

# Translational PK of bevacizumab between monkey and human using PBPK modeling

## Introduction

- PBPK modeling is increasingly used in Model Informed Drug Development (MIDD) of small molecules but its application to development of monoclonal antibodies (mAbs) is recent
- The objective of this study was to develop a translational mAbs PBPK modeling approach based on bevacizumab data from the literature to better support use of MIDD in mAbs development

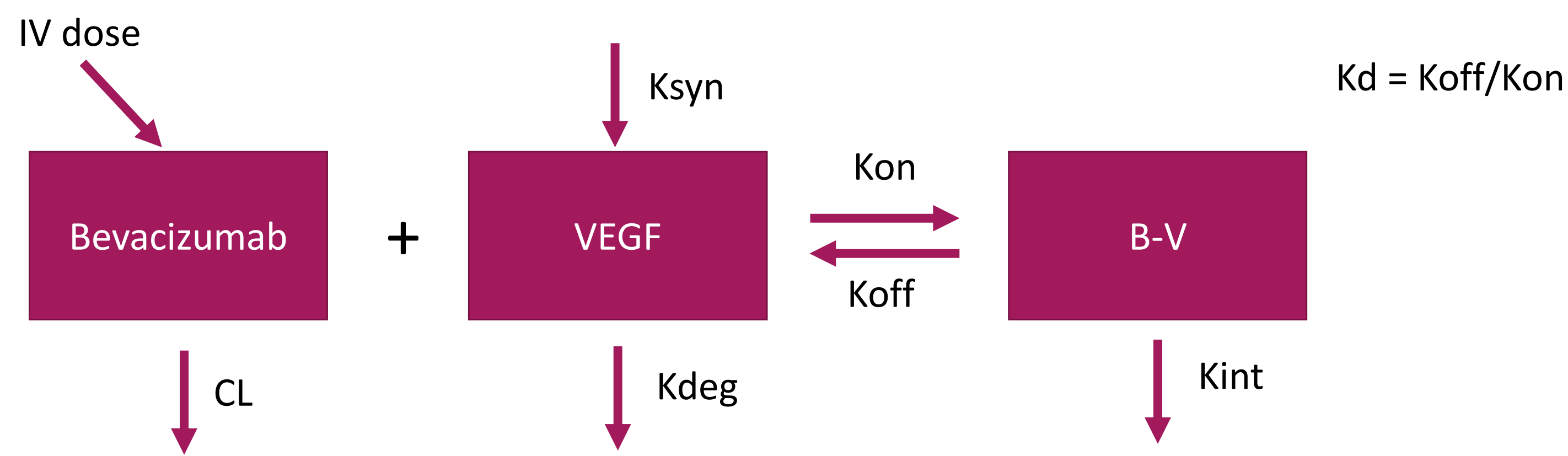


Figure 1 : TMDD model for interaction of bevacizumab with its target VEGF

## Methods

A full PBPK model for mAbs was developed using digitalized PK data of bevacizumab and Xtend-bevacizumab (bevacizumab with higher FcRn affinity) [1,2,3,4,5,6,7,8,9,10] in PK-Sim® and MoBi® (OSPS) software.

The model includes the target-mediated drug disposition (TMDD) phenomenon due to the interaction of bevacizumab with its target (VEGF). The model was built based on monkey data and refined at each step of a theoretical drug development :

- 1 – Model building in cynomolgus monkey (bevacizumab)
- 2 – Validation (a) and refinement (b) in cynomolgus with Xtend-bevacizumab
- 3 – Prediction of HV PK (a), then refinement with the data (b)
- 4 – Prediction of adult cancer patients PK (a), then refinement with the data (b)
- 5 – Prediction of PK in pediatric patients

At each step, the model-predicted AUC and Cmax were compared with the observed values.

Parameters	Description of parameters	Cynomolgus data		Cynomolgus data (xtend)		HV data		Adult patients data		Pediatric patients data
		(1) Cynomolgus Model fitting	(2a) Cynomolgus Xtendbeva Model Prediction	(2b) Cynomolgus Xtendbeva Model fitting	(3a) Human HV Model Prediction	(3b) Human HV Model fitting	(4a) Human patients Model Prediction	(4b) Human patients Model fitting	(5) Pediatric Model Prediction	
Kd-FcRn (nmol/L)	Equilibrium dissociation constant of bevacizumab to FcRn	Fitted value : 0.45	11-fold lower than bevacizumab [10] : 0.041	Same	2-fold higher than monkey [15] : 0.9	Fitted value : 0.94	Same	Same	Same	Same
Kdeg (1/min)	Degradation rate constant of VEGF (1 <sup>st</sup> order)	No TMDD		No TMDD		Fitted value : 1.2x10 <sup>-4</sup>	Same	Same	Same value as adult	Same
Kint (1/min)	Internalization rate constant of B-V (1 <sup>st</sup> order)	No TMDD		No TMDD		Fitted value [16] : 3.35x10 <sup>-5</sup>	Same	Same	Same	Same
Kd-target (nmol/L)	Equilibrium dissociation constant of bevacizumab to VEGF	Human physiological value [14] : 0.058	Same	Same	Same	Same	Same	Same	Same	Same
Koff-target (1/s)	Constant of dissociation rate of B-V (1 <sup>st</sup> order)	No TMDD		No TMDD		In-vitro value [14] : 3.1x10 <sup>-5</sup>	Same	Same	Same	Same
Conc VEGF (nmol/L)	Concentration of VEGF	0.3	Same	Same	Between 0 and 3 [11]	Fitted value : 0.3	10-fold higher than HV [11,12,13] : 3	Fitted value : 3.86	Same value as adult	Same

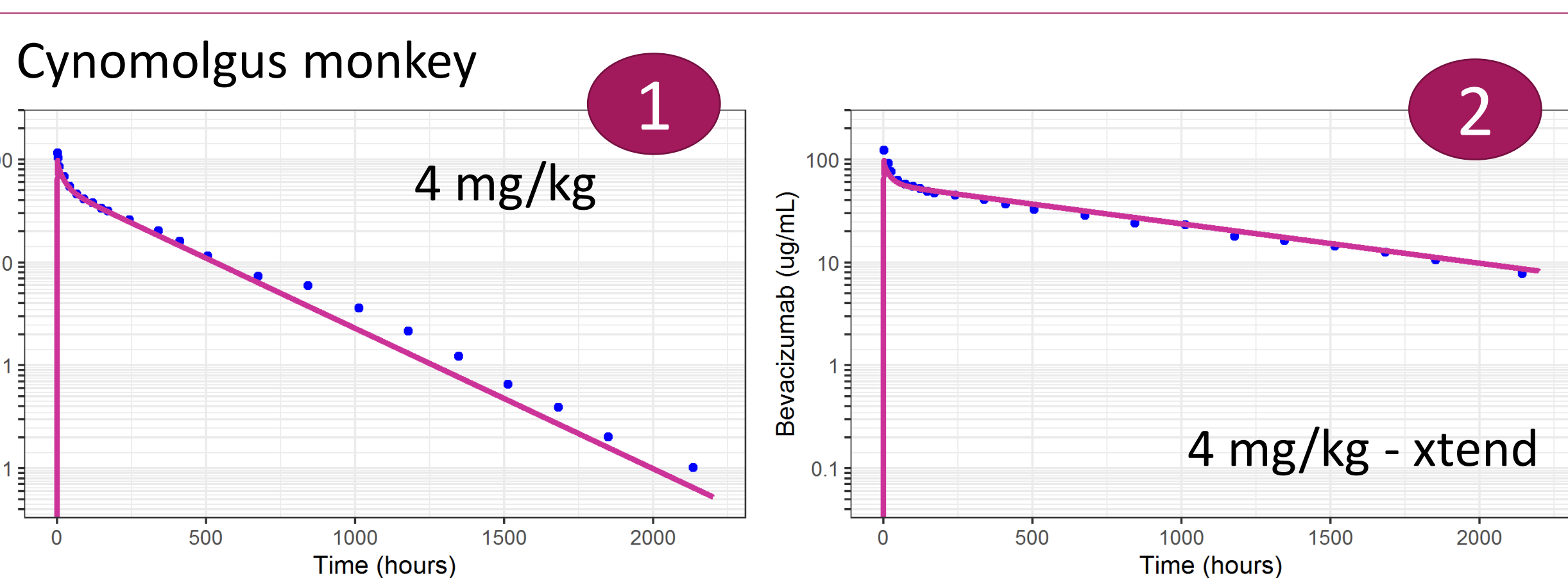


Figure 2 : Model fit of the observed data in cynomolgus monkey

## Iterative process

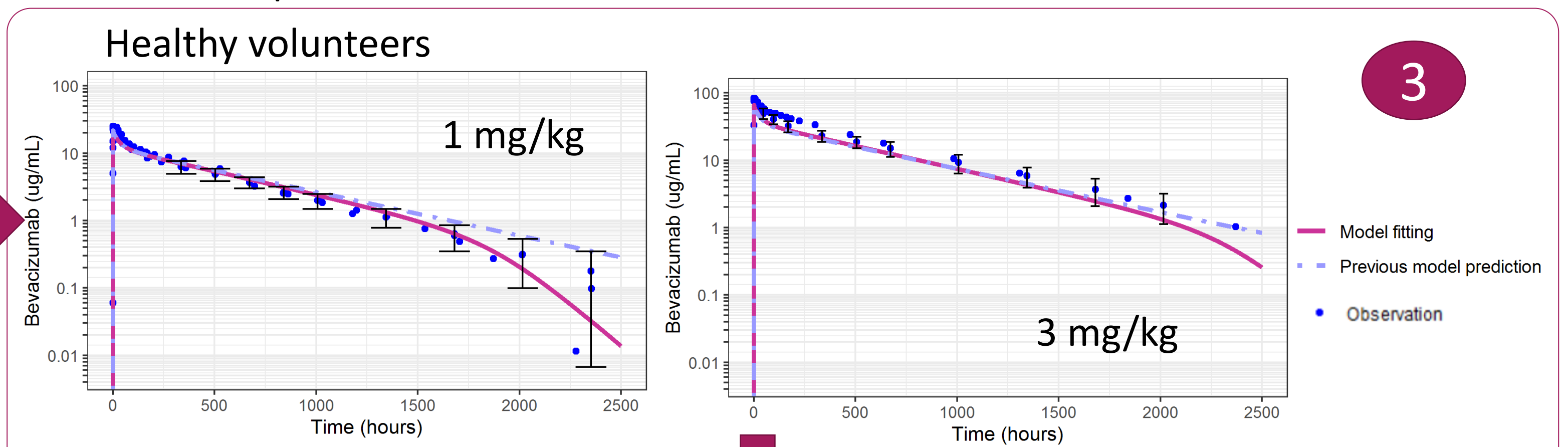


Figure 3 : Model fit of the observed data in HV

## Validation of the model

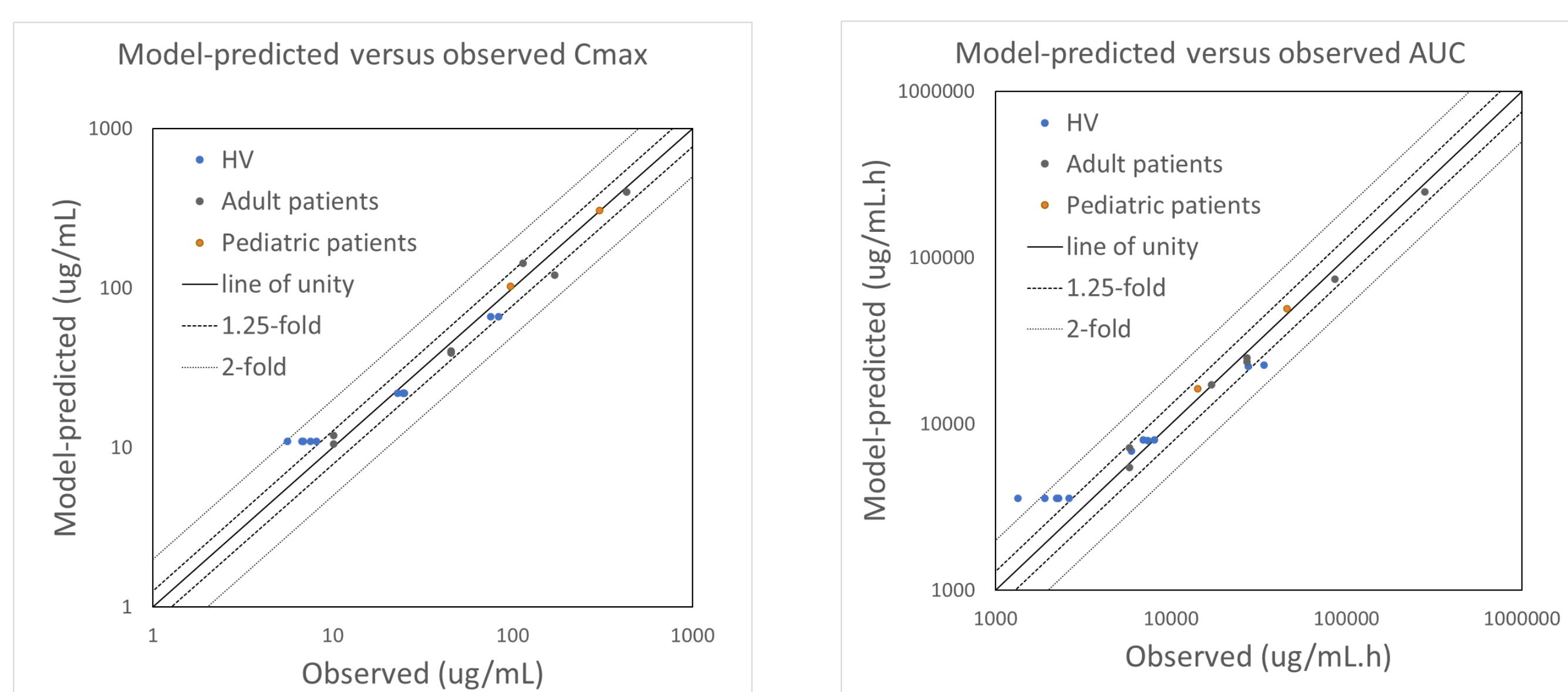


Figure 6 : Observed versus model-predicted AUC and Cmax of bevacizumab.

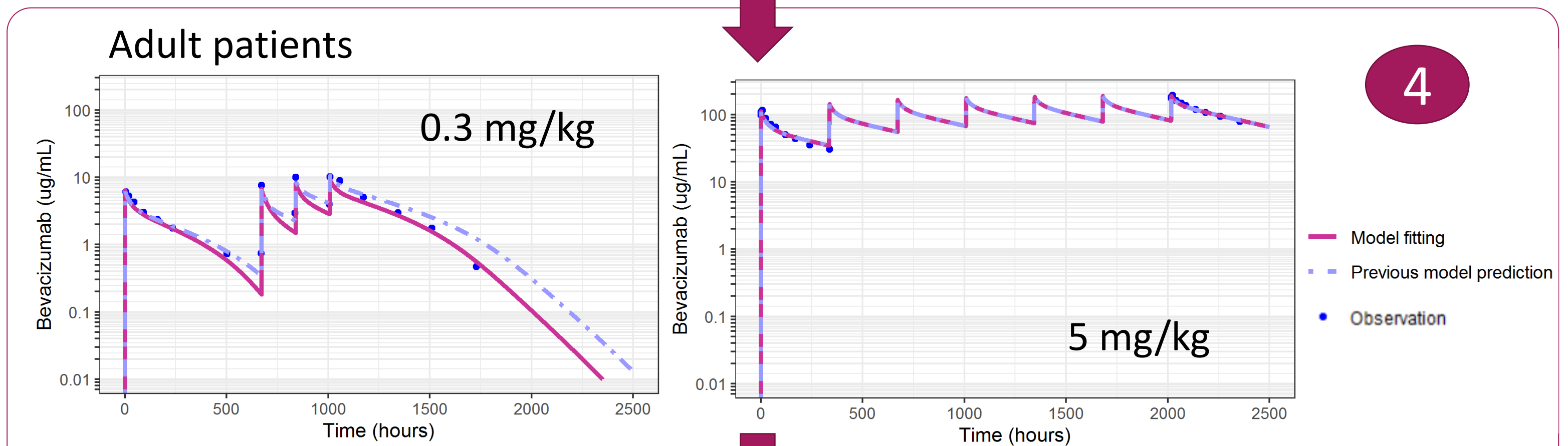


Figure 4 : Model fit of the observed data in patients

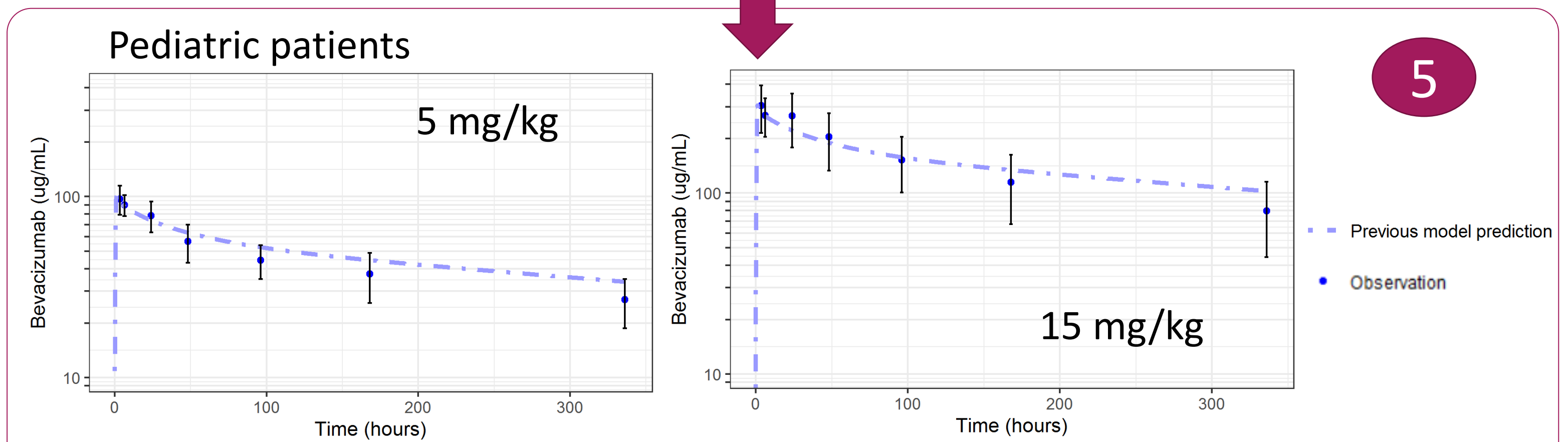


Figure 5 : Model fit of the observed data in pediatric patients

## Conclusion

- The full PBPK model with TMDD describing interaction of bevacizumab with its soluble target (VEGF) was successfully developed using PK-Sim® and MoBi®
  - The model was satisfactorily applied for inter-species (from monkey to human) and inter-molecules (from bevacizumab to Xtend-bevacizumab) PK translation.
  - All model-predicted AUC and Cmax were within 2-fold of the observed values.
- This work is a first step to generalize the use of full PBPK models for mAbs PK translation and optimization.

## References

1. Demarchi, M. et al. *PLoS ONE* (2021).
2. Gordon, M. S. et al. *J Clin Oncol* (2001).
3. Hettema, W. et al. *Expert Opinion on Investigational Drugs* (2017).
4. Hummel, M. et al. *J Cancer Res Clin Oncol* (2022).
5. Romera, A. et al. *Lancet Gastroenterol Hepatol* (2018).
6. Shin, D. et al. *Cancer Chemother Pharmacol* (2020).
7. Sinn, A., et al. *Brit J Clinical Pharma* (2022).
8. Wu, X. et al. *BioDrugs* (2019).
9. Bender, J. L. G. et al. *JCO* (2008).
10. Zalevsky, J. et al. *Nat Biotechnol* (2010).
11. Stefanini, et al. *BMC Syst. Biol.* (2008).
12. Stefanini, et al. *Cancer Res.* (2010).
13. Kut, C, et al. *Br. J. Cancer* (2007).
14. Papadopoulos, N. et al. *Angiogenesis* (2012).
15. Neuber, T. et al. *mAbs* (2014).
16. Basu, S. et al. *Front. Pharmacol* (2020).