

PBPK modeling and simulation of the pharmacokinetics of an antibody drug conjugate in a patient population of phase I clinical trials

S  verine Urdy *¹, Chiara Zunino¹, Sichen Wang², Yanyan Zhang², Xavier Decl  ves³, Alicja Puszkiet³, Nassim Djebli⁴

¹ PhinC Development, Massy (France), ² Jiangsu Hengrui Pharmaceuticals, Shanghai, China, ³ Universit   Paris Cit  , Paris (France), ⁴ Luzsana Biotechnology

* presenting author: severine.urdy@phinc.fr



Introduction

Antibody-drug conjugates (ADCs) represent a promising anticancer approach [1]. Although physiologically based pharmacokinetics (PBPK) modeling is important in the drug development process [2], very few PBPK models have been published so far for ADCs [3], none within an open-source software.

Objectives

- Build a PBPK model of an anti-Claudin 18.2 ADC in PK-Sim   and MoBi   [4]
- Compare the variability range in population simulations to 3 phase I clinical studies after intravenous (IV) administration in patients with gastric, pancreatic and lung cancers

Material & Methods

- Drug:** ADC
- Administration:** Intravenously (IV), every three weeks
- Target:** CLDN18.2
- Patients:** from 3 phase I clinical studies, mostly Asian, age: 27-84 years old, body weight: 37 - 125 kg.
- Observations:** 908 and 824 plasmatic concentrations for ADC and payload, respectively.
- Model structure:** See Fig. 1.
- Model calibration:** See Fig. 2 and Table.
- Model evaluation:** The derived PK parameters are considered inaccurate if the predicted error ratios are outside the two-fold error range (0.5-2) [5]. See Fig. 3.
- Population simulation:** see Fig. 4 & 5.

Model structure

- ADC plasmatic deconjugation**
- Drug-target binding** in healthy tissues
- Competition** between the ADC and the naked antibody for binding to the target.
- Intracellular processing of ADC and payload** within the endosomal compartment leading to **ADC degradation/recycling, payload release, and target recycling**.

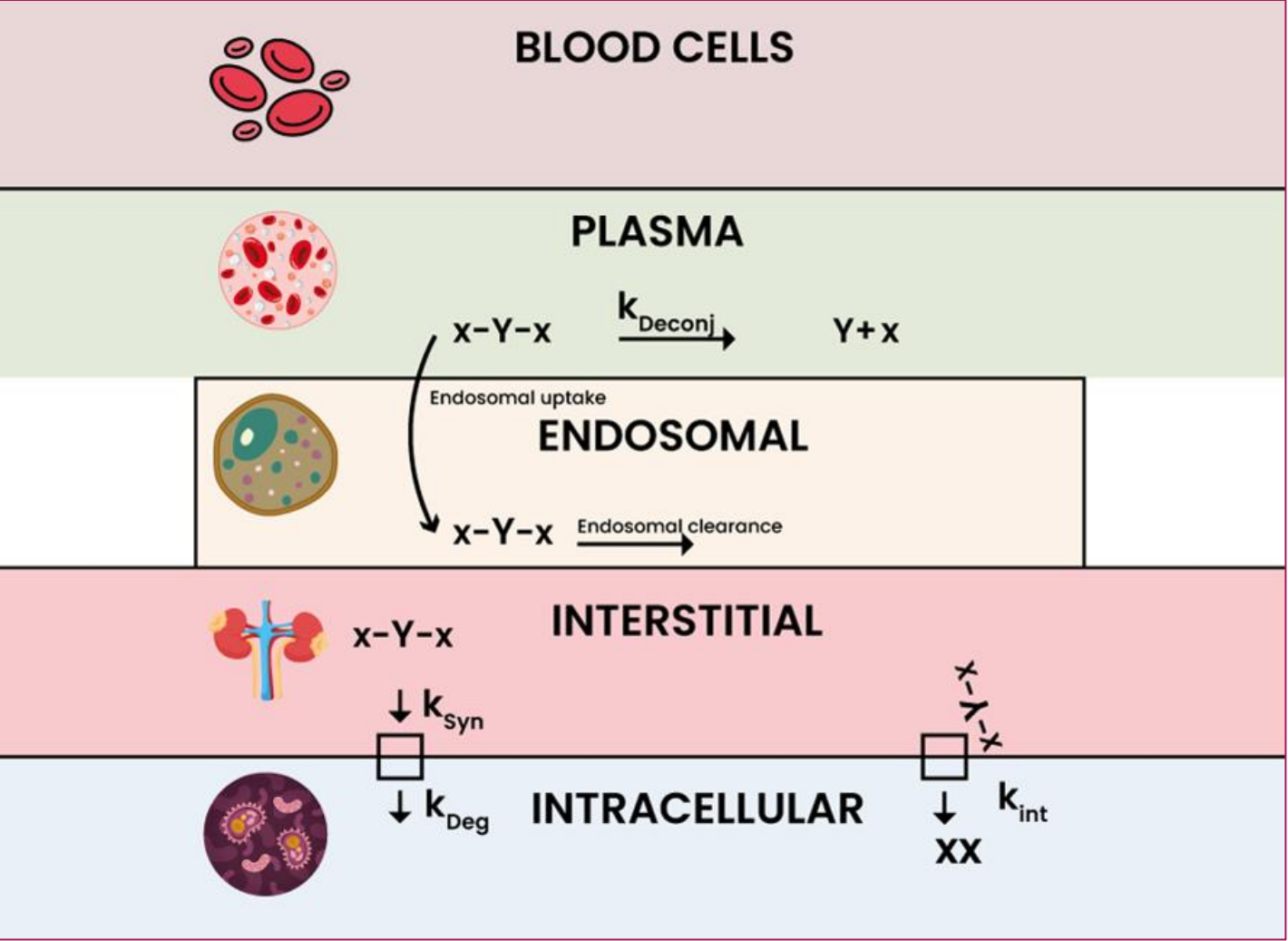
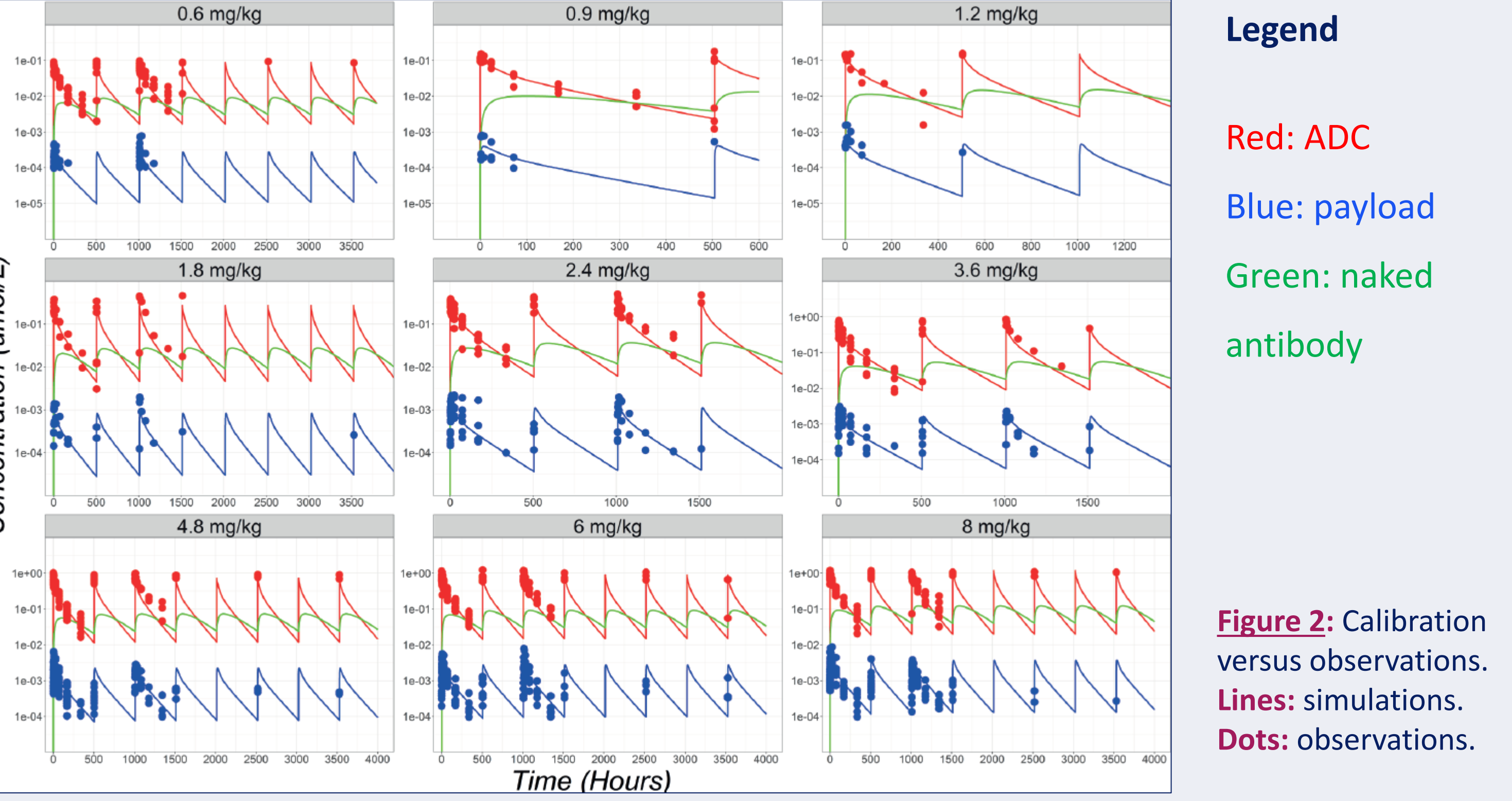


Figure 1: Model structure. Y: antibody. x: payload. x-Y-x: ADC. Quasi-steady state with $k_{syn} = k_{int} = k_{deg}$.

Model calibration in a reference patient



Parameter	Start value	Final value (95% Confidence Interval)	Sensitivity on derived PK parameters
Deconjugation rate constant (k_{Deconj}) (1/h)	1.00 E-03	4.72 E-03 (+/- 3.50 E-04)	AUC_{ADC} : - 0.32 (moderate) $C_{max_Payload}$: 0.35 (moderate) $AUC_{Payload}$: 0.01 (low)
Target degradation rate constant (k_{Deg}) (1/h)	1.00	3.00 E-04 (+/- 5.91 E-03)	Very low sensitivity
Target reference concentration in interstitial space of stomach (nmol/L)	10.00	12.64 (+/- 246.95)	Very low sensitivity
Payload lipophilicity (Log P)	2.21	1.24 (+/- 0.62)	$AUC_{Payload}$: -0.05 (low) $C_{max_Payload}$: -0.05 (low)
Payload passive renal clearance (fraction of glomerular filtration rate %)	10	23.76 (+/- 6.14)	$AUC_{Payload}$: -0.15 (moderate) $C_{max_Payload}$: -0.16 (moderate)

Table: Calibrated parameters, confidence interval and sensitivity on derived PK parameters.

Conclusions

- The final calibration of 5 parameters accurately captures the observed data for both ADC and payload in a population of patients. The deconjugation rate constant is the most sensitive parameter among those which were calibrated.
- This analysis paves the way for PBPK modeling of other ADCs currently in development.

References

[1] Mahmood, I. (2021) 'Clinical Pharmacology of Antibody-Drug Conjugates', *Antibodies*, 10(2), p. 20. [2] Shebley, M. et al. (2018) 'Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective', *Clinical Pharmacology & Therapeutics*, 104(1), pp. 88-110. [3] Li, C. et al. (2020) 'Impact of Physiologically Based Pharmacokinetics, Population Pharmacokinetics and Pharmacokinetics/Pharmacodynamics in the Development of Antibody-Drug Conjugates', *The Journal of Clinical Pharmacology*, 60(S1). [4] Niederalt, C. et al. (2018) 'A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim', *Journal of Pharmacokinetics and Pharmacodynamics*, 45(2), pp. 235-257. [5] Abduljalil, K. et al. (2014) 'Deciding on Success Criteria for Predictability of Pharmacokinetic Parameters from In Vitro Studies: An Analysis Based on In Vivo Observations', *Drug Metabolism and Disposition*, 42(9), pp. 1478-1484.

Model evaluation on derived PK parameters

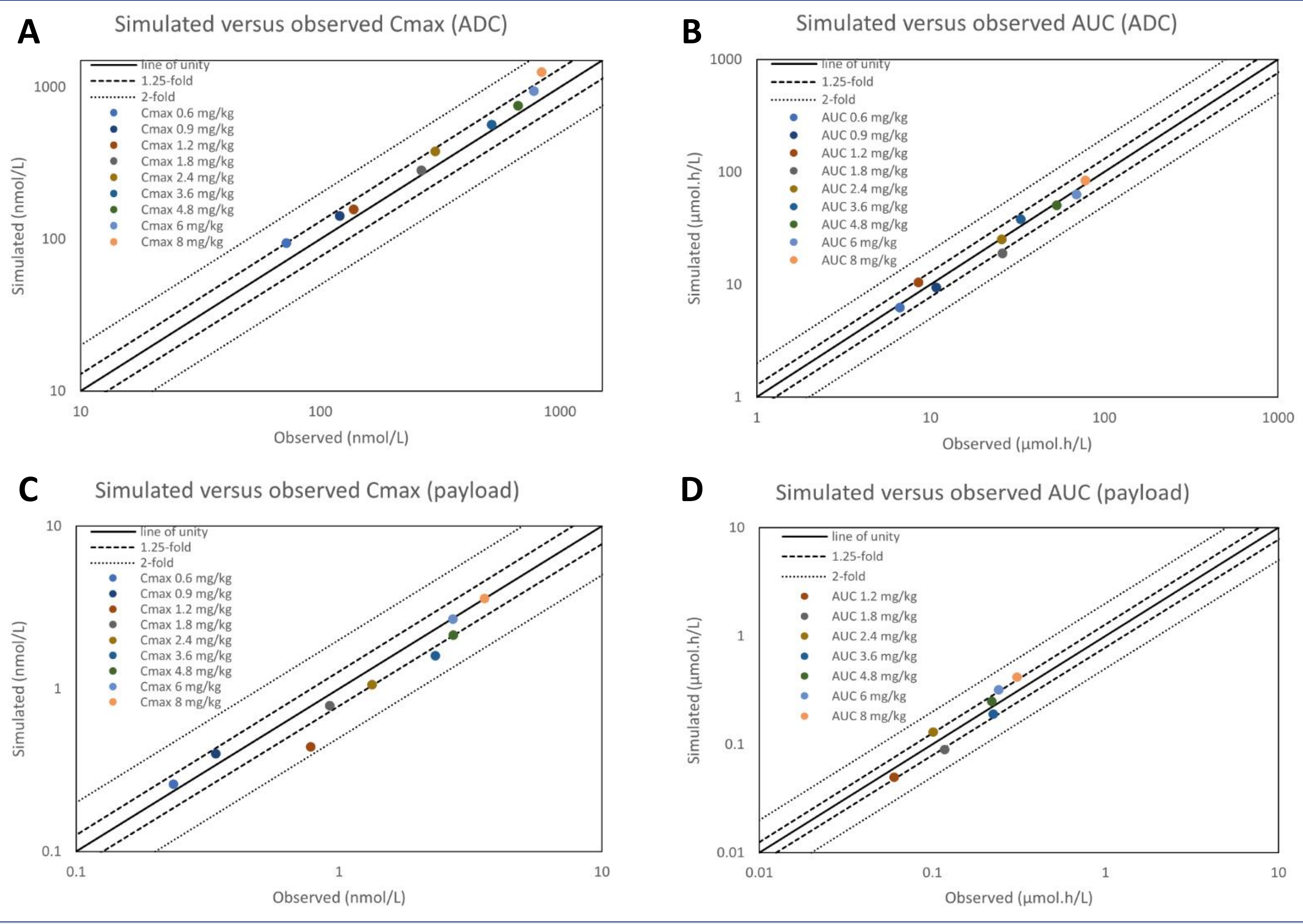


Figure 3: Prediction performance of the model presented as the correlation between simulated versus observed.

The PK derived parameters are adequately captured for both observed compounds, with a predicted error ratio within the two-fold range: **A:** C_{max_ADC} (1.07-1.50), **B:** AUC_{0-504h_ADC} (0.73-1.23), **C:** $C_{max_Payload}$ (0.56-1.18), and **D:** $AUC_{0-504h_payload}$ (0.77-1.37).

Population simulation (physiology + calibrated parameters)

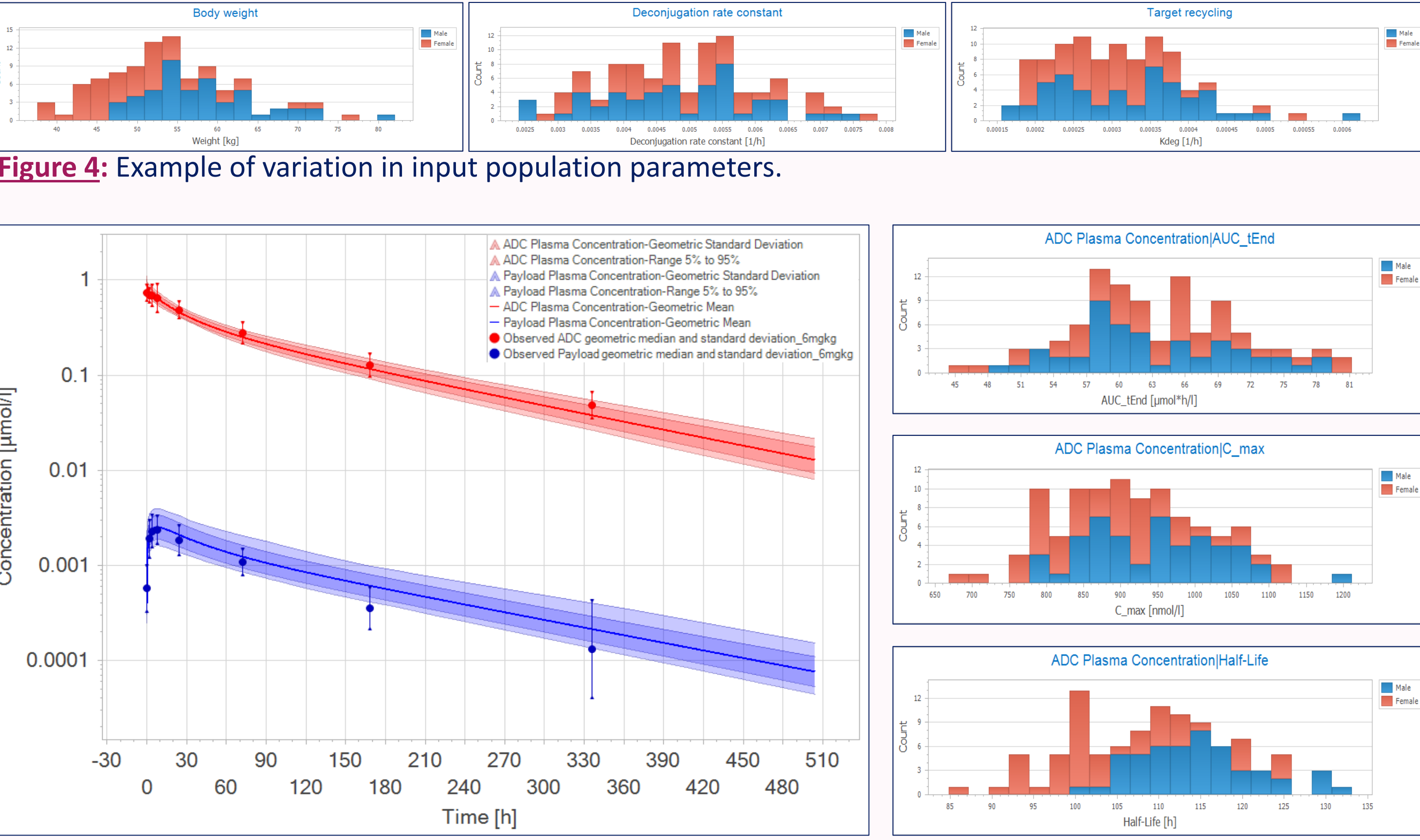


Figure 5: Left: Population simulation of ADC and payload at the dose of 6mg/kg (100 virtual individuals). Right: Distribution of derived PK parameters in the virtual population.

Predicted and observed geometric standard deviations for C_{max} and AUC_{0-504h} of ADC and payload are within the observations range, showing that the PBPK model can predict those plasma concentrations in patients.