

Cabotegravir pharmacokinetics after oral and intramuscular administration using physiologically based pharmacokinetic modelling

Sara Bettonte (1,2), Mattia Berton (1,2), Felix Stader (3), Manuel Battegay (1,2), Catia Marzolini (1,2,4)
(1) University Hospital Basel, Switzerland, (2) University of Basel, Switzerland, (3) Certara UK Limited, United Kingdom, (4) University of Liverpool, United Kingdom

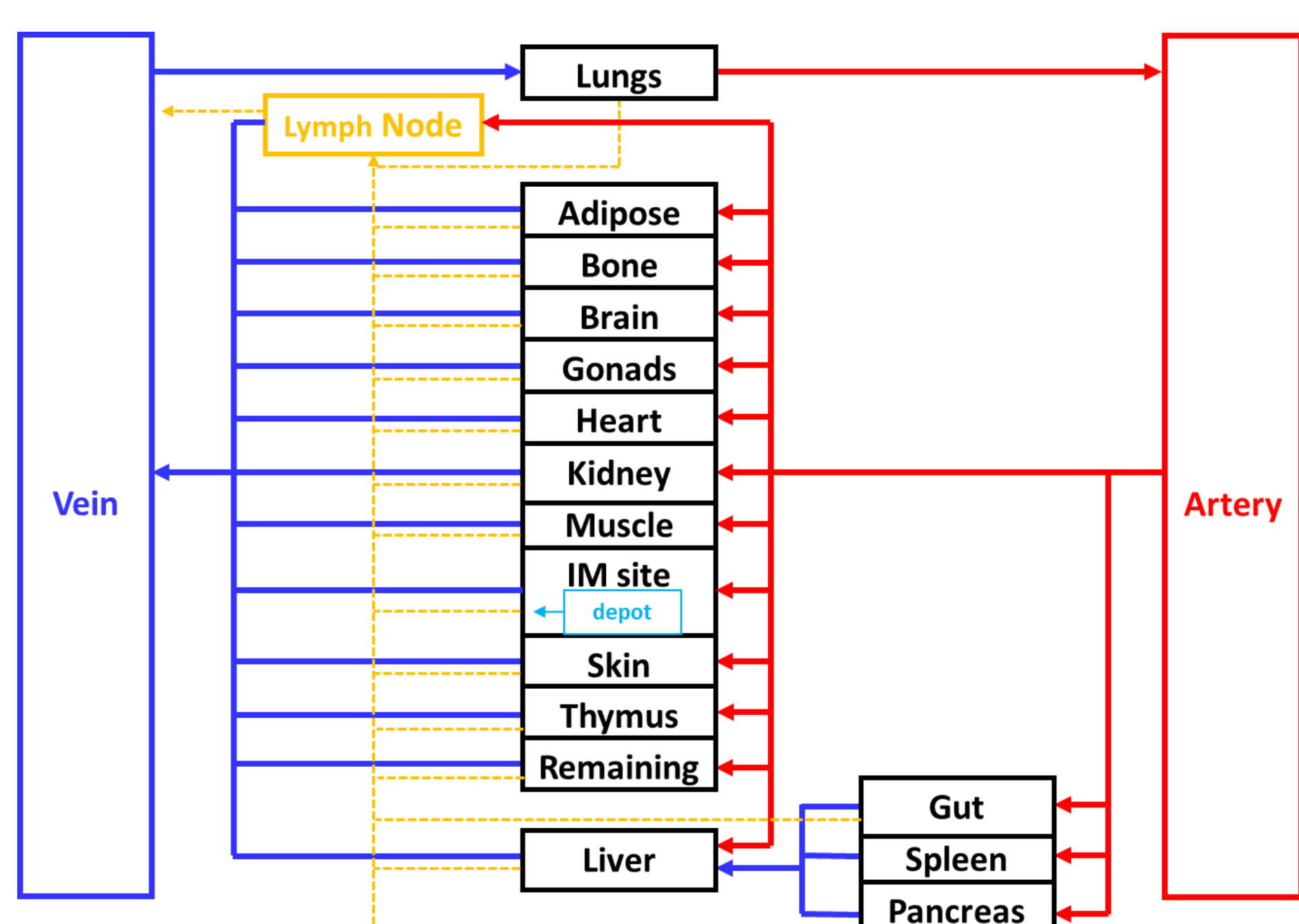
BACKGROUND AND OBJECTIVES

Combined antiretroviral treatment has transformed HIV infection into a chronic condition. However, the efficacy of antiretroviral treatments relies on high levels of adherence to daily oral regimens. The recent approval of cabotegravir and rilpivirine as the first long-acting injectable antiretroviral drugs represents a major milestone for the treatment of HIV infection. These long-acting injectables are formulated to slowly release the drug over weeks after the injection and therefore have the potential to improve adherence with less frequent dosing [1]. Although injectable antiretroviral drugs hold great promises, a number of questions remain unresolved. Physiologically based pharmacokinetic (PBPK) modelling is a useful tool to simulate unstudied clinical scenarios [2]. Only a few PBPK models for intramuscular administration have been published [3, 4], however they rely on clinical data to estimate the release constant of the drug from the intramuscular depot. We overcame this limitation by developing a mechanistic intramuscular model integrating the dissolution process after drug injection. The aim of this study was to evaluate the predictive performance of our mechanistic intramuscular PBPK model to simulate the pharmacokinetics of cabotegravir.

METHODS

- The mechanistic intramuscular framework (Figure 1) was implemented in our in-house PBPK model built using Matlab® [2].
- Cabotegravir drug parameters were obtained from published data both after oral and intramuscular administration as well as during the switch period between the two routes of administration.
- Observed data were extracted from the literature using GetData Graph digitizer®. Non-compartmental analysis was conducted using Matlab® to calculate the primary pharmacokinetic parameters if they were not reported.
- The predictive performance of the model to simulate the pharmacokinetics of cabotegravir was judged by the visual inspection of concentration-time profiles after single and multiple oral and intramuscular administrations.
- The achievement of pharmacokinetic parameters within the 1.25-fold, 1.5-fold, 2-fold limits of observed data (as per FDA guidance) was verified using observed clinical data.

Figure 1. Schematic representation of PBPK model structure



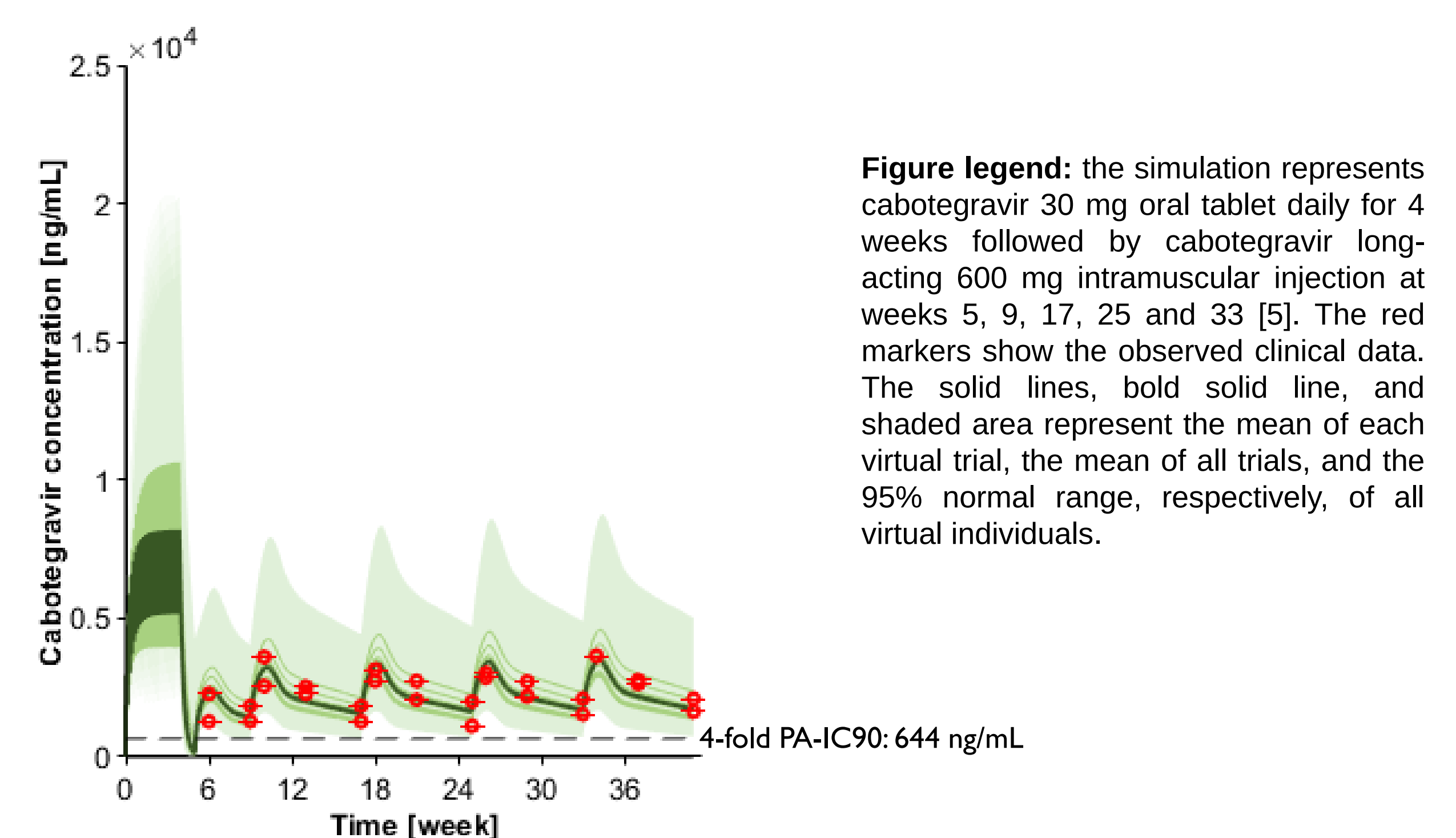
RESULTS

The model simulations were in close agreement with the observed clinical data and the ratios for predicted versus observed area under the curve (AUC) were all within the 1.5-fold limit (Table 1).

Table 1. Observed versus predicted area under the curve ($\mu\text{g}\cdot\text{h}/\text{mL}$) for cabotegravir

PK parameter	Dosing regimen	Observed	Predicted	Ratio
AUC _{0-∞}	30 mg oral, single dose	132.75	171.52	1.29
	30 mg oral, steady state	133.87	160.30	1.20
	400 mg intramuscular, single dose	2260.15	2020.04	0.89
AUC _{0-T}	400 mg, 800 mg multiple doses intramuscular	5666.73	4734.94	0.84
	30 mg oral, 600 mg intramuscular bi-monthly	3986.53	3152.55	0.79

Figure 2. Predicted versus observed concentration-time profile for cabotegravir



CONCLUSIONS

Our developed mechanistic intramuscular PBPK model was able to correctly predict long-acting cabotegravir pharmacokinetics after single, multiple doses, and after transitioning from oral to intramuscular administration. Therefore, the current model represents a useful tool to investigate unstudied clinical scenarios with injectable long-acting antiretrovirals.

REFERENCES

- [1] Owen, A. and S. Rannard, Adv Drug Deliv Rev, 2016. 103: p. 144-156.
- [2] Stader, F., et al., CPT Pharmacometrics Syst Pharmacol, 2019. 8(7): p. 444-459.
- [3] Rajoli, R.K., et al., Clin Pharmacokinet, 2015. 54(6): p. 639-50.
- [4] Lin, Z., et al., J Pharm Sci, 2015. 104(1): p. 233-43.
- [5] Landovitz, R.J., et al., PLoS Med, 2018. 15(11): p. e1002690.

Acknowledgements:

The study was financially supported by the Swiss National Science Foundation (Grant No.: 188504)

For further information, please contact:
sara.bettonte@unibas.ch