

# Combining physiologically-based-pharmacokinetic modelling and a Bayesian estimation method for prediction of ivabradine oral absorption and drug-drug interactions



Jennifer Lang<sup>1</sup>, Ludwig Vincent<sup>2</sup>, Maud Beneton<sup>2</sup>, Claire Denizot<sup>2</sup>, Yannick Parmentier<sup>2</sup>, Marylore Chenel<sup>2</sup>, Kayode Ogungbenro<sup>1</sup> and Aleksandra Galetin<sup>1</sup>  
<sup>1</sup>Centre for Applied Pharmacokinetic Research, School of Health Sciences, University of Manchester  
<sup>2</sup>Servier laboratories, Suresnes, France



## Introduction and objectives

- Ivabradine and its main metabolite are both active and mainly undergo **CYP3A4 metabolism** [1,2]. Nonlinear pharmacokinetics (PK) following oral dosing of the metabolite also suggests role of intestinal **efflux transport by P-gp**.
- Physiologically-based-pharmacokinetic (PBPK) modelling takes into account human physiology and drug-related properties. To overcome the lack of prior knowledge on some parameters, PBPK modelling combined with parameter estimation allows optimisation and refinement of parameters of interest by using clinical data [3].
- The first objective was to **develop a disposition model for ivabradine (parent) and its metabolite separately** and refine the input parameters using a Bayesian estimation method. Then we aimed to **predict the oral absorption** of ivabradine and its metabolite **and drug-drug interactions (DDI)** with ketoconazole.

## Material and methods

- Ivabradine metabolism and permeability input parameters of the whole body-PBPK model were measured in *in vitro* systems or predicted (e.g. blood-to-tissue partition coefficients (K<sub>b</sub>)) and used as **prior information** for the Bayesian analysis.
- A **sensitivity analysis** was performed to assess the influence of drug-specific parameters on systemic drug exposure.
- Prior parameter distributions were updated using plasma concentrations from clinical studies where healthy volunteers received an intravenous bolus of ivabradine or the metabolite. The **Bayesian analysis was performed using MCMC and the Gibbs sampling method** in NONMEM 7.4.
- A **mechanistic gut model** [4] was combined with the lumped disposition model [5] to predict the **intestinal extraction** of ivabradine and its metabolite following oral administration and DDI with ketoconazole (CYP3A4 and P-gp inhibitor).

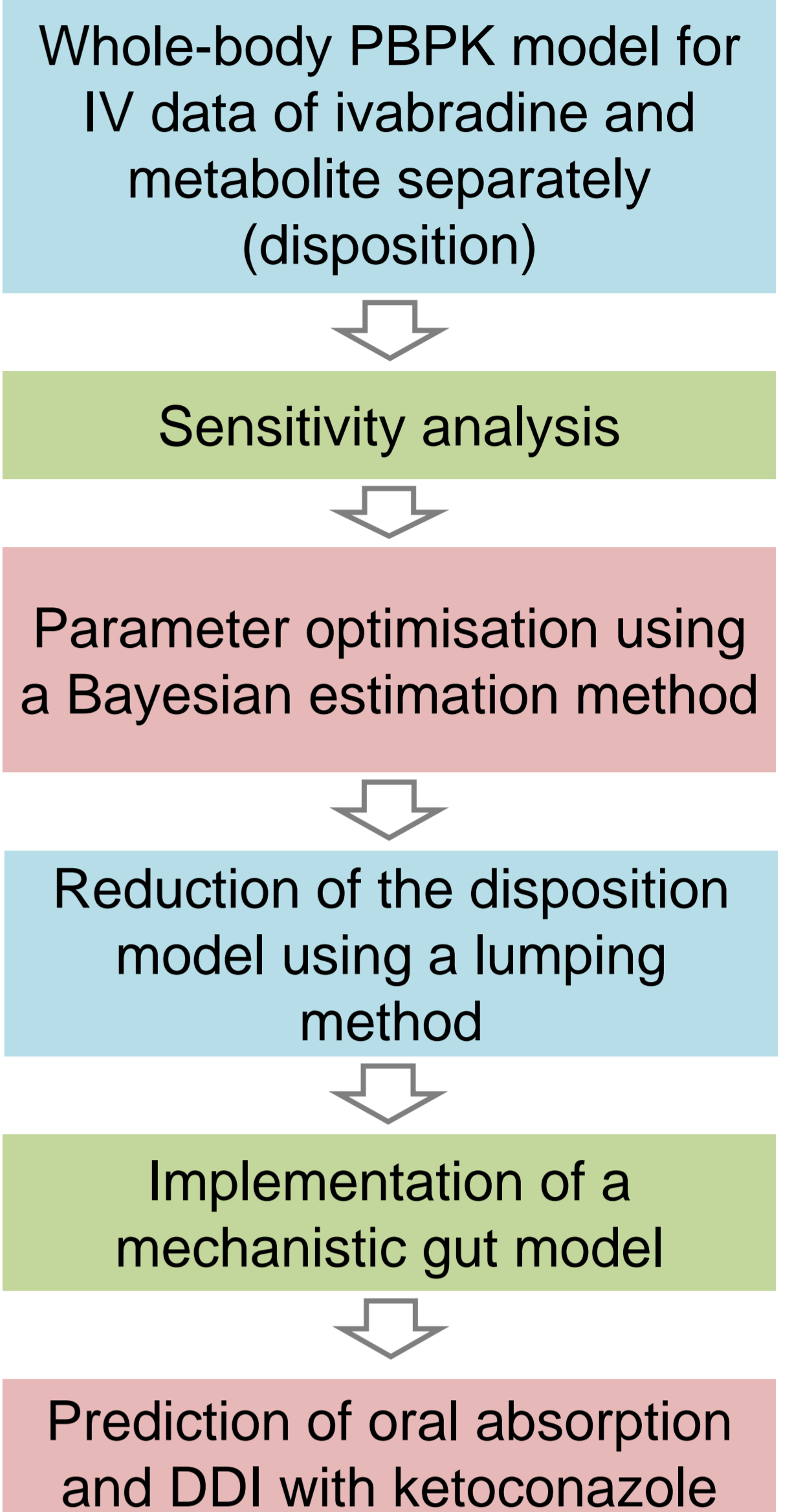


Figure 1. Schematic workflow of the hierarchical modelling approach for ivabradine and its metabolite

## Results

- The sensitivity analysis identified the importance of K<sub>b</sub> in muscle and the hepatic intrinsic clearance (CL<sub>intH</sub>) on systemic exposure for both ivabradine and its metabolite.
- Prior distributions of K<sub>b</sub> in muscle and CL<sub>intH</sub> for ivabradine and the metabolite were updated in the Bayesian analysis (Table 1 and Figure 2). The refined model parameters well described the observed clinical data (Figure 3).
- Model reduction from 14 to 8 compartments for the disposition demonstrated similar performance with reduced model complexity and computational burden.
- The lumped disposition combined with the gut model adequately predicted ivabradine oral absorption (Figure 4) and DDI with ketoconazole (Figure 5).

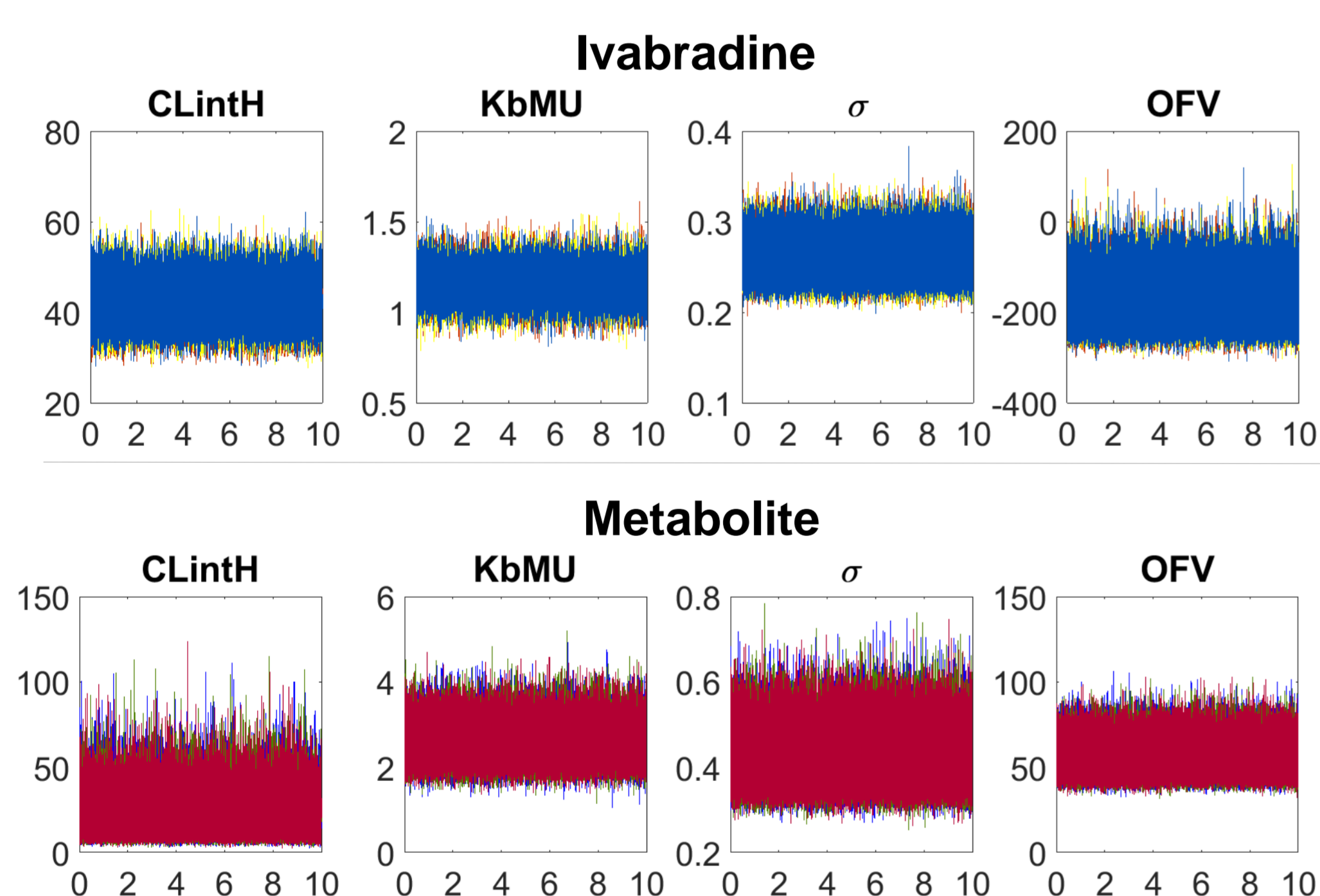


Figure 2. Trace plots of the 3 MCMC chains run for the Bayesian analysis. Parameter values plotted against number of iterations (x10,000).

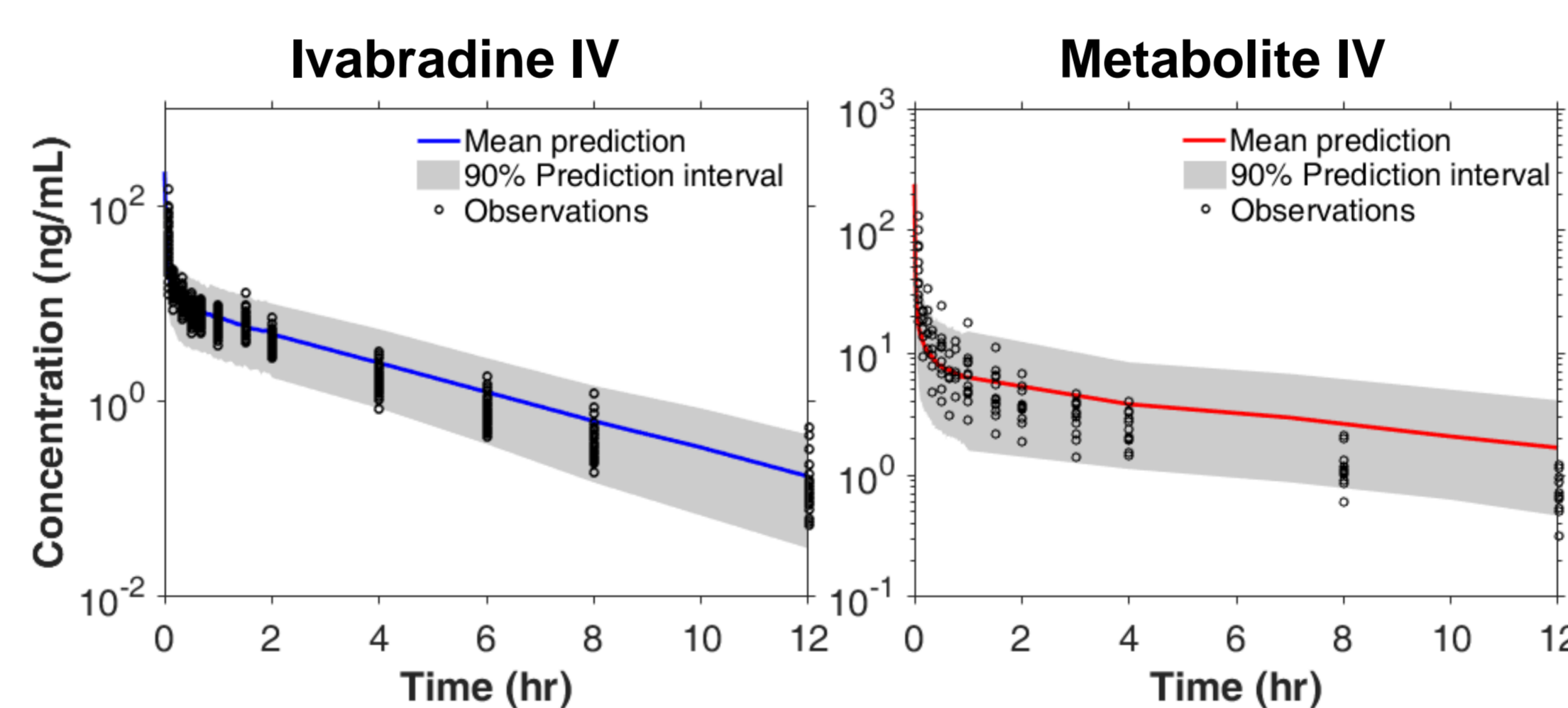


Figure 3. Visual predictive checks of the population disposition models for ivabradine (left panel) and its metabolite (right panel). Dose-normalised concentration-time profiles.

Table 1. Prior and posterior values of the parameters of interest for ivabradine and its metabolite

|            | Parameter                | Prior Value | Posterior value (RSE) |
|------------|--------------------------|-------------|-----------------------|
| Ivabradine | CL <sub>intH</sub> (L/h) | 58.6        | 41.3 (3%)             |
|            | Ω CL <sub>intH</sub>     | -           | 0.128 (31%)           |
|            | K <sub>b</sub> muscle    | 1.28        | 1.15 (55%)            |
|            | σ                        | -           | 0.261 (7%)            |
| Metabolite | CL <sub>intH</sub> (L/h) | 36.6        | 18.7 (15%)            |
|            | Ω CL <sub>intH</sub>     | NC          | NC                    |
|            | K <sub>b</sub> muscle    | 1.82        | 2.54 (16%)            |
|            | σ                        | -           | 0.429 (12%)           |

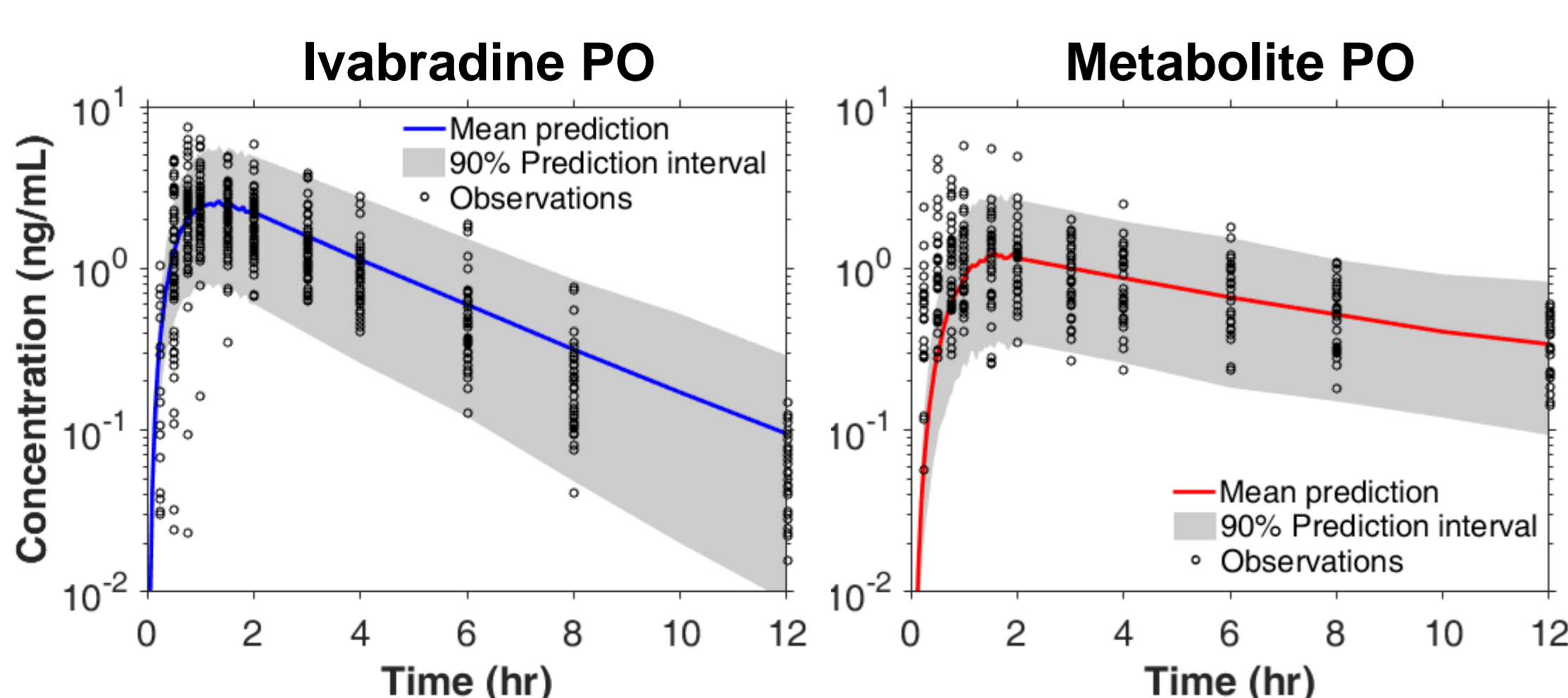


Figure 4. Prediction of concentration-time profile following oral administration of 5 mg of ivabradine (left panel) and 5 mg of metabolite (right panel).

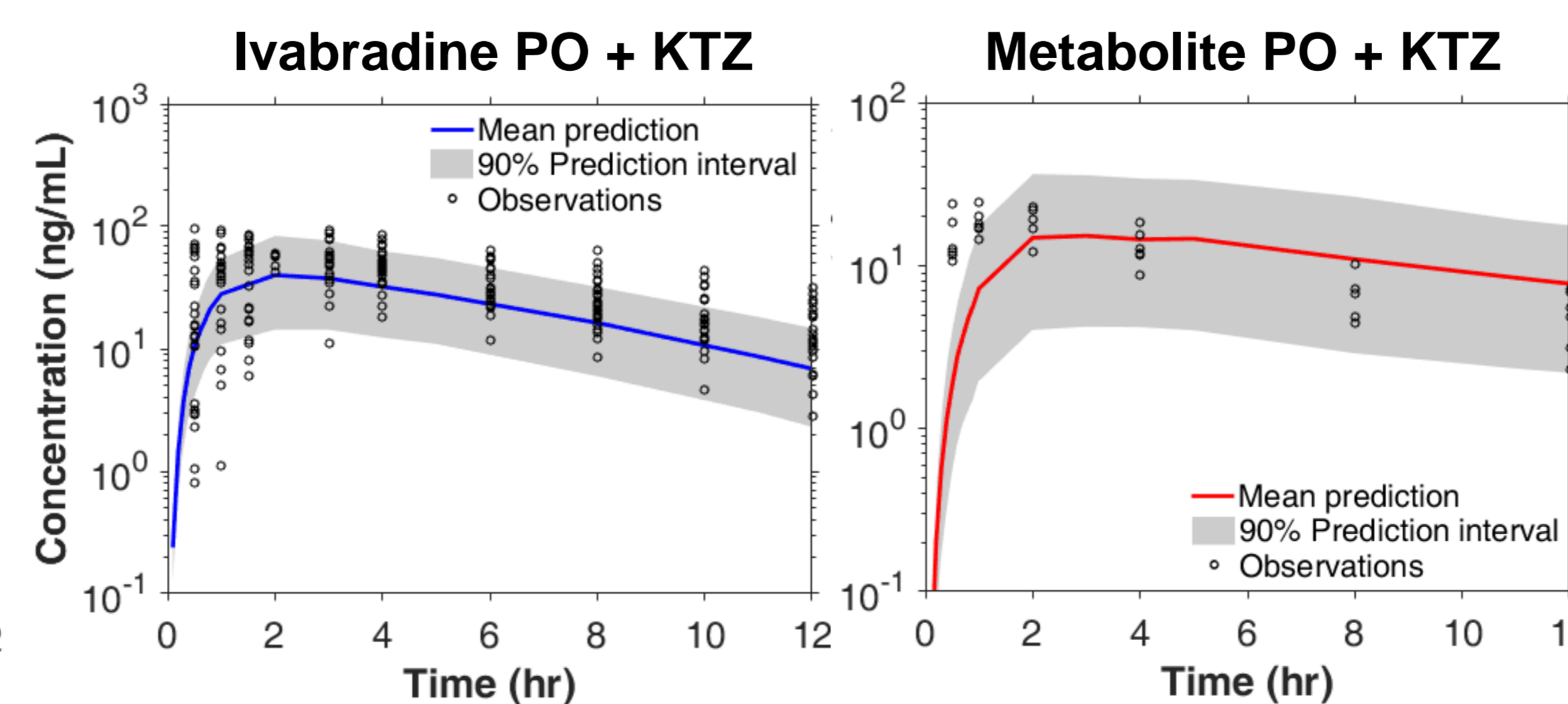


Figure 5. Prediction of concentration-time profile following oral co-administration of 5 mg of ivabradine (left panel) or 5 mg of metabolite (right panel) and 200mg once daily of ketoconazole (KTZ) for 5 days.

## Conclusions

- The integrated population PBPK modelling approach successfully described clinical data for ivabradine and its metabolite when administered separately.
- This hierarchical approach will be subsequently applied to joint parent-metabolite PBPK modelling to account for the metabolite formation from ivabradine metabolism.

## References

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