seen between bamlanivimab and placebo for the 700 mg (-0.20; 95% CI, -0.66 to 0.25; P = 0.38), 7,000 mg (0.09; 95% CI, -0.37 to 0.55; P = 0.70), and pooled doses (-0.22; 95% CI, -0.60 to 0.15) for the primary outcome of change in SARS-CoV-2 viral load from baseline to day 11. Table 2 lists the results of the primary outcome.

Secondary Outcomes

Table 2 lists the results of the mean change in viral load from baseline to day 3 (a post hoc analysis) and from baseline to day 7 (a preplanned secondary outcome). Among the comparisons, only the 2,800 mg dose of bamlanivimab was associated with a statistically significantly greater reduction in SARS-CoV-2 log viral load from baseline to day 3

compared to placebo (−0.64; 95% CI, −1.11 to −0.17; P value not reported) as was the comparison of the pooled doses of bamlanivimab to placebo at day 3 (−0.49; 95% CI, −0.87 to −0.11; P value not reported).

The change in symptom scores from baseline was consistently and statistically significantly larger in the bamlanivimab pooled group compared with placebo on day 2 through day 6 and are provided in Table 2; this was a post hoc analysis. The difference in change in symptom scores from baseline to day 7 through day 11, a preplanned secondary outcome, was not reported, but the study authors noted that “The change from baseline in the symptom score continued to be better in the LY-CoV555 [bamlanivimab] group than in the placebo group from day 7 to day 11, although by these time points most of the patients in the two groups had fully recovered or had only very mild symptoms.”¹ The change in symptom scores over time for the bamlanivimab and placebo groups is provided in Figure 1.

A total of five (1.6%) patients in the bamlanivimab and nine (6.3%) in the placebo group were classified as hospitalized at day 29; it was unclear how many patients visited the emergency department without being admitted to hospital because these patients were reported in the hospitalized group. The proportion of patients hospitalized by dose of bamlanivimab was similar (one of 101 in the 700 mg dose group, two of 107 in the 2,800 mg dose group, and two of 101 in the 7,000 mg group). Only one patient required admission to an intensive care unit (this patient was in the placebo group). In a post hoc subgroup analysis of patients aged 65 years and older with a body mass index of 35 kg/m² or higher, four of 95 (4.2%) patients randomized to the bamlanivimab group were hospitalized compared with seven of 48 (14.6%) in the placebo group.

Only one person in the trial experienced a SAE; this person was in the placebo group, and the SAE was described as upper abdominal pain.¹ A total of 22.3% (69 of 309) of the bamlanivimab group and 24.5% (35 of 143) of the placebo group experienced an AE. Diarrhea was the most common AE reported in the placebo group, occurring in 3.2% (10 of 309) of patients in the bamlanivimab group and 4.9% (seven of 143) of patients in the placebo group. Nausea was the most frequently reported AE in the bamlanivimab group (12 of 309; 3.9% of patients); 3.5% (five of 143) of patients in the placebo group also experienced nausea. Infusion-related reactions occurred in 2.3% (seven of 309) of patients in the bamlanivimab group and 1.4% (two of 143) of patients in the placebo group. The reactions were reported to be mild in most cases. It was reported that some patients received antihistamines for the symptoms associated with an infusion reaction, but the total number of people who received antihistamines and whether this differed between the bamlanivimab and placebo groups were not reported.

Table 2: Mean Change in Log Viral Load and Symptoms Scores From Baseline

Variable	Bamlanivimab (N = 309)	Placebo (N = 143)	Difference (95% CI)
Primary outcome: mean change from baseline in log viral load at day 11 (± 4 days)			
Bamlanivimab 700 mg	-3.67	-3.47	-0.20 (-0.66 to 0.25)
Bamlanivimab 2,800 mg	-4.00		-0.53 (-0.98 to -0.08)
Bamlanivimab 7,000 mg	-3.38		0.09 (-0.37 to 0.55)
Pooled doses	-3.70		-0.22 (-0.60 to 0.15)
Post hoc secondary outcome: mean change from baseline in log viral load at day 3			
Bamlanivimab 700 mg	-1.27	-0.85	-0.42 (-0.89 to 0.06)
Bamlanivimab 2,800 mg	-1.50		-0.64 (-1.11 to -0.17)
Bamlanivimab 7,000 mg	-1.27		-0.42 (-0.90 to 0.06)
Pooled doses	-1.35		-0.49 (-0.87 to -0.11)
Preplanned secondary outcome: mean change from baseline in log viral load at day 7			
Bamlanivimab 700 mg	-2.82	-2.56	-0.25 (-0.73 to 0.32)
Bamlanivimab 2,800 mg	-3.01		-0.45 (-0.92 to 0.03)
Bamlanivimab 7,000 mg	-2.85		-0.28 (-0.77 to 0.20)
Pooled doses	-2.90		-0.33 (-0.72 to 0.06)
Post hoc secondary outcome: change in symptom score from baseline			
Day 2	NR	NR	-0.79 (-1.35 to -0.24)
Day 3	NR	NR	-0.57 (-1.12 to -0.01)
Day 4	NR	NR	-1.04 (-1.60 to -0.49)
Day 5	NR	NR	-0.73 (-1.28 to -0.17)
Day 6	NR	NR	-0.79 (-1.35 to -0.23)

CI = confidence interval; NR = not reported.

Figure 1: Change in Symptom Score From Baseline

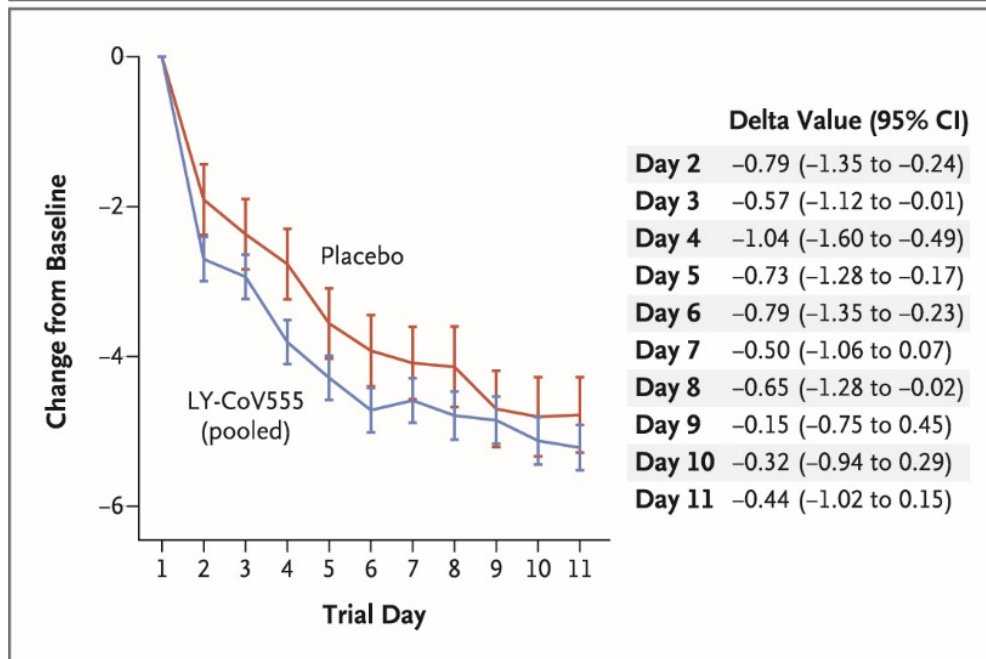


Figure 3. Symptom Scores from Day 2 to Day 11.

Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The I bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.

Source: From the New England Journal of Medicine, Chen P, et al. for the BLAZE-1 Investigators, SARS-Cov-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Critical Appraisal

Internal Validity

The BLAZE-1 trial used accepted methods for randomization. It was unclear how allocation concealment was performed in the trial. It was also unclear whether the placebo was identical-appearing to the bamlanivimab doses, although it was specified in the study protocol that non-blinded study personnel who were not involved in any other aspects of the trial were to prepare the bamlanivimab and placebo doses to maintain blinding.³

There was an imbalance between the groups in terms of age; more patients in the placebo group were 65 years of age or older compared with the bamlanivimab group. This may bias the results in favour of bamlanivimab. However, patients in the bamlanivimab group were more likely to have a body mass index of 40 kg/m² or greater, to have investigator-defined risk factors for severe COVID-19, and to report moderate COVID-19 symptoms at baseline. These differences may bias the results in favour of placebo. Lastly, important prognostic factors for COVID-19, such as hypertension, chronic obstructive pulmonary disease, smoking status, and diabetes, were not reported.⁶

The primary outcome of the BLAZE-1 study and in the published interim results was the change in SARS-CoV-2 viral load from baseline to day 11 (\pm 4 days). As mentioned in the discussion section of the publication, viral load did not appear to be a clinically meaningful outcome because the viral load was greatly reduced in both the treatment and placebo groups by day 11. In addition, it was unclear which day the measurements were taken for patients in the placebo and bamlanivimab groups, since the measurement was allowed to be taken within four days of day 11 (from day 7 to day 15). Given the natural course of the disease with declining viral load over time, if there were differences in the timing of viral load measurement between the placebo and bamlanivimab groups, this may have biased the study results. Lastly, who administered the nasopharyngeal swabs for the measurement of viral load was not reported. If technique for collecting the nasopharyngeal swabs impacts the measurement of SARS-CoV-2 viral load and if there were differences in the collection between the bamlanivimab and placebo groups, the results may be associated with random error.⁷

Inconsistencies were seen in the results for change in viral load from baseline to day 11 (primary outcome), day 3 (a post hoc secondary outcome), and day 7 (a preplanned secondary outcome). Although the change in viral load from baseline to day 11 was found to be statistically better for bamlanivimab 2,800 mg versus placebo, there were no statistical differences found for bamlanivimab 700 mg, 7,000 mg, or the pooled doses of bamlanivimab. Also, the reduction in viral load from baseline was statistically greater with bamlanivimab 2,800 mg and the pooled doses at day 3, but no statistical difference was found between any bamlanivimab dose and placebo at day 7.

Although statistical differences were found between the bamlanivimab and placebo groups for change in COVID-19 symptom scores from baseline, the clinical meaning of the results is unclear. The symptom questionnaire used in the study has not been validated and there is not an established scoring method or minimal important difference to interpret whether the differences between the bamlanivimab and placebo groups are important to patients.

There was also no adjustment for multiplicity of statistical tests, both when assessing the different treatment doses of bamlanivimab and when assessing the primary and secondary outcomes. As a result, type I error cannot be ruled out as a reason for the statistically significant differences found for some comparisons.

External Validity

The BLAZE-1 trial is an ongoing trial at 41 sites in the US. The population studied in this trial may not be representative of Canadian outpatients with mild or moderate symptoms of COVID-19 in terms of age, race, ethnicity, or prognosis. Moreover, the trial may not be generalizable to the Canadian context in terms of SARS-CoV-2 testing processes and health care system use associated with COVID-19. No details were provided regarding the type of sites used for medication administration (for example, in hospital or in an ambulatory clinic), or the process of administering the medication, which is given as a one-time IV dose over one hour with monitoring for two hours after infusion. The study results may not be generalizable to Canadian patients if access to SARS-CoV-2 testing, laboratory facilities, medication administration facilities, and monitoring after infusion differs between Canada and the US.

No details were provided regarding the number of patients screened and excluded from the study, and the reasons for exclusion. The lack of details regarding patient screening limits the ability to evaluate the generalizability of the study inclusion and exclusion criteria to the overall COVID-19 patient population with mild or moderate symptoms in Canada.

Summary and Conclusions

The interim results of the ongoing phase II BLAZE-1 trial found that for outpatients with mild or moderate symptoms of COVID-19, a one-time dose of bamlanivimab 2,800 mg was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11 (± 4 days) compared with placebo. However, when the three dosing regimen groups (700 mg, 2,800 mg, and 7,000 mg) were pooled, administration of bamlanivimab was not associated with a statistically significant reduction compared with placebo. There was not a statistically significant reduction associated with the 700 mg and 7,000 mg doses when individually compared with placebo. Most participants, including those in the placebo group, had substantial viral clearance at day 11.

In terms of secondary outcomes, although a post hoc analysis indicated a greater reduction in symptom severity from day 2 to day 6 in the bamlanivimab group, most patients in both groups had fully recovered or had only mild symptoms by day 11. At day 29, fewer patients were hospitalized in the bamlanivimab group compared with the placebo group but the absolute number of hospitalizations in both groups was small and a statistical comparison was not reported. In an additional post hoc subgroup analysis of patients aged 65 years and older with a body mass index of 35 kg/m² or higher, there was a greater reduction in frequency of hospitalizations but this observation may be due to chance or imbalances in these two small patient subgroups.

In terms of safety, IV administration of bamlanivimab was not associated with any SAEs. The most common adverse event was diarrhea in approximately 2% to 3% of participants in both groups. The cost-effectiveness of bamlanivimab is unknown at this time.

The lack of control for type I error associated with multiple statistical tests in the analyses of the primary and secondary outcomes and the multiple treatment arms limit the interpretability of the interim results of the BLAZE-1 trial. Other limitations include the lack of detail around the clinical characteristics of the trial participants and the number of patients that were screened and subsequently excluded from the study. Furthermore, the clinical

importance of the reduction in SARS-CoV-2 viral load from both a patient and health system perspective are uncertain.

Given the limitations associated with the interim analysis of the BLAZE-1 trial, a phase III trial comparing bamlanivimab to placebo with a clinically important primary end point and adequate adjustment for multiplicity is necessary to determine whether bamlanivimab offers true benefit to outpatients with mild or moderate COVID-19. Therefore, until further evidence becomes available for people who test positive for SARS-CoV-2 and who experience mild to moderate symptoms of COVID-19, decision-makers and health care providers must consider the value of potential but still-uncertain benefits of treatment with bamlanivimab, the potential risks associated with developing severe COVID-19, the potential risk of adverse reactions to the IV infusion of the drug, and the financial and other implications of access to a therapy that may or may not prove to be effective when additional evidence becomes available. In the absence of a vaccine or other proven therapy, for symptomatic patients with a positive SARS-CoV-2 who are at high risk of severe COVID-19, this treatment may offer some value but this cannot be confirmed without additional research and higher quality evidence. Information about how and where this treatment can best be administered is lacking but is essential for health care decision-makers.

References

1. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *N Engl J Med*. 2020 Oct 28.
2. Wu F, Liu M, Wang A, et al. Evaluating the Association of Clinical Characteristics With Neutralizing Antibody Levels in Patients Who Have Recovered From Mild COVID-19 in Shanghai, China. *JAMA Intern Med*. 2020;180(10):1356-1362.
3. Chen P, Nirula A, Heller B, et al. Protocol for: SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Eng J Med*. 2020 Oct 28. https://www.nejm.org/doi/suppl/10.1056/NEJMoa2029849/suppl_file/nejmoa2029849_protocol.pdf. Accessed 2020 Nov 26.
4. U.S. Department of Health and Human Services. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention: Guidance for Industry. In: Silver Spring (MD): Food and Drug Administration; 2020 May: <https://www.fda.gov/media/137926/download>. Accessed 2020 Nov 26.
5. Chen P, Nirula A, Heller B, et al. Supplement to: SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Eng J Med*. 2020 Oct 28. https://www.nejm.org/doi/suppl/10.1056/NEJMoa2029849/suppl_file/nejmoa2029849_appendix.pdf. Accessed 2020 Nov 26.
6. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One*. 2020;15(11):e0241955.
7. Pondaven-Letourmy S, Alvin F, Boumghit Y, Simon F. How to perform a nasopharyngeal swab in adults and children in the COVID-19 era. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2020;137(4):325-327.