



Physiological-based pharmacokinetics/pharmacodynamic modelling for Ivabradine and its major active metabolites, S18982

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BACKGROUND AND OBJECTIVES

Ivabradine and Treatment of Heart Failure

- Ivabradine (IVA), a selective inhibitor of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, used for managing heart failure and chronic stable angina, especially in patients with heart failure with reduced ejection fraction (HFrEF)
- Mainly inhibits the funny current (If) in the sinoatrial nodes, affecting the heart rate (HR)
- S18982 (MET)– IVA metabolites – proved to have bradycardic action

The main pharmacokinetic (PK) characteristic of IVA

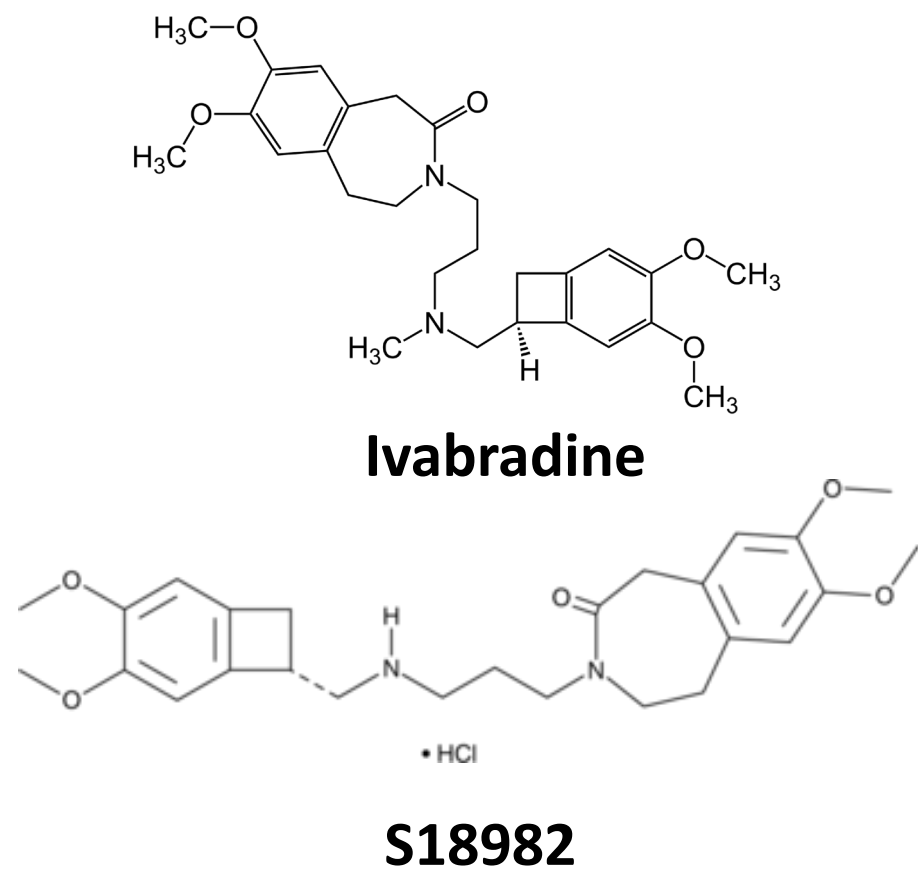
- After oral administration, IVA is **rapidly absorbed**, has a **high volume of distribution**, and a moderate to high clearance
- Extensively metabolized by CYP3A4, producing its major active metabolite, S18982 (40%)
- Half-life of 2 hours.

Pharmacodynamic (PD) characteristics of IVA

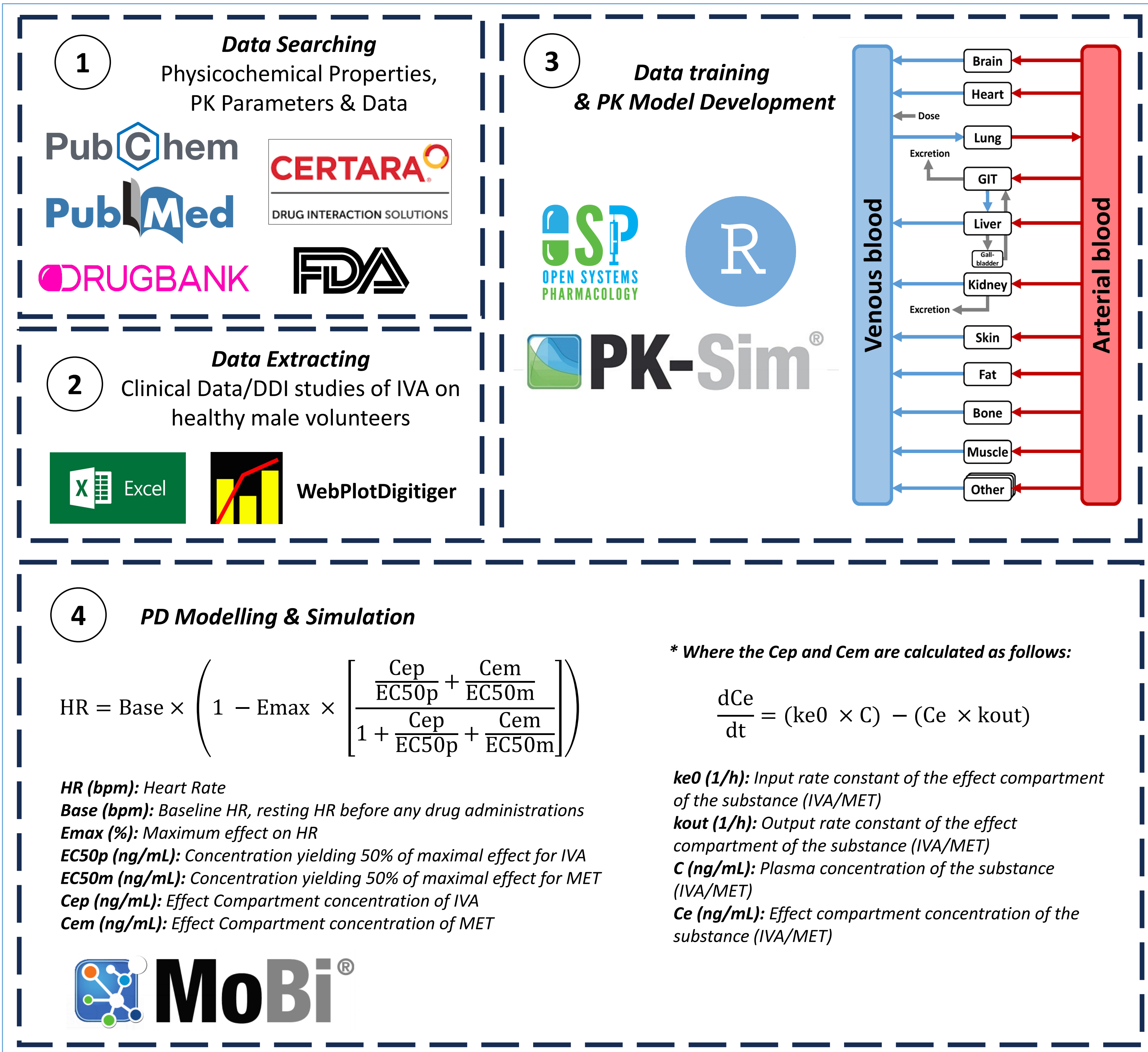
- A linear dose-dependent heart rate-lowering activity
- The peak PD effect occurs approximately 1-3 hours after the time of peak plasma concentration

Study Objectives

- Developing a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model for the prediction of IVA and S18982 pharmacokinetic features, as well as the heart rate-lowering pharmacodynamic effect.



METHODS



RESULTS

Physiological-based pharmacokinetic model

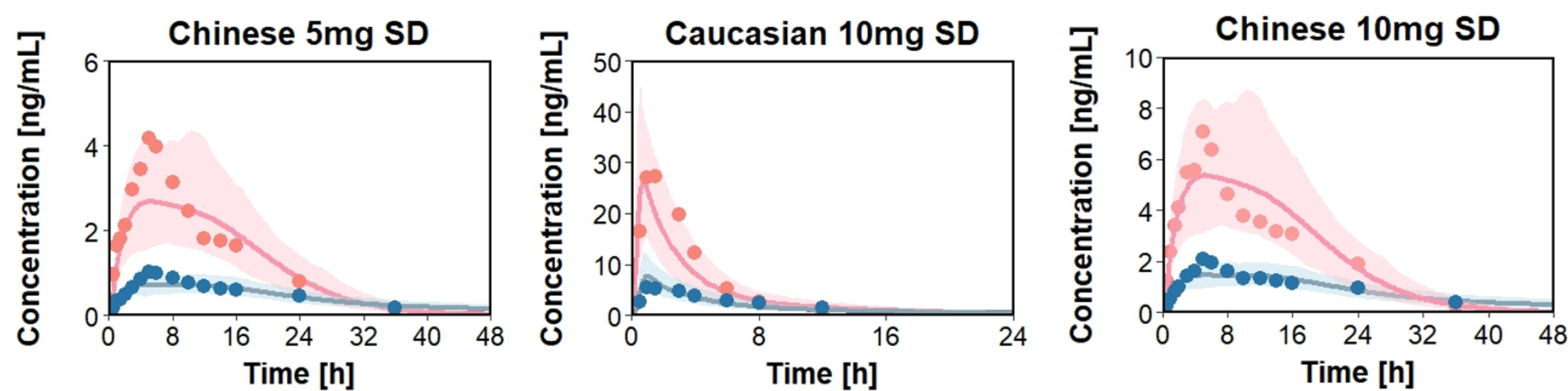
Table 1. Physicochemical & PK Properties of IVA and S18982

Parameter	Initial Values		Unit
	Ivabradine	S18982	
Physicochemical properties			
Molecular weight	468.6	491.0	g/mol
Lipophilicity (LogP)	2.1	2.03	Log units
Fraction Unbound	31	26.73	%
Dissolution shape	0.66	1.24	-
Dissolution time (50% dissolved)	0.68	10.12	h
ADME Parameter			
Absorption			
Specific Intestinal permeability (transcellular)	1.65E-6	-	cm/s
Distribution			
Permeability	5.70E-5	-	cm/s
Metabolism			
Plasma Clearance	0.21	0.10	l/h/kg
In vitro Vmax for liver microsome	-	0.07	pmol/min/mg mic.protein
In vitro CL for liver microsome	3.17	17.09	μl/min/mg mic.protein
Km	-	0.01	μmol

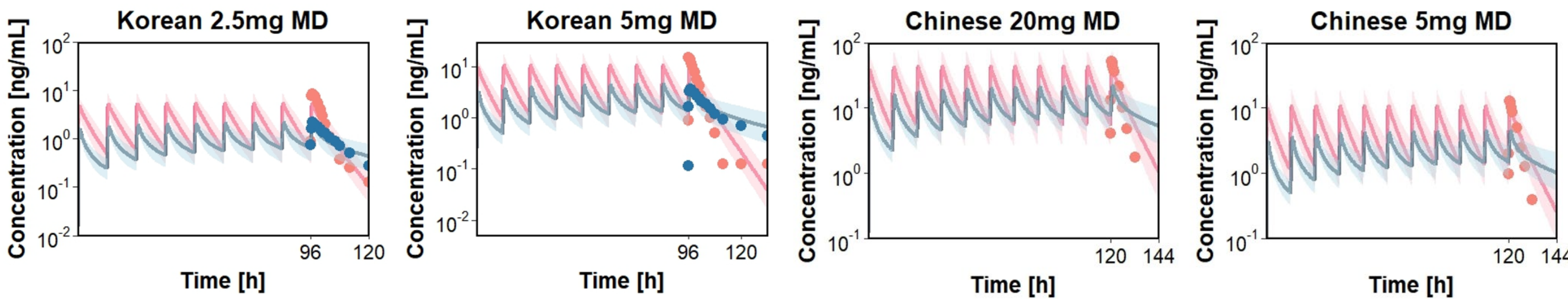
RESULTS

Simulated vs Observed of IVA (red line and dots) and (S18982 (blue line and dots) PK data

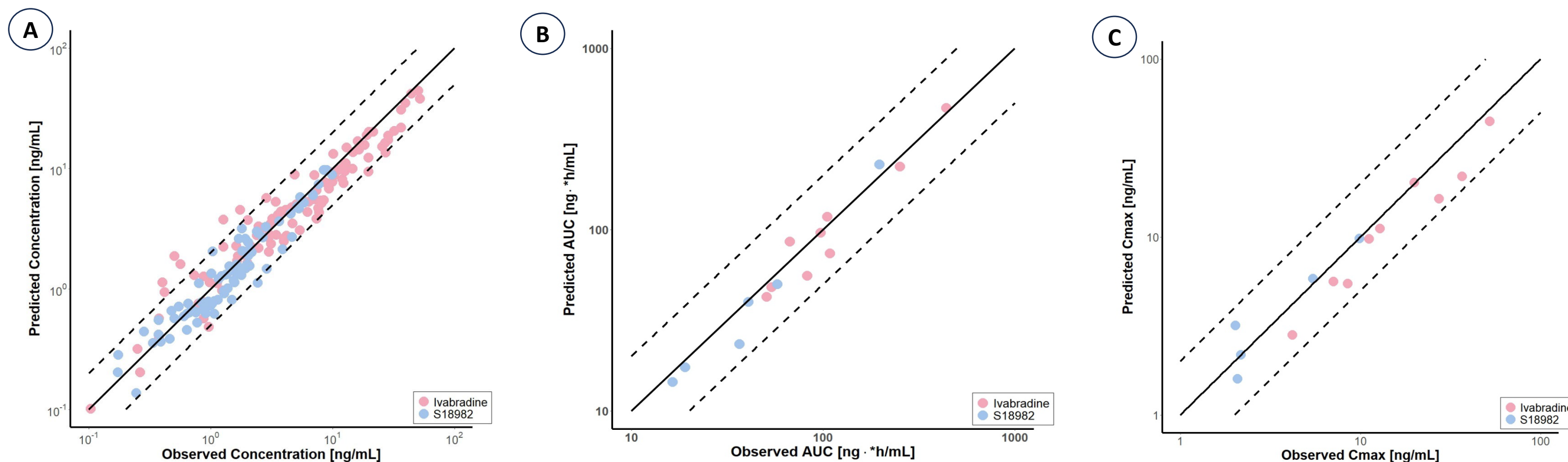
• Single dose



• Multiple dose



Goodness-of-fit plots for the developed PBPK model of IVA for the prediction of (A). Plasma concentration, (B) AUCinf, (C) Cmax



- About 92% of the predicted values of IVA and S18982 plasma level & 100% of AUCinf, Cmax values were within the 2-fold deviations of the observed values
- The MRD of the predicted plasma level of IVA and MET are 1.07 and 1.04, respectively
- The GMFE values of AUCinf & Cmax of IVA are 1.32 and 1.19, while the ones of S18982 are 1.19 and 1.17, respectively

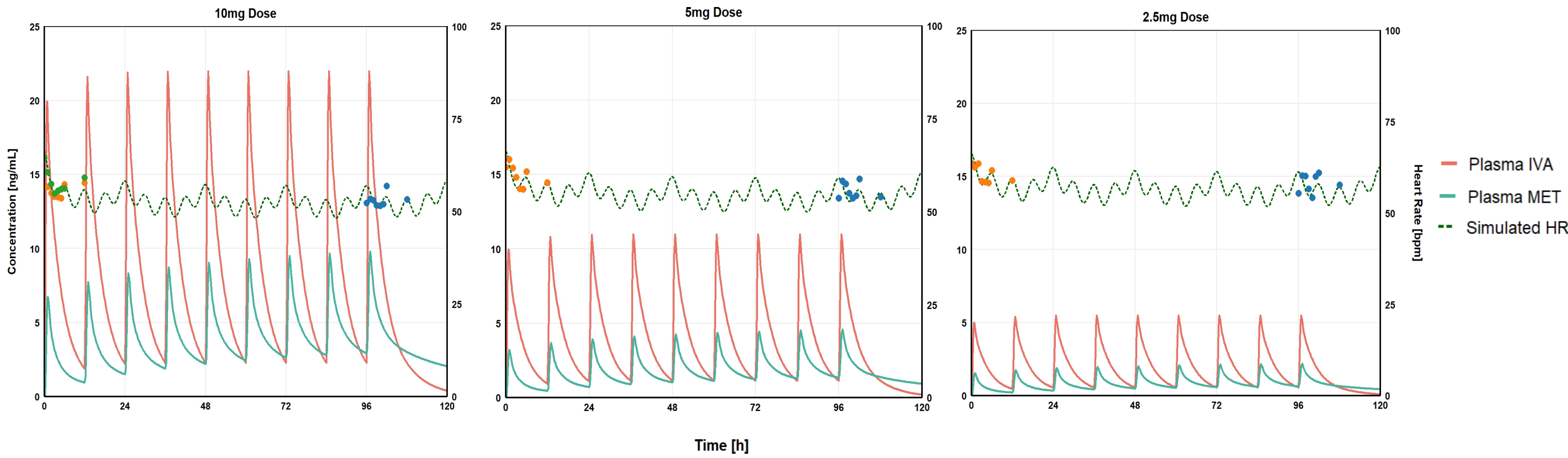
Pharmacodynamic model

Table 2. PD Model Initial Parameters

Parameter (unit)	Initial Value
Base (bpm)	60.7
Emax (%)	41.6
EC50p (ng/mL)	0.089
EC50m (ng/mL)	0.059
ke0m (1/h)	0.24
ke0p (1/h)	0.24
koutm (1/h)	0.05
koutp (1/h)	0.24

- HR is a Turnover-based physiological Response, also affected by biological Circadian Rhythm.
- Apart from the initial model, which describes the PD effect of IVA on HR, a Circadian Rhythm model was added to the equation to increase the prediction as well as the description of the PD effect.

Simulated HR (lines) vs Observed HR (dots) Value



CONCLUSION & DISCUSSION

- A PBPK/PD model of Ivabradine and its active metabolite S18982 was successfully established, accurately capturing plasma concentration profiles and heart rate reduction across different doses
- The model demonstrated good predictive performance and can support understanding of Ivabradine's pharmacokinetics and pharmacodynamics for improved dose evaluation and clinical insight.

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