Population Pharmacokinetics and Pharmacodynamics of the Neutralizing Antibodies Bamlanivimab and Etesevimab in Patients With Mild to Moderate COVID-19 Infection

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Bamlanivimab and etesevimab are neutralizing antibodies indicated for treatment of coronavirus disease 2019 (COVID-19) in patients with early mild or moderate disease. We present the use of pharmacokinetic/pharmacodynamic (PK/PD) modeling that characterizes the timecourse of viral load obtained from 2,970 patients from 2 phase II clinical trials. The model was used for identification of optimal doses that would result in at least 90% of patients achieving serum drug concentrations that result in 90% of maximum drug effect (IC90) for at least 28 days. The serum IC90 (95% confidence interval) was estimated to be 4.2 (3.2–4.3) μg/mL for bamlanivimab and 12.6 (9.7–12.8) μg/mL for etesevimab. Observed clinical trial data confirmed PK and PK/PD model predictions that doses of 700 mg bamlanivimab and 1,400 mg etesevimab would result in maximum reduction in viral load, with no additional effect seen at higher doses. No dose adjustment is recommended as age, sex, race, baseline viral load, and hepatic impairment did not have a significant impact on the PK of the antibodies. Earlier drug administration resulted in greater reductions in viral load, demonstrating the importance of receiving treatment as soon as possible. Relative to placebo, typical reduction in viral load over a 7-day period was estimated to be 80 or 93% (drug administered 4 days or 1 day after the onset of symptoms, respectively), $P < 0.0001$. PK/PD modeling and simulation was pivotal throughout the drug development and emergency use authorization process.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Bamlanivimab and etesevimab are potent neutralizing antibodies that target the spike protein of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study characterizes the pharmacokinetics (PKs) of bamlanivimab and etesevimab and the exposure-response relationship for reduction in viral load in patients with coronavirus disease 2019 (COVID-19). The study identified the optimal doses and investigated the impact of various demographic factors that could affect therapeutic response to the neutralizing antibodies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ A single intravenous dose of 700 mg bamlanivimab and 1,400 mg etesevimab administered together result in maximum reduction in viral load relative to placebo. The earlier the drugs are administered, the greater the reduction in viral load.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study demonstrates the importance of PK/pharmacodynamic (PD) modeling and simulation for dose selection and dose justification in a pandemic situation where maximum speed and efficiency are required. A reliable approach to translation of *in vitro* potency estimates with appropriate PK/PD modeling-based adjustments to the *in vivo* situation is presented.

In recent years, model informed drug development has been thrust into the spotlight, in part due to the Prescription Drug User Fee Amendment VI (PDUFA VI) and the US Food and Drug Administration (FDA) model informed drug development pilot program.[1] This paper as well as others[2,3] (Chigutsa *et al.*, unpublished data on file) illustrate the importance of using

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pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation when dose selection, speed, and efficiency are of the essence in drug development programs,[4] such as in the development of treatments to address the coronavirus disease 2019 (COVID-19) pandemic.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is responsible for COVID-19 disease. Bamlanivimab and etesevimab are potent neutralizing antibodies that bind to the receptor-binding domain of the spike protein of SARS-CoV-2.[5] Such anti-spike neutralizing antibodies are expected to interfere with the ability of SARS-CoV-2 to bind to the angiotensin converting enzyme 2 receptor on host cells (type II pneumocytes in the lungs). This process is anticipated to result in a reduction in the SARS-CoV-2 viral load and clinical improvement of the disease. Therefore, the antibodies were studied as potential treatments for COVID-19. Early in 2021, bamlanivimab and etesevimab administered together received emergency use authorization from the FDA for treatment of COVID-19 infection in patients with mild or moderate disease.

We have applied a PK/PD based approach for selection of the first human dose range in a pandemic situation with paucity of preclinical data and using *in vitro* viral neutralization assay data (Chigutsa *et al*., unpublished data on file). That approach predicted that 700 mg of bamlanivimab would result in maximum reduction of viral load and therapeutic efficacy. PK and viral load data were available from 2 phase II clinical trials and we sought to evaluate the relationship between bamlanivimab and etesevimab concentration on viral load reduction. Based on the established exposure-response relationship, we conducted simulations to provide dose recommendations for adult and pediatric patients weighing at least 40 kg.

METHODS

The BLAZE-1 and BLAZE-4 studies are ongoing phase II dose-ranging, randomized, double-blind, placebo-controlled clinical trials, including patients who test positive for SARS-CoV-2 and have mild or moderate symptoms. They are registered at clinicaltrials.gov (NCT04427501 for BLAZE-1 and NCT04634409 for BLAZE-4). The studies were conducted in accordance with the Helsinki Declaration and with approval from the relevant institutional review boards. In BLAZE-1, patients were randomized to receive placebo, 700, 2,800, or 7,000 mg bamlanivimab monotherapy as a single intravenous dose, or 2,800 mg each of bamlanivimab and etesevimab, or 700 mg bamlanivimab administered together with 1,400 mg etesevimab. Further details about the trial are available in the literature.[6,7] In the BLAZE-4 trial, patients were randomized to receive placebo, 700 mg bamlanivimab, or doses of bamlanivimab/etesevimab of 175/350, 350/700, 700/1,400, and 2,800/2,800 mg.

PK sampling, assay, and population modeling approach

Following a single intravenous dose, about five serum samples for PK analysis were available from each study participant for each drug. The samples were drawn after the end of infusion (day 1), then on days 15, 29, 60, and 85.

The bioanalytical assay for determination of bamlanivimab and etesevimab in human serum was based on validated hybrid liquid chromatography with tandem mass spectrometry methods using protein G-coated magnetic beads for affinity capture of immunoglobulins, followed by sequential reduction and alkylation of cysteines and overnight digestion with trypsin. Specific tryptic peptides from the Fab region of each molecule were used as surrogate peptides for quantitation, with stable isotope-labeled forms included as internal standards. The signature peptides are identified and quantified using reversed-phase high-performance liquid chromatography with tandem mass spectrometry detection over a theoretical analyte concentration range from 10.00 to 1,000.00 μg/mL. Samples above the limit of quantification were diluted to yield results within the calibrated range. For both analytes, interassay accuracy (% relative error) during validation was within ± 10%, and the interassay precision (% relative standard deviation) was < 12%.

PK data from BLAZE-1 and BLAZE-4 were pooled with data from 38 study participants from 2 phase I trials. The first phase I trial (J2W-MC-PYAA; NCT04411628) had 78 observations from 18 participants who were hospitalized with severe COVID-19 disease. The second phase I trial (J2Z-MC-PGAA; NCT04441931) had 196 observations from 20 healthy study participants. In total, the PK dataset for bamlanivimab included 5,915 bamlanivimab concentration measurements from 1,899 study participants either alone or together with etesevimab. Approximately 80% of the 1,899 study participants had bamlanivimab administered together with etesevimab. The PK dataset for etesevimab included 4,961 etesevimab concentration measurements from a total of 1,498 study participants. Population PK analyses of bamlanivimab and etesevimab concentration-time data were performed for each drug separately using the nonlinear mixed-effects modeling program, NONMEM 7.4.2 (Gaithersburg, MD). First order conditional estimation with epsilon-eta interaction was used as the estimation method. The PK data for each antibody were characterized using a two-compartment model. Body weight was incorporated on clearances and volumes according to allometric principles.[8] Other covariates that were tested included age, sex, race, baseline viral load, and hepatic impairment. A stepwise covariate modeling process (forward inclusion ($P < 0.01$) and backward deletion ($P < 0.001$)) implemented in PsN 4.8.1[9] was used for covariate testing. Other criteria for covariate inclusion included plausibility of parameter estimates, clinical relevance, and reduction in interindividual variability.

Viral load data and population modeling approach

A total of 17,805 viral load measurements from 2,970 study participants pooled together from BLAZE-1 ($N = 2,303$) and BLAZE-4 ($N = 667$) were available for analysis. A target-cell limited viral dynamic model[10] was developed to analyze the viral load data. Briefly, the model included a pool of uninfected target cells (type II pneumocytes expressing the ACE2 receptor). These cells were then available for the COVID-19 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 (production rate), and a death rate of infected cells. The differential equations describing the models are shown below:

$$\frac{\mathrm{dvirus}}{\mathrm{d}t} = \mathrm{pv} \times \mathrm{IC} - \mathrm{cv} \times \mathrm{virus} \quad (1)$$

$$\frac{\mathrm{dIC}}{\mathrm{d}t} = \beta \times \mathrm{TC} \times \mathrm{virus} - \mathrm{DI} \times \mathrm{IC} \quad (2)$$

$$\frac{\mathrm{dTC}}{\mathrm{d}t} = -\beta \times \mathrm{TC} \times \mathrm{Virus} \quad (3)$$

where virus is the viral load; pv is the production rate of new virions; IC is the pool of infected target cells; cv is the elimination rate of the virus; β is the rate of infection of target cells; DI is the death rate of infected target cells; and TC is the pool of uninfected target cells.

The Stochastic Approximation Expectation Maximization algorithm followed by importance sampling was used as the estimation method,

with mu-referencing of parameters whenever possible (NONMEM 7.4.2 guide). The model was fit to viral load data which was converted from the polymerase chain reaction cycle time (in days) to logarithmic values according to the equation below:

$$\text{Log(10) viral load} = \frac{40 - \text{Cycle time}}{\log 2(10)}$$

Cycle time values > 40 were censored and considered to be a negative result for SARS-CoV-2. Given this right censoring of data and the fact that viral load cannot be negative, Beal's M4 method was implemented.[11] Log(10) viral load measurements below 0.05 were treated as a likelihood that they were below 0.05, whereas measurements above 0.05 were treated as continuous data. In order to best describe the dynamics of viral infection, the independent variable used in the analysis was time relative to the onset of symptoms. Therefore, patients would receive antibody treatment or placebo at a time relative to the reported onset of symptoms. A sequential PK/PD modeling approach was implemented where the individual post hoc PK parameters were used to predict the concentration-time profile of bamlanivimab and etesevimab during the exposure-response modeling. Drug effect was evaluated on multiple model parameters, including the elimination rate of the virus and binding to free virus to inhibit cellular infection. Similar to the PK modeling, the stepwise covariate modeling was used for covariate testing. Covariates tested included body weight, body mass index (BMI), age, and being identified as "at high risk" of developing severe COVID-19 disease (based on various patient factors, including having at least one of high BMI (≥ 35 kg/m^2), older age (≥ 65 years), immunosuppression, cardiovascular disorders with age ≥ 55 years, diabetes, or chronic kidney disease). The covariates were tested on drug effect parameters as well as on the production rate and the elimination rate of the virus.

PK/PD model-based simulations

Using the final PK/PD model, various simulations were performed to determine the following aspects following treatment with the neutralizing antibodies:

- Impact of bodyweight on PK and viral load reduction.
- Impact of timing of drug administration relative to the onset of COVID-19 symptoms.
- Comparison of bamlanivimab monotherapy to bamlanivimab administered together with etesevimab.
- Selection of the optimal doses of bamlanivimab and etesevimab.

RESULTS

The demographics of the study participants included in the PK and PK/PD analysis are shown in **Table S1**. Plots of the observed viral load data stratified by study arm are presented in **Figure S1**. The observed data are more difficult to interpret due to variability in the time of drug administration relative to the onset of symptoms as well as variability in the baseline viral load. Hence the need for a modeling and simulation approach to gain a better understanding of the complex data.

PK modeling

A two-compartment model adequately described the PK of bamlanivimab and etesevimab, independently. The PKs for both drugs were linear and exposure increased linearly in proportion with dose. The population PK parameter estimates are reported in **Table S2**. The half-life (% coefficient of variation) was 20.9 (17.3%) days and 32.6 (21.7%) for bamlanivimab and etesevimab, respectively. No covariates were identified to be significant on PK in the analysis. Therefore, age, sex, race, baseline viral load, and hepatic impairment did not have a significant impact on the PKs of either drug. A visual predictive check (VPC) indicated that the models could adequately predict the observed data (**Figure 1**).

Viral dynamic modeling

The target cell limited model adequately described the change in viral load over time. Administration of the neutralizing antibodies was found to result in an increased elimination rate of the virus (objective function value drop of 760 points, $P < 0.0001$), implemented through a maximum effect (E_{max}) model driven by the serum drug concentration, as predicted using the PK models. Because the dataset was comprised of patients on placebo, bamlanivimab monotherapy, or combination therapy, an additional effect of etesevimab in increasing viral clearance was included. Due to lack of clinical efficacy data for etesevimab administered alone, the concentration that results in half of the maximum drug effect of etesevimab was assumed to be three times that of the estimated

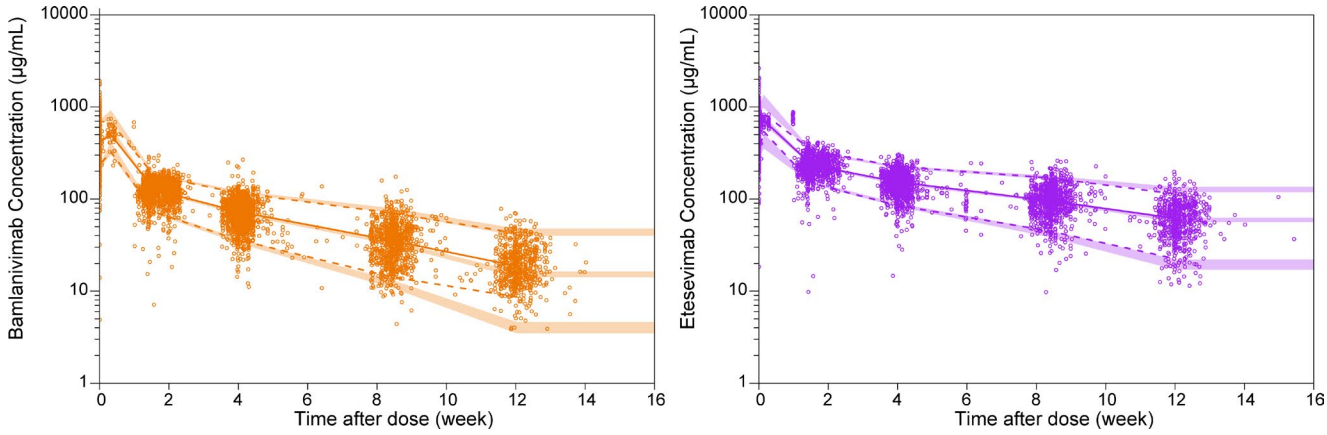

Figure 1 Visual predictive check for bamlanivimab and etesevimab population pharmacokinetic models. Open circles represent observed data. The upper and lower dashed lines are the 95th and 5th percentiles of the observations, respectively. The continuous line is the median of the observations. The shaded areas represent the model predicted 95% confidence interval for the corresponding percentiles.

bamlanivimab value, based on relative *in vitro* potency estimates. Estimating an additional parameter representing a different E_{max} for etesevimab separately from bamlanivimab was not significant. Therefore, the two drugs were assumed to have the same maximum effect. The parameter estimates from the final model are reported in **Table 1**. None of the covariates tested were found to be statistically significant. Therefore, body weight, BMI, age, or high-risk status did not have an impact on the response to bamlanivimab or etesevimab after accounting for the impact of body weight on PK. A VPC indicated that the viral dynamic model could adequately predict the observed viral load data (**Figure 2**). NONMEM code for the viral dynamic model is provided in the **Supplementary Material**.

Applications of PK and PK/PD model

Impact of bodyweight. Bodyweight was incorporated in the bamlanivimab and etesevimab PK models using allometric scaling. Consistent with the PK of most monoclonal antibodies,[12] the structure of the PK models dictated that individuals with higher bodyweight would have lower drug concentrations of bamlanivimab and etesevimab. A deterministic simulation was performed to evaluate the clinical relevance of the impact of bodyweight on PK and subsequently on the viral load reduction. The simulation was done for an individual weighing 40 kg and another individual weighing 220 kg. These bodyweights represent the extremes of the distribution of bodyweight in the BLAZE-1 and BLAZE-4 studies. **Figure 3** shows that whereas individuals with higher bodyweight would have lower drug concentrations, the clinical effect of bamlanivimab and/or etesevimab in reducing viral load is not compromised. This is because the lower drug concentrations would still be significantly above the 90% of maximum drug effect (IC90) of both drugs for a lengthy period (at least 28 days after dosing). Therefore, dosing of either neutralizing antibody according to bodyweight is not necessary.

Impact of timing of drug administration on viral load reduction. Deterministic simulations were conducted to evaluate the impact of timing of drug administration on reduction of viral load. The median duration between the onset of symptoms and drug administration in both clinical trials was 4 days. **Figure 4** and **Table 2** indicate greater viral load reduction with earlier drug administration.

Comparison of bamlanivimab monotherapy and bamlanivimab together with etesevimab. The viral dynamic model included a drug effect for bamlanivimab and an additional effect of etesevimab. **Figure 4** illustrates the additional reduction in viral load for bamlanivimab together with etesevimab as opposed to bamlanivimab alone.

Dose justification. The serum IC90 (95% confidence interval) was estimated to be 4.2 (3.2–4.3) μg/mL for bamlanivimab and 12.6 (9.7–12.8) μg/mL for etesevimab. Using the PK/PD model, Monte-Carlo simulations were carried out using the observed distribution

Table 1 Population viral dynamic model parameters

Parameter description	Population estimate (%SEE)	%CV interindividual variability (%SEE)	Bootstrap 95% CI for population estimates	Bootstrap 95% CI for %CV interindividual variability
Target-cell pool	4×10^8 (Fixed)[a]	0 Fixed	4×10^8 (Fixed)[a]	—
Log_{10} viral load at onset of symptoms	7.60 (9.05)	15% Fixed[b]	7.44, 7.67	15% Fixed[b]
Infection rate constant, β ([copies/mL]$^{-1}$ day^{-1})	5.23×10^{-7} (31.2)	2526 (7.71)	4.03×10^{-7}, 8.94×10^{-7}	1,310, 3,288
Production rate of virus, PV (day^{-1})	0.0844 (26.1)	47.2 (21.9)	0.0799, 0.0935	44.0, 51.9
Elimination rate of virus, CV (day^{-1})	1.42 (2.30)	85.4 (4.54)	1.30, 1.47	80.8, 95.0
Death rate of infected cells, DI (day^{-1})	0.290 (3.04)	15% Fixed[b]	0.265, 0.331	15% Fixed[b]
Additive error (log viral load)	0.939 (0.656)	—	0.924, 0.963	—
E_{max} (fractional increase in CV)[c]	0.462 (3.90)	15% Fixed[b]	0.438, 0.570	15% Fixed[b]
EC_{50} (μg/mL)	0.467 (16.3)	15% Fixed[b]	0.358, 0.473	15% Fixed[b]
Correlation between the random effects of β and PV	—	0.939 (13.6)	—	0.987, 0.999
Correlation between the random effects of β and CV	—	0.344 (17.9)	—	0.271, 0.391
Correlation between the random effects of PV and CV	—	0.359 (105)	—	0.257, 0.406

%CV, percent coefficient variation; CI, confidence interval; EC_{50}, half maximal effective concentration; E_{max}, maximum effect; SAEM, Stochastic Approximation Expectation Maximization; SEE, standard error of the estimate.

[a]Fixed to Baccam *et al.*[10]

[b]Fixed to 15% to allow efficiency of SAEM algorithm per NONMEM user guide.

[c]$CV_t = CV + \frac{E_{max} \times conc1}{EC_{50} + conc1} + \frac{E_{max} \times conc2}{(EC50 \times 3) + conc2}$ where conc1 is the serum concentration of bamlanivimab at time, *t* and conc2 is the serum concentration of etesevimab at time, *t*.

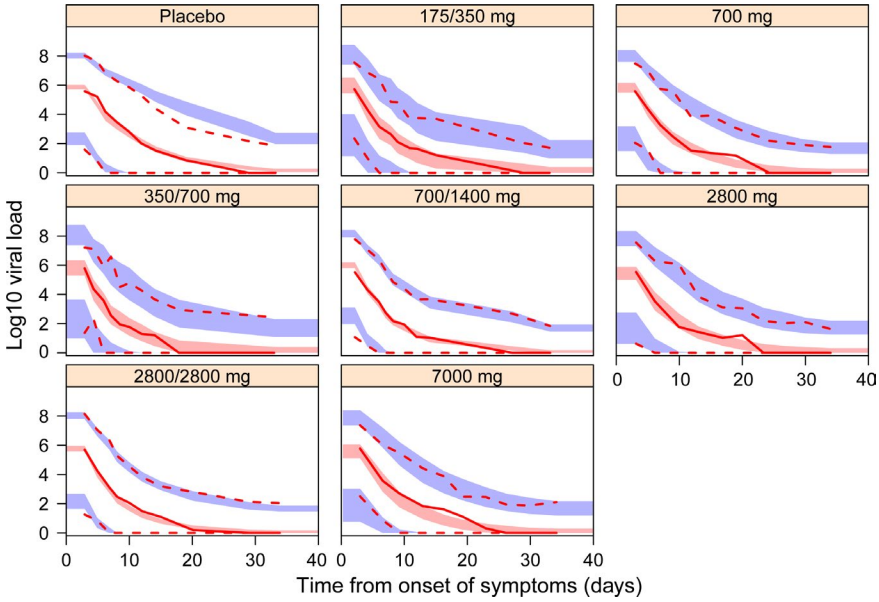

Figure 2 Visual predictive check of the viral dynamic model. The upper dotted lines, continuous red lines, and lower dotted lines are the 95th, 50th, and 5th percentiles of the observations, respectively. The shaded areas represent the model-predicted 95% confidence interval for the corresponding percentiles. Doses of 700, 2,800 and 7,000 mg represent bamlanivimab monotherapy. Doses of 175/350, 350/700, 700/1,400, and 2,800/2,800 mg represent the doses of bamlanivimab/etesevimab together.

of bodyweight in the dataset to determine the adequacy of various doses to achieve sufficient drug exposure through a period of 28 days following a single dose. Twenty-eight days was selected as a conservative duration to ensure therapeutic concentrations through the course of a COVID-19 infection, which normally lasts up to 2 weeks. **Figure 5** shows that the currently authorized doses of 700 mg bamlanivimab and 1,400 mg etesevimab are more than sufficient to meet the required PD target concentrations (> IC90). A sensitivity analysis was conducted to determine the impact of etesevimab being less potent than the current potency of three times lower than bamlanivimab. Simulations were conducted using an IC90 (95% confidence interval) of 25.2 (19.4–25.6) μg/mL for etesevimab. Based on this sensitivity analysis which assumes a lower potency, **Figure S2** shows that although a higher etesevimab dose than that in **Figure 5** would be needed to attain PD target concentration at day 28, the authorized dose of 1,400 mg etesevimab remains adequate.

DISCUSSION

This is the first time the PK and exposure-response relationship of the neutralizing antibodies bamlanivimab and etesevimab have been described in patients with COVID-19. The PKs of bamlanivimab and etesevimab are consistent with most monoclonal antibodies. The half-life of etesevimab (about 4 weeks) was longer than that of bamlanivimab (about 3 weeks). The PKs of bamlanivimab administered alone was similar to the PKs of bamlanivimab when administered with etesevimab. This indicates that there is no interaction between the two drugs, as expected for monoclonal antibodies, which undergo general catabolism as the main route of elimination. The PK simulations showed the impact of the expected relationship between bodyweight and PK, where individuals with higher bodyweight would have lower drug concentrations. This relationship was not of clinical relevance because the attained drug concentrations remained significantly above concentrations needed for near-maximum drug effect (IC90) regardless of bodyweight. Although individuals with lower bodyweight may achieve higher than necessary drug concentrations, safety of bamlanivimab and etesevimab is of limited concern, even with doses as high as 7,000 mg.[6] Other covariates were tested on PKs or viral dynamics including age (range of 12–94 years), mild or moderate hepatic impairment, race (White, Asian, Black, or African American), and baseline viral load. None of these covariates were found to significantly impact the PKs or viral dynamics of bamlanivimab or etesevimab. Therefore, no dose adjustment is necessary for any of these covariates. Similarly, no dose adjustment is necessary for renal impairment because monoclonal antibodies are not excreted renally, but cleared via catabolic processes.[12]

The viral dynamic model quantitively described the effects of bamlanivimab and etesevimab in reducing viral load, through increasing the rate of clearance of the virus. The VPCs showed that the model provided a good fit to the data. This viral dynamic model is the target cell limited model that has been previously used for influenza,[10] as outlined in the Methods section. It worked well for SAR-CoV-2 infection in this study without need of modification apart from including the drug effect and estimating the relevant model parameters based on the current clinical trial data. The viral load reduction was highly significant and could be as much as a 93% reduction relative to placebo if the drugs are administered 1 day after the onset of symptoms. Consistent with many viral infections, the simulations demonstrated greater therapeutic benefit with earlier drug administration (**Figure 4**). Cognizant of this fact and based on prior viral dynamic modeling, the vast majority of study participants in the BLAZE-1 and

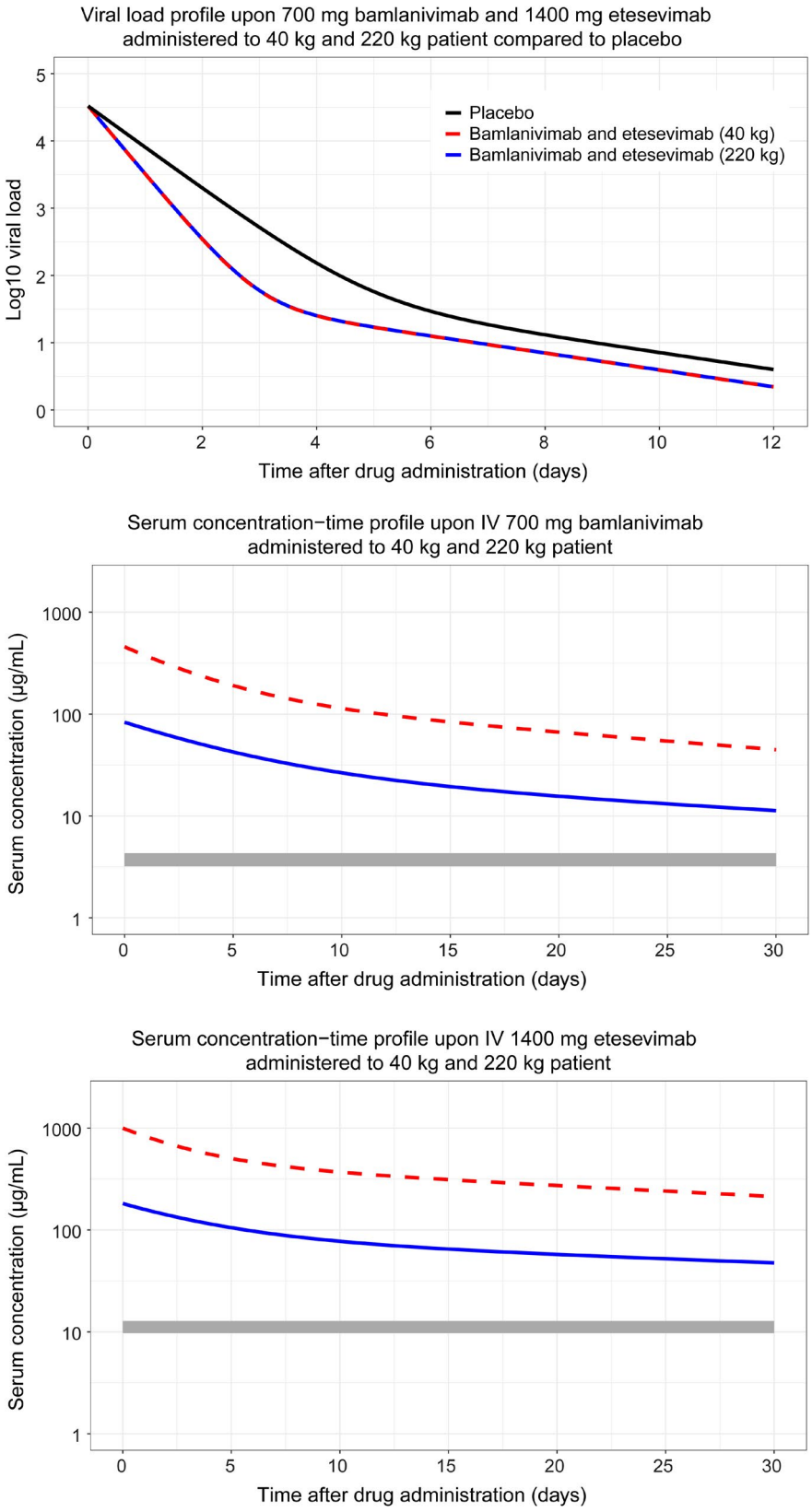

Figure 3 Viral load profiles (top), bamlanivimab pharmacokinetic (PK; middle) and etesevimab PK (bottom) profiles after single dose intravenous administration of 700 mg bamlanivimab and 1,400 mg etesevimab (combo) or placebo for an individual weighing 40 kg compared with an individual weighing 220 kg. Grey shaded bar is the 95% confidence interval for the *in vivo* 90% of maximum drug effect from the viral dynamic model. The model predicted viral load lines for the patient weighing 220 kg (blue solid line) and 40 kg (red dotted line) completely overlap.

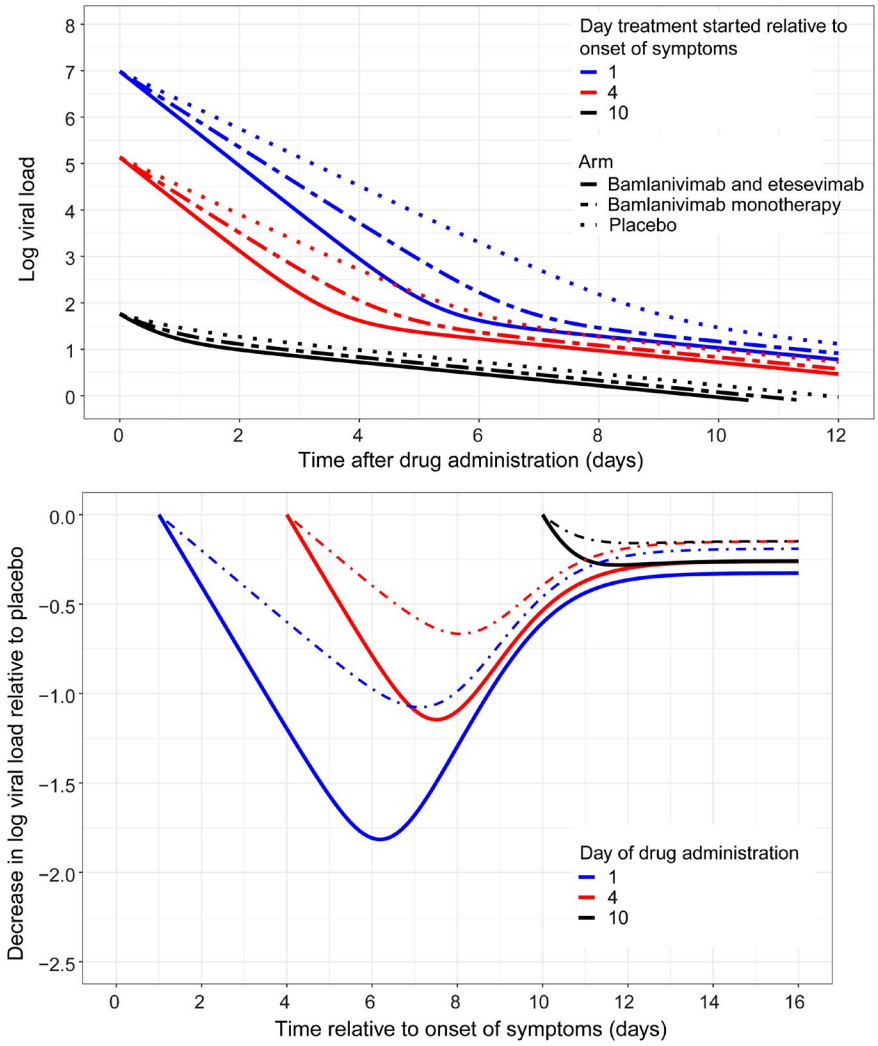

Figure 4 Simulated typical viral load profiles (top panel) and difference of viral load between placebo and patients (bottom panel) administered with a single dose 700 mg i.v. bamlanivimab (dot-dashed lines) or bamlanivimab (700 mg) together with etesevimab (1,400 mg; solid lines).

Table 2 Model-estimated reduction in viral load following a single intravenous dose of 700 mg bamlanivimab together with 1,400 mg etesevimab relative to placebo depending on the time of treatment

Bamlanivimab and etesevimab administration relative to symptoms onset (days)	Reduction in time-weighted average $\log_{10}$ viral load from days 0 to 7 relative to placebo (% absolute decrease)[a]	Reduction in time-weighted average $\log_{10}$ viral load from days 0 to 11 relative to placebo (% absolute decrease)[a]	Maximum reduction in $\log_{10}$ viral load relative to placebo on any day (% absolute decrease)[a]
1	1.15 (92.9)	0.99 (89.8)	1.82 (98.5)
4	0.70 (80.0)	0.55 (71.8)	1.15 (92.9)
10	0.25 (43.8)	0.24 (42.5)	0.28 (47.5)

[a]The % absolute reduction is calculated from the $\log_{10}$ values according to the equation: $P = (1 - 10^{-L}) \times 100$, where P is the percent absolute decrease, and L is the $\log_{10}$ reduction.

BLAZE-4 clinical trials received drug treatment within 10 days of the onset of symptoms. Consequently, the authorized factsheet indicates bamlanivimab together with etesevimab for patients who present with a duration of symptoms that is up to a maximum of 10 days. The factsheet also states the treatment must be administered as soon as possible after a positive test result for SARS-CoV-2. As suggested in **Figure 4** and **Table 2**, drug administration as soon as possible is recommended to achieve the best possible reduction in viral load.

The estimated *in vivo* serum IC90 in the viral dynamic model was comparable to *in vitro* virus neutralization assay results upon adjusting for drug penetration into the lung tissue (epithelial

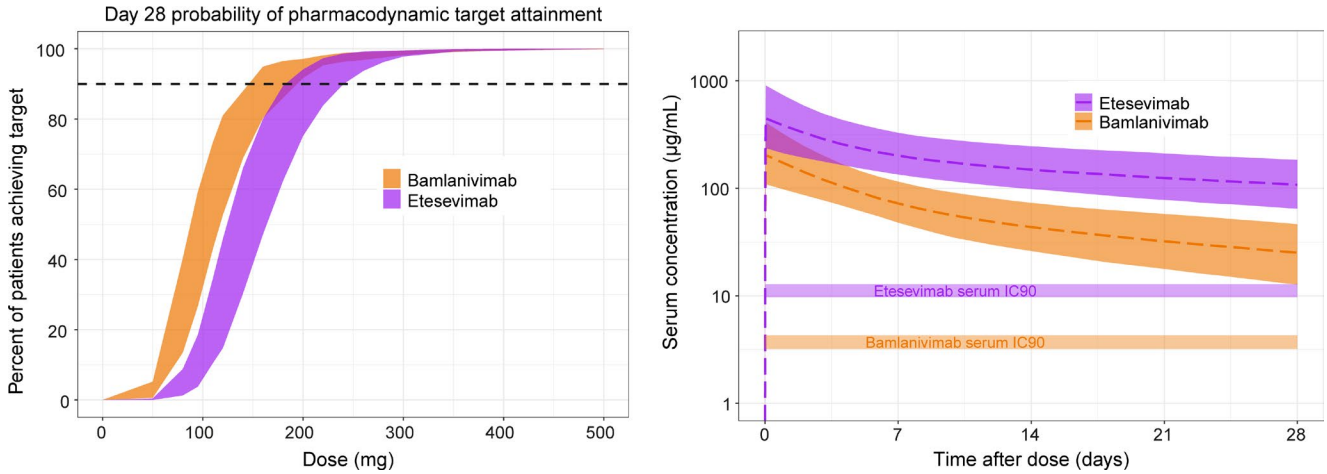

Figure 5 Probability of target attainment (left) and pharmacokinetic (PK) profiles (right) upon intravenous administration of bamlanivimab and etesevimab. Left panel—shaded areas represent 95% confidence interval. Right panel—horizontal bars represent 95% confidence interval of the serum 90% of maximum drug effect (3.2–4.3 µg/mL for bamlanivimab and 9.7–12.8 µg/mL for etesevimab). Shaded PK profiles represent 90% prediction interval following a 700 mg dose of bamlanivimab and a 1,400 mg dose of etesevimab.

lining fluid). Based on a physiologically-based PK model for bamlanivimab, the serum:lung penetration ratio was 6.5% (Chigutsa *et al*., unpublished data on file). A physiologically-based PK model was not available for etesevimab, hence a typical literature value of 15% was used.[13] Taking lung penetration into account yields adjusted *in vitro* IC90 (95% confidence interval) values of 1.34 (0.45–4.1) µg/mL and 2.73 (0.73–10) µg/mL for bamlanivimab and etesevimab, respectively. These values are similar to the *in vivo* model estimated values of 3.2–4.3 µg/mL for bamlanivimab and 9.7–12.8 µg/mL for etesevimab. This finding signifies reliable translation of *in vitro* virus neutralization assay results to the *in vivo* situation. *In vitro* potency estimates were a key input for prior modeling and simulation toward prediction of an efficacious dose (Chigutsa *et al*., unpublished data on file) and subsequently confirmed by the clinical trial results. Although the *in vivo* IC90 estimates correlated well with the *in vitro* values, the values should still be interpreted with caution given that the doses that were studied were all on the upper end of the exposure-response relationship. Although the data in the current modeling already included a wide dose range from 175 to 7,000 mg of bamlanivimab, data from doses lower than 175 mg could further help in characterization of the exposure-response relationship.

Although bamlanivimab significantly reduced the viral load compared to placebo, the modeling showed that there was additional reduction in viral load when bamlanivimab was administered together with etesevimab, as opposed to bamlanivimab alone. Because the achieved bamlanivimab exposures already resulted in maximum drug effect, it stands to reason that there must be some virus particles that were less sensitive to the neutralizing activity of bamlanivimab but remained sensitive to etesevimab. Lilly requested the FDA to revoke the emergency use authorization of bamlanivimab alone and recommended that it be administered together with etesevimab due to the changing variant landscape within the United States.[14] At this point, it is known that there are some "variants of concern," such as B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), and B.1.427/B.1.429 (epsilon), in circulation. During preliminary sequencing analysis at the time, the epsilon variant was identified in 45 study participants and was not found to have an impact on treatment with bamlanivimab together with etesevimab. Sequencing analysis is still ongoing for these studies. Future work will be needed to determine the clinical impact of the variants of concern and response to treatment with the neutralizing antibodies.

Importantly, an earlier analysis (data not shown), that included bamlanivimab monotherapy data between 700 and 7,000 mg and a bamlanivimab/etesevimab combination dose level of 2,800/2,800 mg, PK/PD modeling and simulation were used to determine that doses of 700 mg bamlanivimab and 1,400 mg etesevimab would result in equivalent reduction in viral load to the studied combination doses of 2,800 mg of each antibody. It was these data and the supporting PK/PD modeling that served as the basis for the currently authorized dose of 700 mg bamlanivimab together with 1,400 mg etesevimab. The FDA granted emergency use authorization for PK/PD model-based doses before the clinical trial data for the dose of 700/1,400 mg had become available.[15] The PK/PD parameter estimates for the prior interim analysis were similar to those reported in this paper.

Whereas **Figure 5** suggests that doses lower than the authorized doses of 700/1,400 mg could be sufficient, lowering the doses in the absence of further clinical information around variants of concern is not recommended at this time.

In summary, PK/PD modeling and simulation played a pivotal role in the development program for bamlanivimab and etesevimab, including selection of the first in human dose (Chigutsa *et al*., unpublished data on file), and informing the currently authorized dose for bamlanivimab together with etesevimab and ultimately in describing the PK and exposure-response relationship to inform the factsheet.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST
All authors are employees of Eli Lilly and Company.

AUTHOR CONTRIBUTIONS
E.C., L.O., L.F.S., A.L., and J.C. wrote the manuscript. E.C. and J.C. designed the research. E.C., L.O., L.F.S., and A.L. performed the research. E.C., L.O., L.F.S., and A.L. analyzed the data.

DATA AVAILABILITY STATEMENT
NONMEM model code has been provided in the **Supplementary Material**. Other data may be available upon request in accordance with Lilly scientific disclosure policy.

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