

Physiologically-based pharmacokinetic modeling to predict systemic and liver exposure to bosentan

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Introduction

Bosentan is the first approved oral medication for treating pulmonary arterial hypertension. Regular liver function monitoring is required when using it, owing to its risk of drug-induced liver injury – considerable occurrence of abnormal liver function tests in clinical studies.

Unmet need Accumulating endeavors have been devoted to identifying the underlying mechanisms of bosentan-induced liver injury. However, using the (unbound) plasma level as a proxy in the mechanistic studies could run the risk of underestimating the toxicity or setting the wrong threshold for key liver injury pathways.

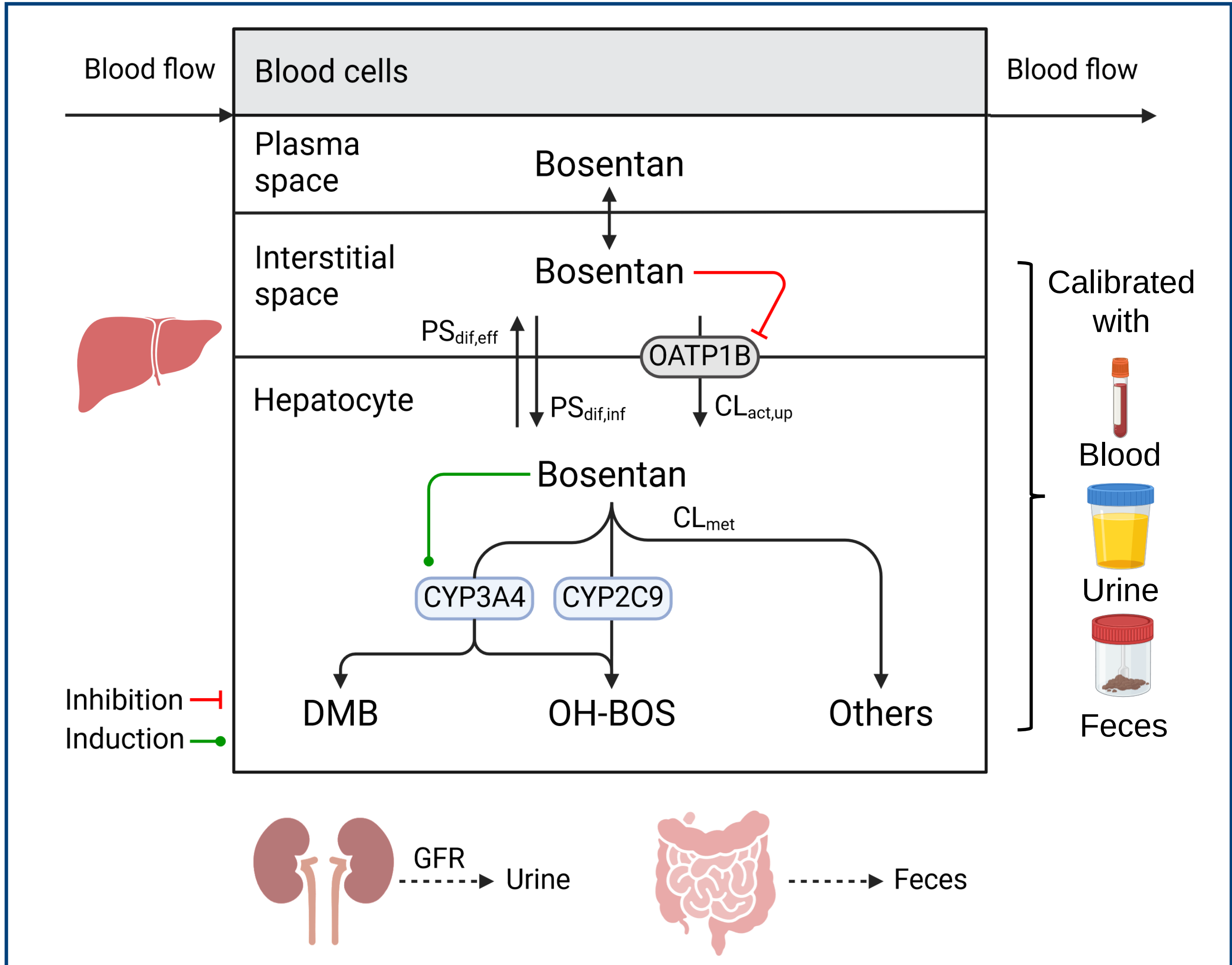
Objectives

- Develop a PBPK model to capture bosentan's liver disposition
- Predict bosentan concentration in systemic circulation and liver
- Provide bosentan scalar between liver & plasma (unbound)

Methods

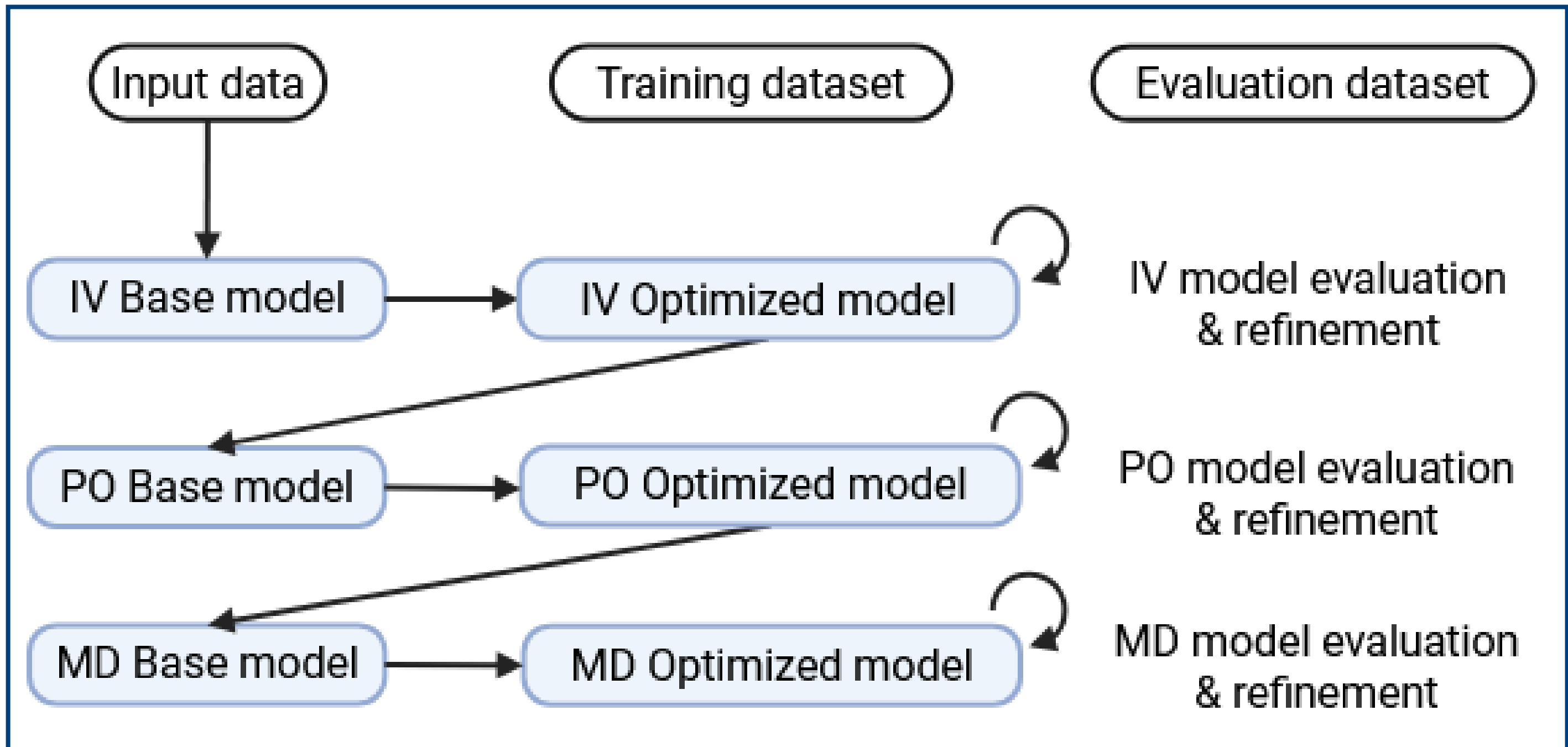
Data from 12 clinical studies were used for model development.

Fig 1. Bosentan's liver disposition in the model



PS_{dif,inf/eff}, passive diffusion influx/efflux rate; CL_{act,up}, active uptake clearance; CL_{met}, metabolic clearance; DMB, desmethyl bosentan; OH-BOS, hydroxy bosentan; GFR, glomerular filtration rate.

Fig 2. Model development workflow



IV, intravenous; PO, per os; MD, multiple-dose.

Model evaluation & verification

- Predictive-to-observation ratio (fold error, FE) within two-fold
 - Phase I pharmacokinetic studies of bosentan
 - Drug-drug interaction (DDI) studies w/ketoconazole & rifampicin
- Intrinsic hepatic clearance (CL_{int,h})
 - Retrograded clinical CL_{int,h} (well-stirred model)
 - Model-derived $CL_{int,h} = (CL_{act,up} + PS_{dif,inf}) \times \frac{CL_{int,met}}{PS_{dif,eff} + CL_{int,met}}$

Scalar between unbound liver and unbound plasma

$$K_{puu} = \frac{C_{u,liver}}{C_{u,plasma}}$$

References

[1] Treiber et al., 2007. [PMID: 17496208]
[2] Weber et al., 1999. [PMID: 10383925]
[3] USFDA. Drug approval package: Tradeleer (bosentan) tablets. Application No. 21-290. Figs 1 & 2 were created in BioRender.com
[4] Varma et al., 2014. [PMID: 25107633]
[5] Hanke et al., 2021. [PMID: 34664206]
[6] Prieto Garcia et al., 2024. [PMID: 38576225]
[7] Weber et al., 1996. [PMID: 8823230]

Results

Model-derived CL_{int,h} was <1.25 folds of retrograded clinical CL_{int,h} (440 L/h).

Fig 3. Simulated systemic and excretion bosentan profiles

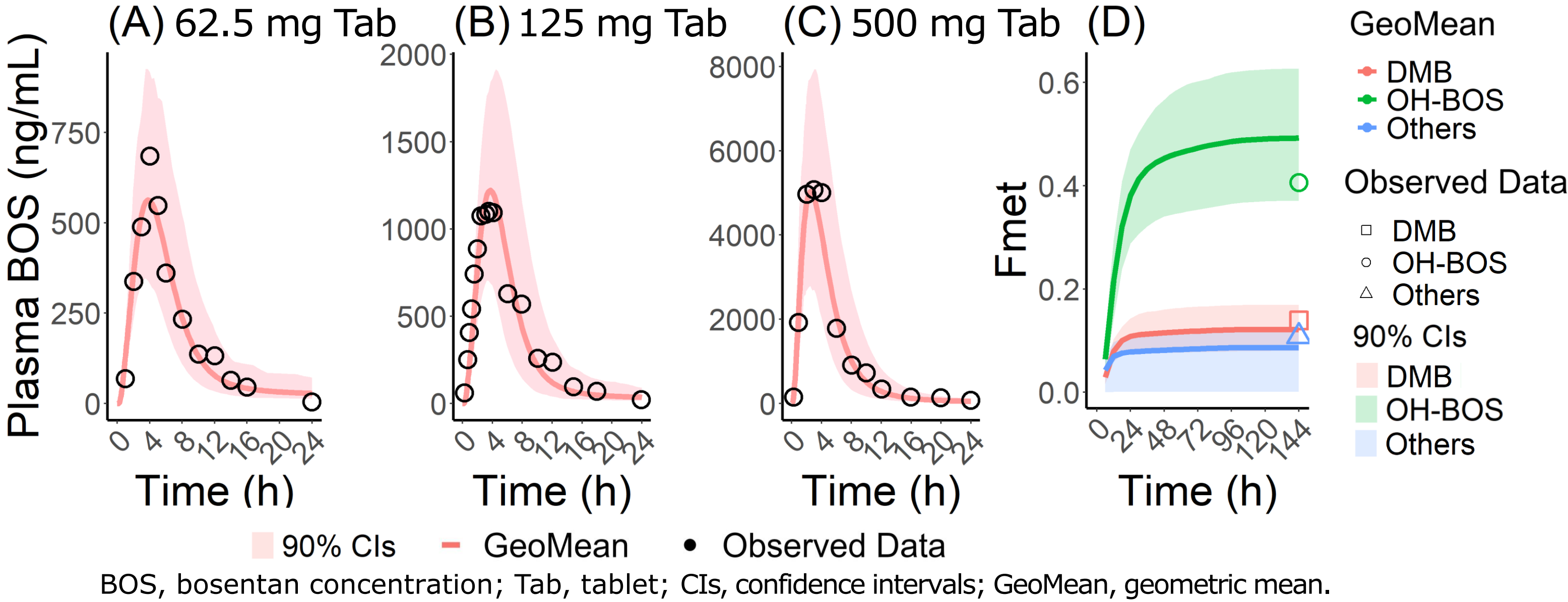


Fig 4. Model predictive performance

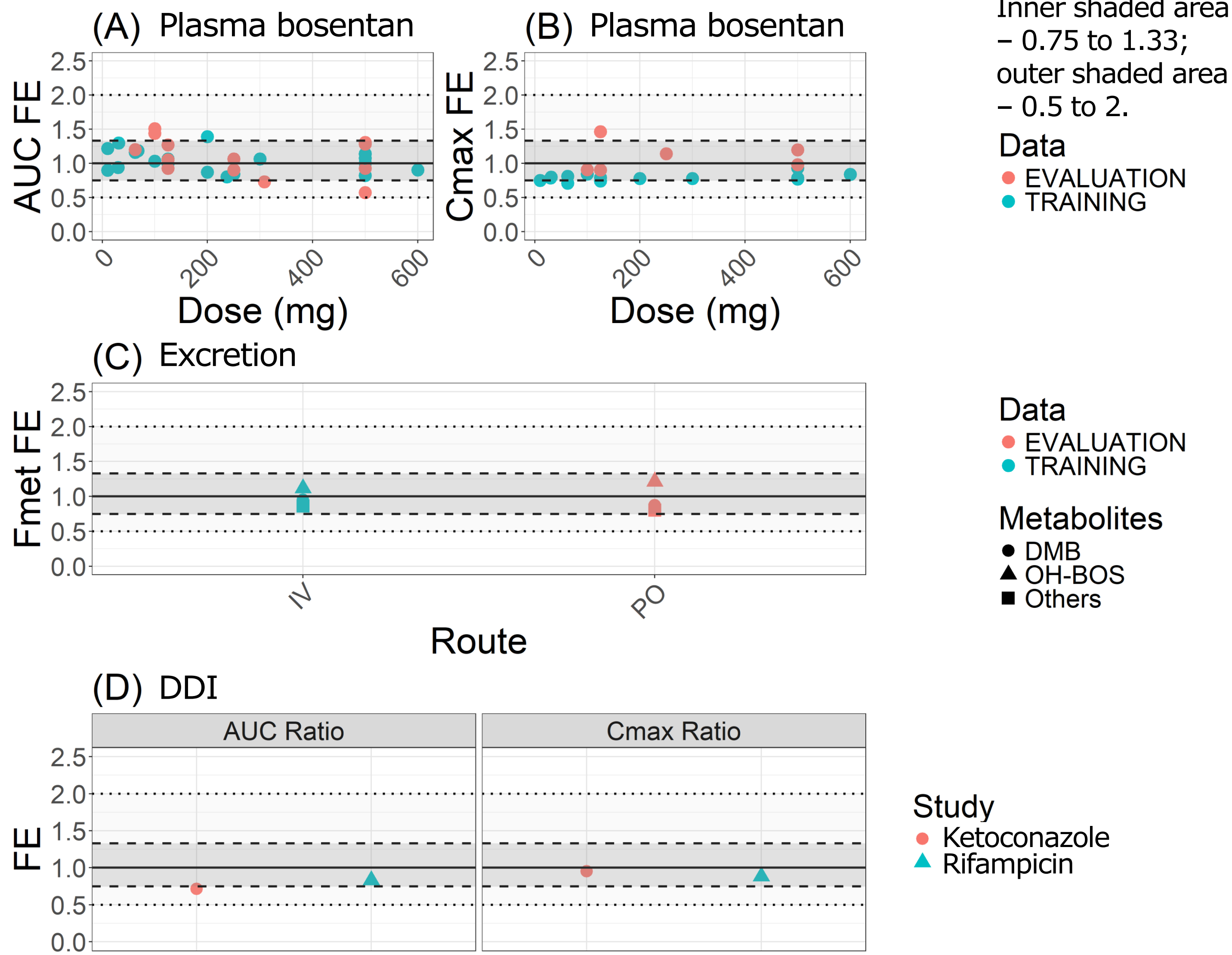


Fig 5. Simulated unbound profiles of bosentan (Day 8)

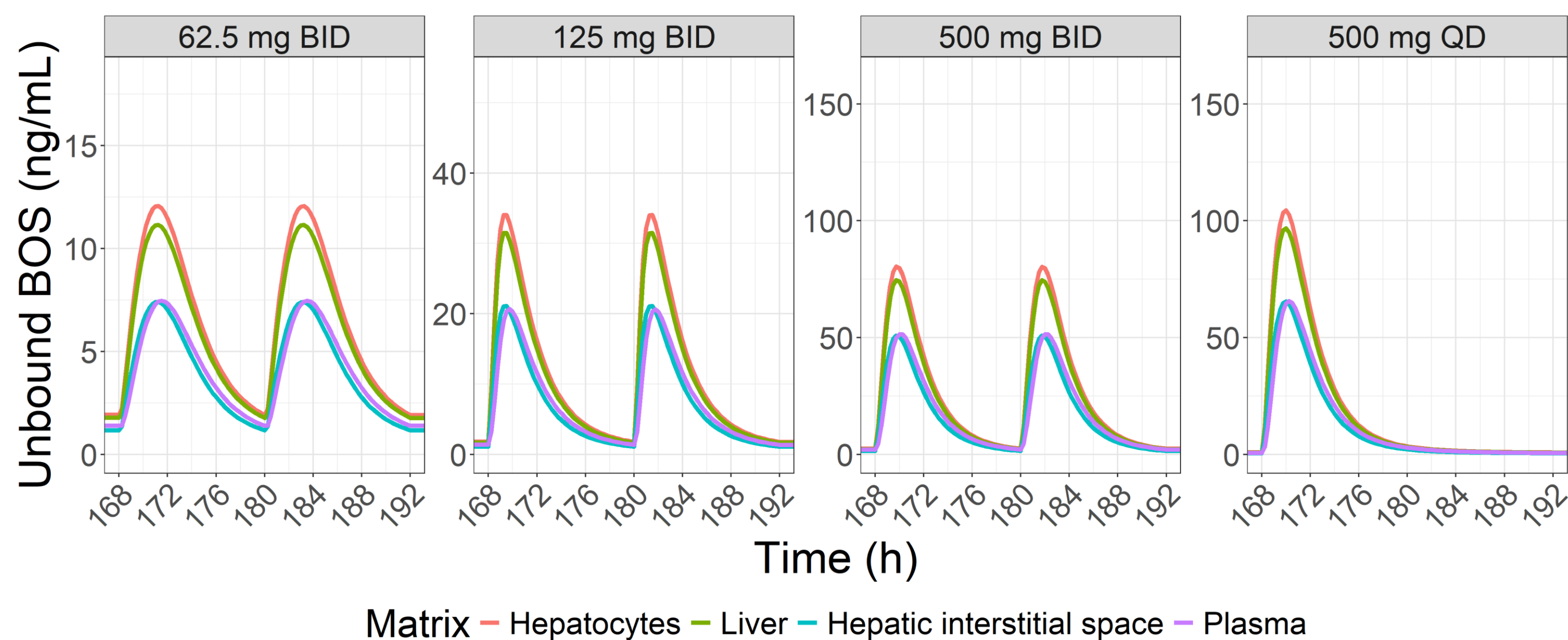
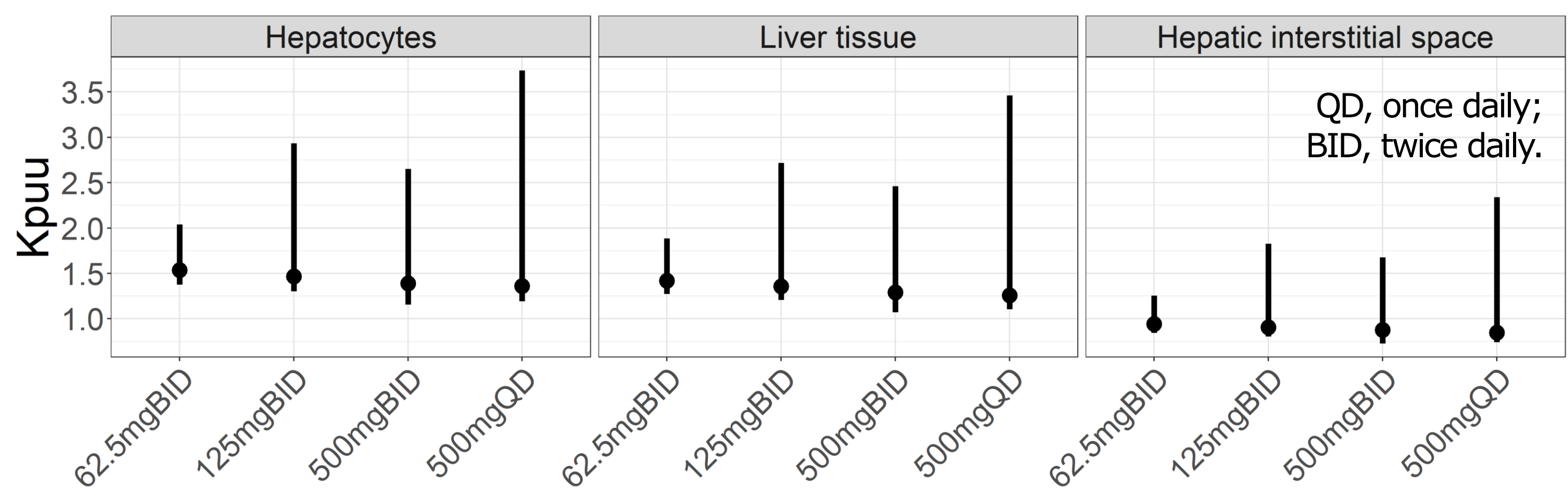


Fig 6. Simulated range of bosentan K_{puu} (Day 8)



Conclusion

- The developed bosentan PBPK model well described bosentan in systemic plasma and excreta.
- The closely matched CL_{int,h} and DDI verification reflected the confidence of the model to capture bosentan's hepatic disposition.
- The simulated K_{puu} can be used to facilitate mechanistic studies with relevant clinical concentrations.

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