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

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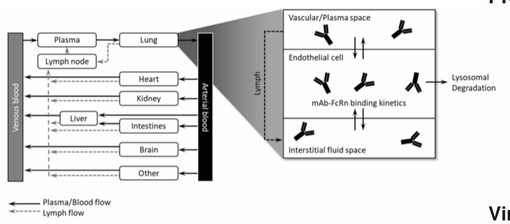
Introduction

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 the mAb candidates, the following characteristics were considered:



(Reproduced from Jones, H. M. *et al.* 2019[6])

Figure 1: *Model schematic*

PK:

- 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

A population PK model for bamlanivimab was 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 [3]. Serum concentrations of bamlanivimab in study PYAA (NCT04411628) were determined with a validated affinity capture, LC-MS/MS method.

Acknowledgements

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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.

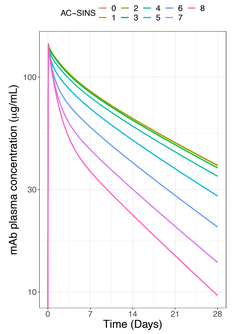

Figure 2
mAb plasma conc. over time

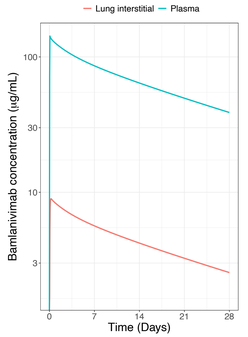

Figure 3
Bamlanivimab conc. over time

Table 1: *Predicted effective dose range for considered mAbs*

					Dose[a] (mg) expected to maintain concentration above live virus IC90[b] in the lung Geometric mean (min, max)					
					For a typical patient			For 90% of patients		
mAb	Domain	ACE2 Blocking	AC-SINS Score	Live Virus IC50 (mg/mL)	Day 14	Day 21	Day 28	Day 14	Day 21	Day 28
1	S1	No	2·25	0·841	1273 (918·7-2303)	1664 (1197-3043)	2153 (1542-3988)	3295 (2369-6023)	5583 (3981-10440)	9236 (6984-17960)
2	RBD	Yes	0	2·685	4210 (2607-11580)	5662 (3450-16830)	7600 (4534-25280)	11190 (6828-32350)	20200 (11890-67670)	37020 (20620-70000)
3	NA	Yes	0	1·3	1977 NA	2599 NA	3387 NA	5145 NA	8838 NA	14990 NA
4	RBD	Yes	0	1·112	1684 (1295-2607)	2208 (1692-3450)	2867 (2187-4534)	4370 3349-6828)	7446 (5665-11890)	12510 (9370-20620)
5[c]	RBD	Yes	1	0·04609	68·28 (25·16-237·5)	88·16 (32·48-307·3)	112·3 (41·38-392·2)	174·3 (64·21-607·5)	286·4 (105·4-1002)	454·9 (166·9-1598)

[a]Dose for mAB 1,2,4 and 5 is the geometric mean of data from three assay laboratories. Data for mAb 3 was available from one assay laboratory only [b]IC90 = 9 x IC50 [c]mAb 5 corresponds to bamlanivimab

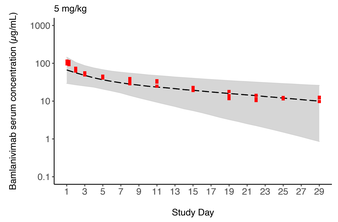

Figure 4: *Monkey PK compared to prospective model predictions*

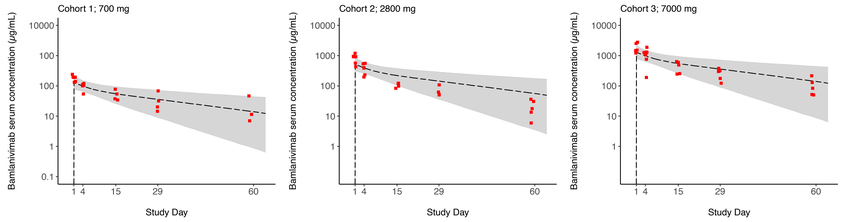

Figure 5: *Human PK compared to prospective model predictions*

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.

References

[1] Jones et al. CPT:PSP 2019; 8(10): 738-747; [2] Shah and Betts. MAbs 2013; 5(2): 297-305; [3] Jones et al. STM 2021; eabf1906; [4] Wu et al. Protein Eng Des Sel 2015; 28(10): 403-414

PBPK model code available at:
https://github.com/metrumresearchgroup/bioPBPK/tree/main/mAb_bamlanivimab