

ARTICLE

PK/PD modeling links accelerated resolution of COVID-19-related clinical symptoms to SARS-CoV-2 viral load reduction in patients following treatment with Bamlanivimab alone or Bamlanivimab and Etesevimab together

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Abstract

The relationship between severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) viral load reduction and disease symptom resolution remains largely undefined for coronavirus disease 2019 (COVID-19). While the vaccine-derived immunity takes time to develop, neutralizing monoclonal antibodies offer immediate, passive immunity to patients with COVID-19. Bamlanivimab and etesevimab are two potent neutralizing monoclonal antibodies directed to the receptor binding domain of the spike protein of SARS-CoV-2. This study aims to describe the relationship between viral load and resolution of eight common COVID-19-related symptoms in patients following treatment with neutralizing monoclonal antibodies (bamlanivimab alone or bamlanivimab and etesevimab together), in a phase II clinical trial. Corresponding pharmacokinetics (PKs), viral load, and COVID-19-related symptom data were modeled using Nonlinear Mixed Effects Modeling to describe the time-course of eight COVID-19-related symptoms in an ordered categorical manner (none, mild, moderate, and severe), following administration of bamlanivimab or bamlanivimab and etesevimab together to participants with COVID-19. The PK/pharmacodynamic (PD) models characterized the exposure-viral load-symptom time course of the eight preselected COVID-19-related symptoms. Baseline viral load (BVL), change in viral load from baseline, and time since the onset of symptoms, demonstrated statistically significant effects on symptom score probabilities. Higher BVL generally indicated an increased probability of symptom severity. The severity of symptoms decreased over time, partially driven by the decrease in viral load. The effect of increasing time resulting in decreased severity of symptoms was over and above the effect of decreasing viral load. Administration of bamlanivimab alone or together

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with etesevimab results in a faster time to resolution of COVID-19-related symptoms compared to placebo.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

BLAZE-1 is an ongoing, multipart trial investigating bamlanivimab and etesevimab for the treatment of coronavirus disease 2019 (COVID-19) in adolescent and adult patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

A pharmacokinetic/pharmacodynamic (PK/PD) modeling approach was used to determine the relationship between severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) viral load clearance and symptom resolution among 571 participants following treatment with bamlanivimab monotherapy or bamlanivimab and etesevimab combination therapy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study adequately describes the effectiveness of bamlanivimab monotherapy and bamlanivimab and etesevimab together in the treatment of patients with symptomatic COVID-19, linking viral load clearance to time-to-symptom resolution. Results revealed that the earlier treatment is started, the faster the time to COVID-19-related symptoms resolution.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This study highlights the effectiveness of PK/PD modeling in determining the impact that SARS-CoV-2 viral load clearance has on COVID-19-related clinical symptom resolution following treatment with monoclonal antibodies.

INTRODUCTION

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the viral agent at the center of the ongoing global pandemic, is the causative agent of coronavirus disease 2019 (COVID-19). Individuals who contract COVID-19 may be asymptomatic carriers of the virus¹ and never present to healthcare or testing centers, thus facilitating the spread of the disease in the community. Other individuals may experience disease symptoms ranging from mild (fatigue, and muscle or body aches) to life-threatening (progressive pulmonary infection, and respiratory failure).^{2,3} With high morbidity and mortality rates being reported among a vulnerable subset of individuals,⁴⁻⁸ the importance of early testing, detection, and treatment of the disease is ever more apparent.

Immunotherapy is a rapidly advancing treatment option, providing a positive benefit–risk ratio for patients with COVID-19.⁹ Bamlanivimab and etesevimab administered together are two such immunotherapeutic agents which previously received Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) (As of January 24, 2022, due to the high frequency of the Omicron variant, bamlanivimab and etesevimab are not currently authorized

in any US region. The current authorization status can be accessed at <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs>.) for the treatment of mild-to-moderate COVID-19 in pediatric (≥ 12 years of age) and adult patients presenting with a positive SARS-CoV-2 test and who are at a high risk for progressing to severe COVID-19 or hospitalization or death.¹⁰ The EUA for bamlanivimab alone was granted November 2020.¹¹ This was later revoked after the EUA for bamlanivimab and etesevimab was granted in February 2021.¹² Unlike vaccine-derived immunity that develops over time, monoclonal antibody (mAb) treatment provides immediate, passive immunity to patients. Bamlanivimab and etesevimab function by targeting the spike protein of SARS-CoV-2 and are designed to block viral attachment and entry into human cells, thus preventing viral replication and mitigating COVID-19 disease severity.^{13,14} This mechanism of action is particularly important as the viral load (the quantity of virus present in a given volume of bodily fluid) has been shown to influence COVID-19 disease severity and progression.¹⁵⁻²⁰ Insights into the relationship between reduction in SARS-CoV-2 viral load and disease symptom resolution have the potential to offer important understanding surrounding a

patient's extent and duration of viral shedding and transmission, and to-date such insights remain largely undefined.

Statistical analyses of symptom resolution related to administration of bamlanivimab and etesevimab have focused on a total symptom score (range, 0–24) by rating eight symptom domains (cough, shortness of breath, feeling feverish, fatigue, body aches and pain, sore throat, chills, and headache) from none or absent (score of 0) to severe (score of 3) and combining them to provide an overall score.^{21,22} This approach is based on empirical statistical analysis of aggregate parameters (total score and area under the curve [AUC]). The outcomes from the BLAZE-1 trials^{21,22} demonstrated that the change in the total symptom score from baseline was better in the group administered with 700 mg bamlanivimab and 1400 mg etesevimab together than in the placebo group from day 2 to day 6, when examining the total symptom score over time. In addition, the change from baseline in the total symptom score continued to be better in the group which received bamlanivimab and etesevimab together than in the placebo group from day 7 to day 11, when examining the total symptom score over time, although by these timepoints most of the patients in the two groups had fully recovered or had only very mild symptoms.²¹ However, when examining the total symptom score as a cumulative measure (AUC) results were not as clear,²² and appeared to be significant for only one dose group at one timepoint. In addition, stratification based on time from symptom onset was not considered. As the premise that overall change in viral load from baseline should have an impact on the time to symptom resolution, inclusion of these factors in a continuous fashion over time should provide insight to symptom resolution.

In this pharmacokinetic/pharmacodynamic (PK/PD) model-based analyses, we sought to determine and quantify the relationship between SARS-CoV-2 viral load clearance and the resolution for each of the eight prominent COVID-19-related symptoms (independently instead of a total symptom score) in patients who received bamlanivimab monotherapy or bamlanivimab and etesevimab together over the entire timecourse. To harmonize the data, time from symptom onset was used as the time-course measure for both viral load clearance and symptom resolution. The PK-viral load model specifically used time from symptom onset, and this modeling allows calculation of the baseline viral load at the beginning of symptoms rather than the measured value at study entry. This provides a more uniform assessment of the baseline and change in viral load from baseline impact on symptom resolution. In addition, we utilized the model to simulate the impact of a dosing regimen of bamlanivimab and etesevimab, not studied, on symptom resolution.

METHODS

Data

Data were obtained from the phase II portion of the BLAZE-1 trial^{8,21,22} (NCT04427501), a placebo-controlled, double-blind study in which participants with mild-to-moderate COVID-19 were randomized to receive single doses of 700- ($N = 101$), 2800- ($N = 107$), or 7000 ($N = 100$) mg bamlanivimab or placebo ($N = 152$), or single-doses of 2800 mg bamlanivimab in combination with 2800 mg etesevimab ($N = 111$) within 3 days of the first positive SARS-CoV-2 test sample collection. The trial was conducted with approval from the relevant institutional review boards and in accordance with the Helsinki Declaration. Study end points included clinical outcomes and virologic responses to treatment. Outpatients rated the severity of each of their COVID-19-related symptoms using a daily questionnaire. The eight prospectively selected key symptoms detailed in the analyses were; body aches and pain, chills, cough, fatigue, feeling feverish, headache, shortness of breath, and sore throat. Other symptoms (loss of taste, smell, and appetite) were not included as they are less strongly associated with worsening clinical outcomes. Symptom scores were generally recorded daily by participants and reflected the severity of COVID-19-related symptoms that were experienced in the past 24 h. The possible categories were none or absent = 0, mild = 1, moderate = 2, and severe = 3. The dataset comprised a total of 120,862 symptom scores from 571 patients, bamlanivimab and etesevimab dosing information, and individual post hoc PK and viral load parameter estimates. The number of observations over the time course of the study by dose are presented in Table S1.

PK/PD modeling approach

NONMEM version 7.4.2 (Icon Plc., Gaithersburg, MD) was used for the analysis. The Stochastic Approximation Expectation Maximization for parameter estimation followed by importance sampling for objective function evaluation were used. The Laplacian option was added because the data were categorical.

Base model

The model diagram for the joint model that included PK, viral dynamics, and symptoms is shown in Figure 1. Details on the previously published PK and viral load exposure-response model-based analyses are described elsewhere.²³ Briefly, a linear two-compartment model described the PK

of bamlanivimab and etesevimab, independently. The viral dynamic model included a pool of uninfected target cells that are available for the SARS-CoV-2 virus to infect, subsequently replicate, and be released to infect more cells. The model parameters included the number of the target cells, the amount of virus, the rate of elimination of virus, a rate of infection of target cells, a rate of viral replication, and a death rate of infected cells. The drug effect of the neutralizing antibodies worked to reduce the viral load through increased elimination of the virus in the model.

An ordered categorical model was developed²⁴ to determine the probability of a patient having none/absent, mild, moderate, or severe COVID-19-related symptoms during treatment. Because each symptom indicated different levels of improvement using the same scale, they were combined into one unique ordered categorical dependent variable (DV): DV = 3, if severe; DV = 2, if moderate; DV = 1, if mild; and DV = 0, if no symptoms.

The dependent variable Y had four possible levels (0, 1, 2, and 3), and $Y_i = (Y_{0i}, Y_{1i}, \dots, Y_{ni})$ is the vector of observations for the *i*th individual. The logit of the probability that Y_{ij} are less than or equal to the score m is given by the logit-function:

$$\text{Logit}_{Y_{ij} \leq m} \leq f_{mi}$$

where $f_{m,i}$ is:

$$f_{m,i} = \sum_{L=0}^m B_L$$

B_L specifies the baseline probabilities of the different levels of Y. B_L (for $m = 0$) was not estimated because the cumulative probability Y is equal to 1. The corresponding probability is given by:

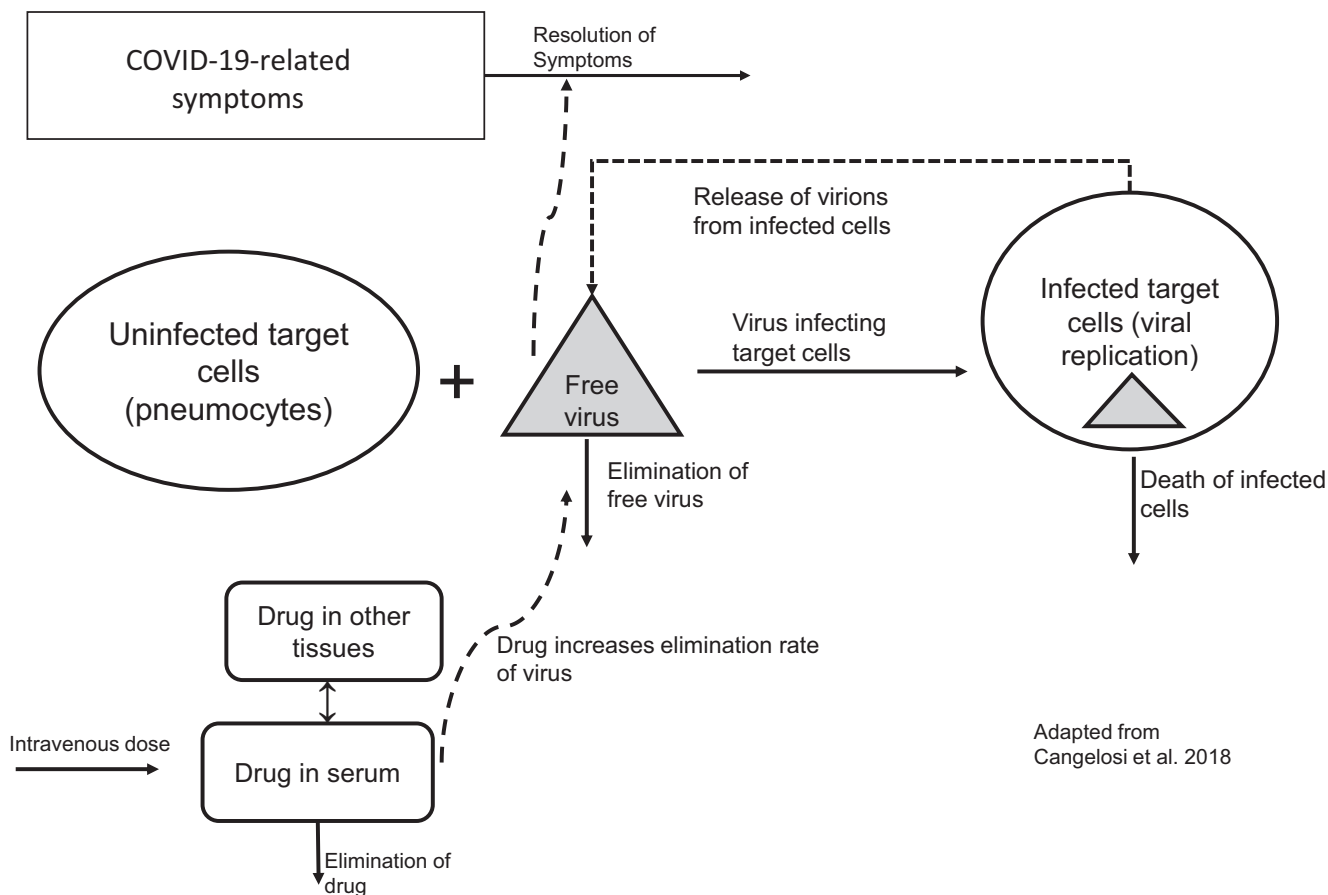
$$P_{Y_{ij} \leq m} = \frac{e^{\text{logit}_{Y_{ij} \leq m}}}{1 + e^{\text{logit}_{Y_{ij} \leq m}}}$$

The actual probabilities of observing particular levels of Y (0, 1, 2, or 3) are given by:

$$P_{Y_{ij}=0} = P_{Y_{ij} < 0}; \text{ no symptoms}$$

$$P_{Y_{ij}=1} = P_{Y_{ij} < 1} - P_{Y_{ij} \leq 0}; \text{ mild symptoms}$$

$$P_{Y_{ij}=2} = P_{Y_{ij} < 2} - P_{Y_{ij} \leq 1}; \text{ moderate symptoms}$$



Adapted from Cangelosi et al. 2018

FIGURE 1 Pharmacokinetic/pharmacodynamic (PK/PD) model diagram highlighting PK, viral dynamics and symptoms under assessment. COVID-19, coronavirus disease 2019

$$P_{Y_{ij}=3} = 1 - P_{Y_{ij} \leq 2}; \text{ severe symptoms}$$

Covariate testing

The impact of baseline viral load (BVL), change of viral load from baseline (Δ VL), and time since the onset of COVID-19 symptoms were tested for their effect on the probability of each symptom. Covariate relationships tested included power, linear (normal and log-transformed), and exponentiation of these continuous values. The inclusion of the covariates would influence $f_{m,i}$ as follows:

$$f_{m,i} = \sum_{L=0}^m (B_L + \theta_1 \times \text{BVL}) + \theta_2 \times \text{time} + \theta_3 \times \Delta\text{VL}$$

where θ_1 , θ_2 , and θ_3 are fixed effect parameters describing the magnitude of BVL, time, and Δ VL effects, respectively.

The criterion for significance was a decrease of 6.635 in the minimum objective function for inclusion of one parameter (p value > 0.01). In addition, the precision of parameter estimates was assessed. BVL and Δ VL were predicted for each patient using a PK-viral dynamic based on each individual's post hoc estimates, as described above.

PK/PD model-based simulations

Using the final PK/PD model, various simulations were performed:

- Visual predictive checks (VPCs) were performed to ensure that the model maintained fidelity with the data used to develop it. The simulations were performed by fixing model parameters to the population estimates and symptom-time data were simulated 100 times using the analysis dataset. The model-predicted 95% confidence intervals were computed and compared to the observed data to ensure concordance. The PK-viral dynamic model was based on each individual's post hoc estimates.
- Symptom data were simulated after placebo administration and a dosing regimen of single dose administration of 700 mg bamlanivimab and 1400 mg etesevimab together, which was not studied. The simulations ($N = 100$) were performed by fixing model parameters to the population estimates and uncertainty for the symptom data was included by applying a symmetrical distribution of error based on the variance for each symptom model parameter estimate. Graphical and tabular data present the model-predicted difference of symptom data over time after treatment compared to placebo as follows:

% Difference in patients achieving symptom resolution after treatment compared to placebo

$$= \left(P_{Y_{ij}=0} (\text{combination therapy}) - P_{Y_{ij}=0} (\text{placebo}) \right) * 100$$

RESULTS

The average symptom data were adequately described by the base structural model. However, the time course of symptom resolution was not captured by this average symptom data model. Inclusion of BVL, Δ VL, and time since the onset of symptoms were statistically significant for each symptom and improved the capture of symptom resolution. BVL and Δ VL were found to be best included as normal linear functions, and the effect of time was described by both a normal and log-transformed linear functions.

The summary of parameter estimates for the base structural model are included in Table 1. The “positive” values for the impact of BVL on the B_L parameters indicate an increased probability of severity of symptoms as the BVL increased. The “negative” values for both the time and Δ VL indicate the probability of having symptoms decreased over time and as viral load decreased from baseline. In contrast, cough displayed a “positive” value as viral load decreased from baseline. This observation possibly indicates a lag time for resolution of cough compared to the decreased viral load.

The current model described the severity of each symptom (which ranged from none to severe) over time and demonstrated reasonable agreement between observed and predicted values. The observed symptom data and model-predicted symptom data with the corresponding 95% confidence intervals (CIs) related to the proportion of subjects who experienced these symptoms are illustrated in Figure 2 and in Figure S1. It should be noted that there were lower number of observations at the beginning of the observational period and very few observations after 35 days from the time of symptom onset (Table S1). These lower number of observations would impact the visual interpretation of the model fits around these time points as the CIs could be skewed. However, as time from symptom onset progressed, most of the symptoms would have resolved and the impact of differing observational numbers would be less obvious. Therefore, additional diagnostics²⁵ were performed and demonstrated that the model was consistently fitting the data well (data not shown).

By linking the PK-viral model to the symptom model with the inclusion of viral load on symptom resolution, other dosing regimens not studied may be explored. As observed and model-predicted clinical trial data demonstrated, doses of 700 mg bamlanivimab and 1400 mg

TABLE 1 Parameter estimates (%RSE) from the final structural symptom model

Model parameter	Symptoms							
	Population and model estimates							
	BAP	Chill	Cough	Fatigue	FFEV	HA	SOB	STHRT
$B_{L=1}$								
Model estimate (% RSE)	0.675 (45.93)	-1.62 (22.41)	1.68 (16.67)	0.844 (42.42)	1.42 (20.70)	0.533 (46.53)	-1.39 (29.21)	-1.77 (19.60)
$B_{L=2}$								
Model estimate (% RSE)	2.04 (9.36)	2.57 (10.35)	3.48 (7.64)	3.03 (9.01)	2.93 (8.94)	2.17 (8.89)	3.19 (14.80)	3.08 (14.97)
$B_{L=3}$								
Model estimate (% RSE)	1.95 (5.44)	1.74 (10.11)	2.10 (14.71)	4.83 (8.76)	2.24 (8.62)	3.07 (14.30)	2.45 (8.20)	2.36 (10.00)
Time ^a								
Model estimate (% RSE)	-0.732 ^b (49.73)	-0.182 ^c (14.18)	-2.12 ^b (5.14)	-0.092 ^c (16.67)	-2.00 ^b (8.15)	-0.895 ^b (23.02)	-1.23 ^b (18.62)	-0.081 ^c (21.29)
BVL ^d								
Model estimate (% RSE)	0.098 (6.39)	0.071 (10.07)	0.107 (6.79)	0.121 (8.76)	0.074 (7.49)	0.080 (7.23)	0.120 (11.58)	0.066 (9.54)
ΔVL on $Y_{ij} = 1$ ^e								
Model estimate (% RSE)	-0.580 (23.62)	-0.244 (18.28)	-	-0.598 (14.82)	-0.272 (18.57)	-0.348 (23.74)	-0.180 (47.11)	-0.210 (36.29)
ΔVL on $Y_{ij} = 2$ ^e								
Model estimate (% RSE)	-0.513 (25.93)	-	0.093 (48.76)	-0.459 (14.81)	-	-0.238 (30.29)	-	-

Abbreviations: BAP, body aches and pain; $B_{L=1}$, base value for $DV \geq 1$; $B_{L=1} - B_{L=2}$, base value for $DV \geq 2$; $B_{L=1} - B_{L=2} - B_{L=3}$, base value for $DV \geq 3$, where $DV = 0$ corresponds to no symptom, $DV = 1$ corresponds to mild symptom, $DV = 2$ corresponds to moderate symptom, $DV = 3$ corresponds to severe symptom; $Y_{ij} = 1$, $Y_{ij} = 2$, and $Y_{ij} = 3$ are the corresponding logits for $DV \geq 1$, $DV \geq 2$, and $DV = 3$, respectively; BVL, baseline viral load; FFEV, feeling feverish; HA, headache; SOB, shortness of breath; STHRT, sore throat; ΔVL , change in viral load from baseline.

^aSame structure on $Y_{ij} = 1$, $Y_{ij} = 2$, and $Y_{ij} = 3$.

^b $qx \times \text{LOG}(\text{time} + 1)$.

^c $qx \times \text{time}$.

^d $qx \times (BVL - 64)$ on $BL = 1$.

^e $qx \times \Delta VL$.

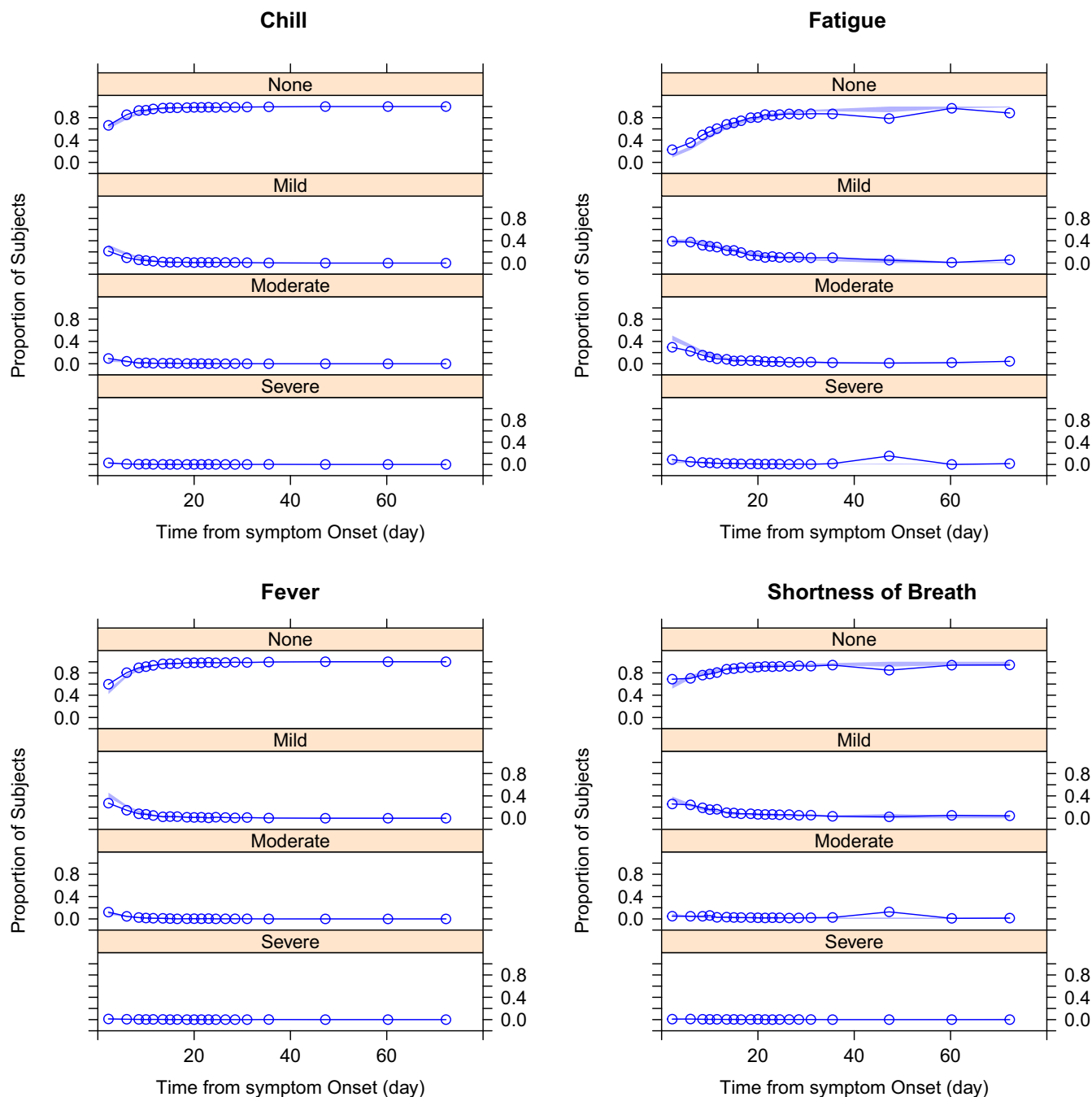


FIGURE 2 Visual predictive check for chills, fatigue, fever, and shortness of breath. Open circles represent observed symptoms data, shaded regions represent model-predicted 95% confidence intervals. The severity of symptoms ranged from none to severe

etesevimab would result in the maximum reduction in the viral load.²³ The symptoms outcomes resulting from this dosing paradigm were predicted using the final symptom model. The resulting model-predicted difference from placebo in the percentage of patients achieving symptom resolution over time following single dose administration of 700 mg bamlanivimab and 1400 mg etesevimab together, is illustrated in Figure 3 for chills, fatigue, fever, and shortness of breath and 5 days after

symptom onset for all symptoms in Table 2. The results show that the percent of patients achieving symptom resolution is highly dependent on time of treatment administration from symptom onset and the difference from placebo wanes as the time between therapeutic intervention and time from symptom onset increases. In addition, the simulation demonstrates that there is a difference between the different symptoms' responses to treatment interventions.

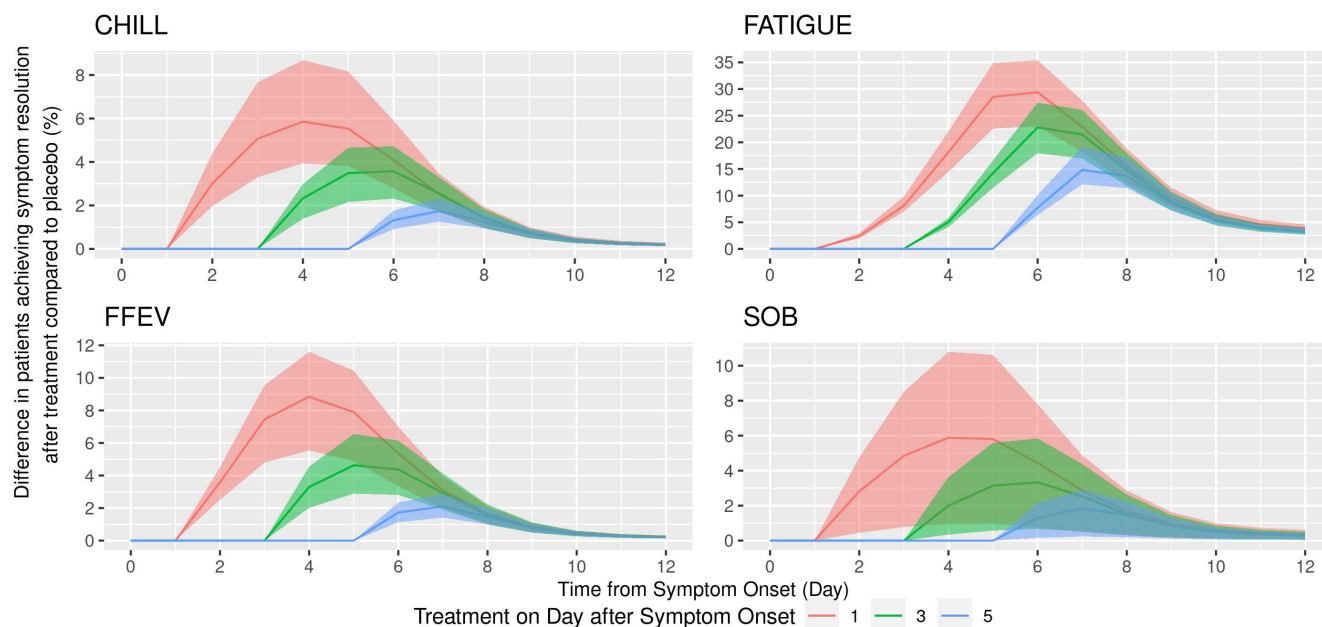


FIGURE 3 Model-predicted percent difference in patients achieving symptom resolution after 700 mg bamlanivimab and 1400 mg etesevimab compared to placebo on days 1, 3, and 5 after symptom onset. The shaded regions represent model-predicted 95% confidence intervals and the solid represents the median model-predicted symptom resolution. FFEV, feeling feverish; SOB, shortness of breath

Symptom	Percent difference in patients achieving symptom resolution after treatment compared to placebo (median; 95% CI)	
	Treatment on day 1 after symptom onset	Treatment on day 3 after symptom onset
	5 days from treatment	5 days from treatment
BAP	24.8 (16.8–31.9)	14.8 (10.0–20.1)
Chills	5.53 (3.81–8.16)	3.49 (2.16–4.66)
Cough	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Fatigue	28.5 (22.6–34.9)	14.2 (11.5–16.6)
FFEV	7.90 (4.89–10.4)	4.63 (2.89–6.55)
HA	16.2 (10.3–21.9)	9.27 (5.90–13.1)
SOB	5.81 (0.970–10.6)	3.14 (0.574–5.59)
STHRT	6.74 (2.24–10.5)	3.71 (1.50–6.05)

Abbreviations: BAP, body aches and pain; CI, confidence interval; FFEV, fever; HA, headache; SOB, shortness of breath; STHRT, sore throat.

TABLE 2 Model-predicted percent difference in patients achieving symptom resolution after 700 mg bamlanivimab and 1400 mg etesevimab compared to placebo

DISCUSSION

With high morbidity and mortality rates associated with SARS-CoV-2 infection, understanding the underlying mechanisms related to COVID-19-related symptom severity and viral load clearance allows assessment of drug effect on clinical outcomes. Examination of the surrogates of the clinical end point provides a high-level view of the inherent similarities and differences between groups or treatments. However, summarizing the collective data into clinical end point surrogates does not maximize the utility of the

quantitative biomarkers of drug effect. Thus, understanding the probability of transitioning between severity stages by using a nonlinear, mixed-effect model provides an opportunity to better understand the impact of change in viral load to clinical outcome. This can provide a pathway for potentially predicting drug efficacy and future clinical trial execution that facilitate viral load elimination.

The current study is the only work we know of that demonstrates a link between mAb treatment-associated viral load reduction and accelerated COVID-19-related symptom/disease resolution. The nonlinear, mixed-effect, ordered categorical

model presented, was developed with the intent of providing a useful tool for understanding the relationship between viral load and COVID-19-related symptom severity transition probabilities in patients who received bamlanivimab alone or together with etesevimab. This approach linked COVID-19-related symptom resolution to time from symptom onset, changes in viral load, and baseline viral load, as well as the subsequent PKs of bamlanivimab and etesevimab, within a semimechanistic pharmacological framework.

Implementation of the nonlinear, mixed-effect, ordered categorical model facilitated the model-prediction of difference from placebo in the percent of patients achieving symptom resolution after single dose i.v. administration of 700 mg bamlanivimab and 1400 mg etesevimab together. In general, administration of bamlanivimab alone or together with etesevimab early on from symptom onset shortens the time to symptom resolution by increasing the viral load clearance. These results mirror those observed in previous studies in which the change in COVID-19-related symptom resolution from baseline to day 11 was statistically significant in patients who received 700 mg bamlanivimab monotherapy²² as well as in those who received treatment consisting of 2800 mg bamlanivimab and 2800 mg etesevimab together.²⁶ The current study also revealed the earlier the treatment intervention, the faster the time to symptom resolution. These findings have practical implications in the healthcare setting, potentially mitigating hospitalization or reducing the length of time a patient requires hospitalization and the likelihood of downstream hospitalizations and/or risk of serious complications due to COVID-19. Subsequently, immunocompromised individuals may face a longer time to recovery and a concurrently greater risk of developing more serious COVID-related or hospital-acquired illness if not treated early. Such a prospect ultimately results in diminished patient well-being and a greater burden to the healthcare system. One advantage of using a nonlinear mixed-effect model to explore this kind of data is that it provides additional information on understanding the effects of drug intervention on different symptom transition and the time course related to such intervention. With model-based analyses, new dosing regimens can be explored for designing future studies and regimens without actual symptom data, as presented above. Simulations may be performed to predict the outcome of compounds with similar mechanism of action but different PK profiles.

The simulations from this study demonstrated a slight overprediction of events at the beginning of the observational period. A standard mixed effects modeling approach may produce biased parameter estimates when ordered categorical data with a skewed distribution are analyzed using the Laplacian method.²⁷ As interindividual variability and skewness in the distribution of the data increase, the bias associated with parameter estimation increases. The consequence of biased parameter values can lead to an

overestimation of the frequency of rare events when simulations are performed. Additionally, whereas the current model directly linked viral load to symptom resolution, there might be a delay related to physiological changes that persist after the infection is cleared. This might account for the inverse relationship for cough.²⁸ Attempts were made to account for a delay between viral load changes and symptoms by including transit compartments, latent variable models, and an effect compartment. However, none of these models improved the fit compared to the model presented. Furthermore, there could be significant covariates that affect the transition probabilities. For this particular data, several potential covariates were available, such as age ≥ 65 years, certain underlying medical conditions, including chronic kidney disease, type 1 or type 2 diabetes mellitus, hypertension, weight, alcohol habits, and gender, as these have demonstrated some pronounced effects on symptom severity. Therefore, future refinement of the model can include identifying significant covariates that can affect the transition probabilities, reducing the model structure, or different mechanisms to explore a delay between viral load clearance and symptom resolution.

In conclusion, the proposed nonlinear mixed-effect model resulted in a robust estimation of transition probabilities between symptom severity and symptom resolution associated with reduction in viral load. The VPC demonstrated that the proposed model suitably predicted the clinical end points. In addition, the general model structure is easily adaptable to allow significant changes for dosing regimens during simulation. This unique model-based evaluation demonstrated a robust characterization of the relationship between SARS-CoV2 viral load and symptom resolution.

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Bamlanivimab emerged from the collaboration between Eli Lilly and Company and AbCellera Inc. to create antibody therapies for the prevention and treatment of COVID-19. Lilly developed the antibody after it was discovered by AbCellera and scientists at the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center. Etesevimab emerged from the collaboration between Eli Lilly and Company and Junshi Biosciences/IMCAS. The authors thank Lynn Naughton, PhD, of Eli Lilly for providing medical writing and editorial support.

CONFLICT OF INTEREST

All authors are employees and stock/shareholders of Eli Lilly and Company.

AUTHOR CONTRIBUTIONS

C.S.E., J.Y.C., and E.C. wrote the manuscript. J.Y.C., D.R.P., and E.C. designed the research. J.Y.C., D.R.P., and E.C. performed the research. C.S.E. and E.C. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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