A physiologically-based pharmacokinetic modeling approach to support candidate and first in human dose selection for bamlanivimab

Introduction
Neutralizing monoclonal antibodies (mAb) to provide novel therapeutics for COVID-19 treatment, were urgently researched from the start of the pandemic. The selection of an optimal mAb candidate and therapeutic dose were expedited prior to acquisition of preclinical PK and animal PD data using open-access in silico models.

Methods
Candidate selection and effective therapeutic dose projection were supported by innovative adaptation of models obtained through open-science initiatives [1,2]. A physiologically-based pharmacokinetic (PBPK) model was modified by incorporating affinity-capture self-interaction nanoparticle spectroscopy data from the mAbs (AC-SINS) (Figure 1). The PBPK model was then used to predict mAb clearance, tissue distribution, and estimated mAb exposures needed to maintain lung interstitial fluid (ISF) concentrations above IC90 of in vitro neutralization for up to 4 weeks in 90% of patients. AC-SINS score and in vitro neutralization of SARS-CoV-2 virus infection were determined as described [3,4]. Specific to this goal and to explore differentiation of models obtained through open-science initiatives [1,2]. A physiologically-based pharmacokinetic modeling approach to support candidate and first in human dose selection for bamlanivimab

Results
The PBPK model using molecule-specific AC-SINS predicted antibody clearance (Figure 2) and organ-specific concentrations and projected 17-fold lower concentrations in lung ISF than corresponding plasma levels (Figure 3). Evaluation of early candidate antibodies primarily showed AC-SINS < 3, which alone was not sufficient for final candidate selection. Therefore, the final candidate was selected based on therapeutic doses that were expected to maintain mAb concentrations above IC90 of in vitro neutralization in the lung ISF for up to 4 weeks in at least 90% of patients (Table 1). In vitro neutralization data, with virtual patient simulations, were used to support the selection of the most potent candidate where a clinical dose of 175 - 500 mg was expected to maintain the target ISF mAb concentrations. The first-in-human trial with bamlanivimab (NCT04411628) proceeded with a 700 mg starting therapeutic dose, escalating to higher doses to evaluate the upper limit of safety and tolerability. Non-clinical (Figure 4) and clinical (Figure 5) a posteriori results confirmed the model predictions for PK, viral clearance, and ultimately the authorized dose.

Acknowledgements
This study was funded by Eli Lilly and Company.

Table 1: Predicted effective dose range for considered mAbs

References

© Metrum Research Group 2021

Presented at Population Approach Group Europe Annual Meeting; 2-3 and 6-7 September 2021

Copies available at: www.metrumrg.com/all-publications

Tim Knab1, Ahmed Elmokadem1, Emmanuel Chiguta2, Eric Jordie1, Matthew Riggs1, Patricia Brown-Augsburger2, Christopher Wiethoff2, Ajay Nirula3, Jenny Y Chien2, Lisa O’Brien2

1 Metrum Research Group, Tarryville, CT USA, 2 Eli Lilly and Company, Indianapolis, IN USA

Figure 1: Model schematic

A population PK model for bamlanivimab fit to human data simulated from the PBPK model to rapidly facilitate cross-collaborative allometric scaling across species. Parameter estimates obtained using NONMEM® were scaled allometrically to predict serum concentration in primates and human. Inter-individual variability and parameter uncertainty (30-50%) were incorporated in the model predictions.

Serum concentrations of bamlanivimab were determined in cynomolgus and rhesus monkeys by ELISA, and bamlanivimab in vivo activity was determined in a rhesus prophylaxis model [S]. Serum concentrations of bamlanivimab in study PYAA (NCT04411628) were determined with a validated affinity capture, LC-MS/MS method.

Figure 2: Monkey PK compared to prospective model predictions

Conclusion
The accelerated selection of bamlanivimab as the first neutralizing mAb drug candidate to enter clinical evaluation and the prediction of the maximum therapeutic dose of bamlanivimab for the treatment of COVID-19 prior to acquisition of preclinical PK and animal PD data was supported by an in silico quantitative modeling and simulation framework.

Figure 3: Human PK compared to prospective model predictions

• Candidate mAb target distribution (ISF)
• mAb-specific properties affecting PK of individual candidates
• Interpatient variability based on intrinsic factors in the model (body weight, age, etc.)

Viral Neutralization data:
• mAb-specific neutralization IC90 to establish target exposure for each candidate

Figure 4: In vitro neutralization of SARS-CoV-2 virus (25-100%)