



# Model-Based Approach for a New Prolonged-Release (PR) Formulation of Ivabradine: PK and PKPD Assessment to Support Bioequivalence (BE)



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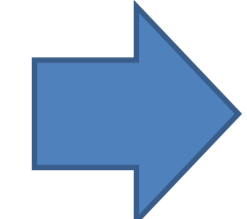
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## Background

### Context :

#### Ivabradine IR 5 mg (bid)

First in new class of HR-reducing agents for chronic heart failure and stable angina



#### Ivabradine PR 11,5 mg (od)

- Reduce plasma drug concentration fluctuations
- Enhance patients adherence

### Pivotal phase I study

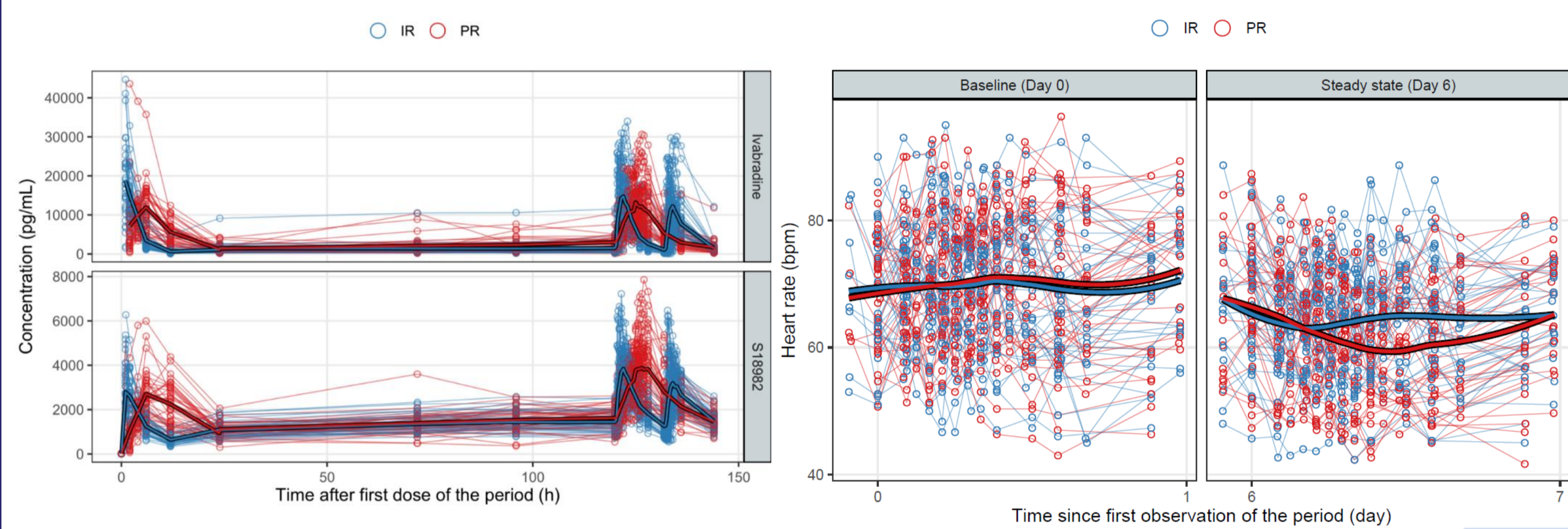
Pharmacometric modeling has been proposed as a tool to compare the PK and PD of ivabradine and its active metabolite after administration of IR or PR formulations

### Objectives :

- To characterize the **popPK** of ivabradine and its metabolite (S18982) after single and repeated administrations of both PR and IR (Immediate Release) tablet formulations,
- To identify the **PKPD** relationship between ivabradine and its active metabolite (S18982) concentrations and **heart rate (HR)** following PR and IR tablet administration,
- To assess the **bioequivalence (BE)** between the PR and IR tablet formulations, both in terms of **PK exposure at steady state** and in terms of PKPD, as **mean HR change over 24h from baseline**.

## Pivotal Phase I study

Data from a completed 2-way cross over study with PK and PD data available from 37 and 36 healthy volunteers, respectively



- Lower Ivabradine C<sub>max</sub> after PR
- Effect morning vs evening dosing occasion for IR for Ivabradine and S18982 (lower concentration at evening)
- Good overlay of Ivabradine and S18982 PK
- Similar trend for HR at baseline
- Larger HR decrease after PR at steady state
- Faster return to steady state levels for IR

## Modeling framework

### 1. PK modeling:

- Sequential modeling approach to estimate the parent and then the metabolite PK
- Final model : Ivabradine and S188982 parameters estimated simultaneously through a **joint parent-metabolite popPK model**
- Body weight included *a priori* on all clearance and volume parameters using allometric scaling

### 2. PKPD relationship modeling:

- **Baseline HR model**
- **Drug effect model**

**Evaluated covariates :** Formulation and subject characteristics (age, sex) for the PK and the PKPD models

**Exploratory covariate :** Evaluated with SCM (Stepwise Covariate Model) using Adaptive Scope Reduction (ASR)

**3. Analysis of potential deviation between formulations:** Computation of AUC<sub>0-24ss</sub> and the mean HR change from baseline over 24 hours

**4. Simulations to support the results from BE study:** 1000 replicate dataset simulated with the final PK and PKPD models, each including 1000 subjects

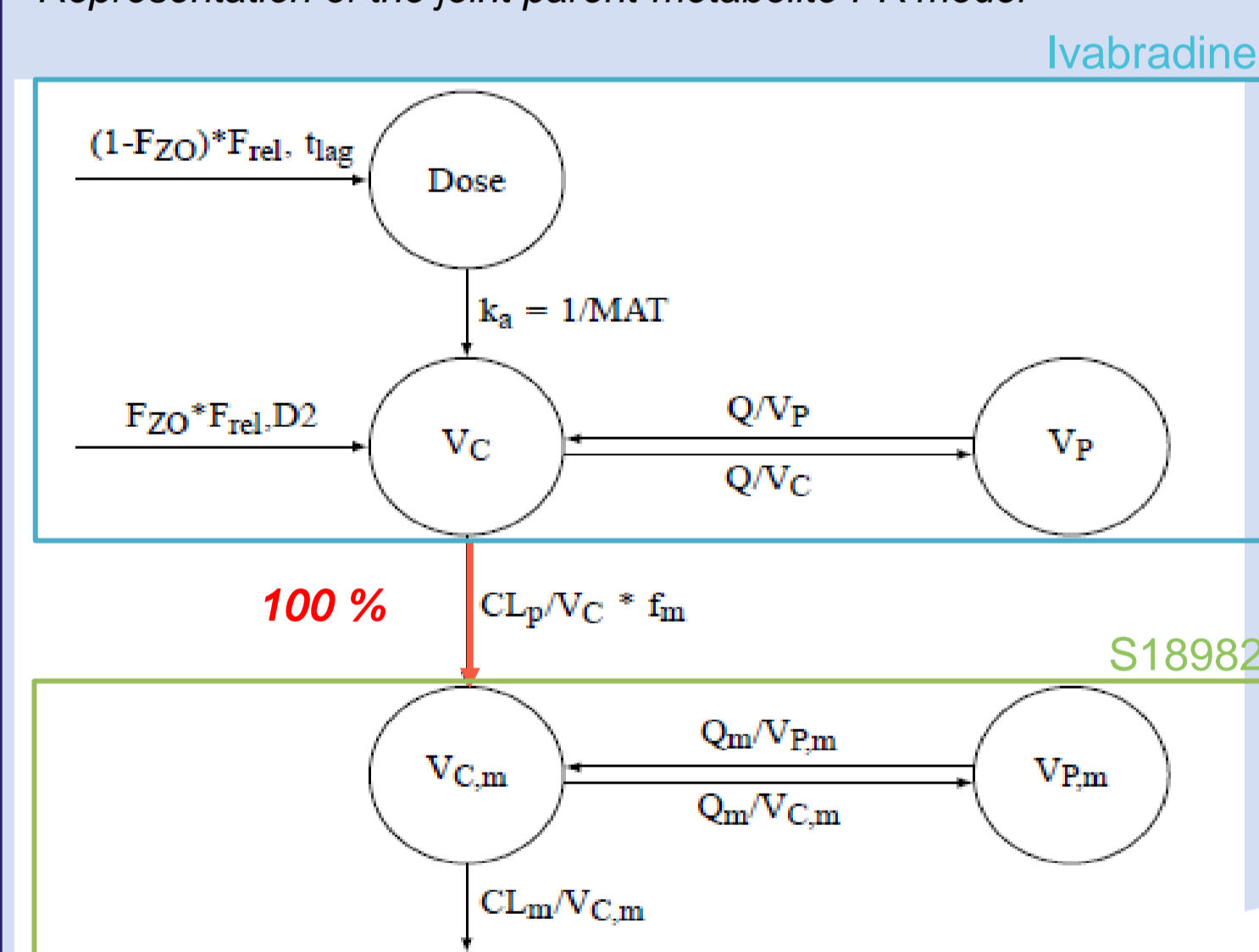
**Software:** NONMEM v7.5, FOCEI method

**Steps in italics are not included in the Results section.**

## Results

### 1. PK modeling:

Representation of the joint parent-metabolite PK model



#### PK model results

Run	4025	OFV	-4789	Condition number	148251
	Unit	Value	RSE (%)	SHR (%)	
	CL (L/h)	83.1	7.33		
	V <sub>c</sub> (L)	243	22.0		
	Q (L/h)	12.4	10.8		
	V <sub>p</sub> (L)	449	2.20		
	WT on CL	0.750	(FIX)		
	WT on V	1.00	(FIX)		
	F <sub>rel</sub> for IR	1.00	(FIX)		
	MAT for IR evening dose	(h)	0.649	167	
	Morning dose effect on MAT IR		-0.381	147	
	MAT for IR formulation	(h)	0.450	11.0	
	Mixture: t <sub>lag</sub> for evening dose of IR	(h)	1.43	4.01	
	Mixture: fraction of subjects with longer t <sub>lag</sub> *	(h)	0.412	(FIX)	
	F <sub>rel</sub> for PR		0.902	9.80	
	F <sub>20</sub> for PR	(h)	0.315	5.72	
	D2 for PR	(h)	5.77	44.5	
	MAT for PR	(h)	6.88	33.9	
	t <sub>lag</sub> for PR	(h)	2.56	6.21	
	f <sub>m</sub>		1.00	(FIX)	
	CL <sub>m</sub>	(L/h)	202	23.9	
	Relative change in f <sub>m</sub> for PR		0.0898	17.2	
	V <sub>c,m</sub>	(L)	6.84	949	
	Q <sub>m</sub>	(L/h)	327	35.0	
	V <sub>p,m</sub>	(L)	1750	20.4	
	IIV RUV	(CV)	0.262	38.0	3.06
	IIV F <sub>rel</sub>	(CV)	0.440	140	2.71
	IIV CL	(CV)	0.176	50.8	9.88
	IOV MAT for IR	(CV)	1.44	53.1	10.0
	IIV MAT for PR	(CV)	0.401	71.8	7.51
	IIV D2 for PR	(CV)	0.605	141	3.85
	IIV f <sub>m</sub>	(CV)	0.311	138	5.50
	IIV CL <sub>m</sub>	(CV)	0.199	115	16.0
	IIV V <sub>p,m</sub>	(CV)	0.171	269	36.2
	RUV	(CV)	0.389	32.9	0
	RUV <sub>m</sub>	(CV)	0.190	23.1	0.494

### 2. PKPD modeling:

#### 24 hours circadian rhythm model

$$HR(t) = M + A \cdot \cos\left(\frac{2\pi}{T}(t - \phi)\right)$$

- M : baseline
- A : amplitude
- T : period of circadian cycle (24h)
- $\Phi$  : circadian phase shift

#### Effect model : Competitive inhibitory model with delayed effect compartment

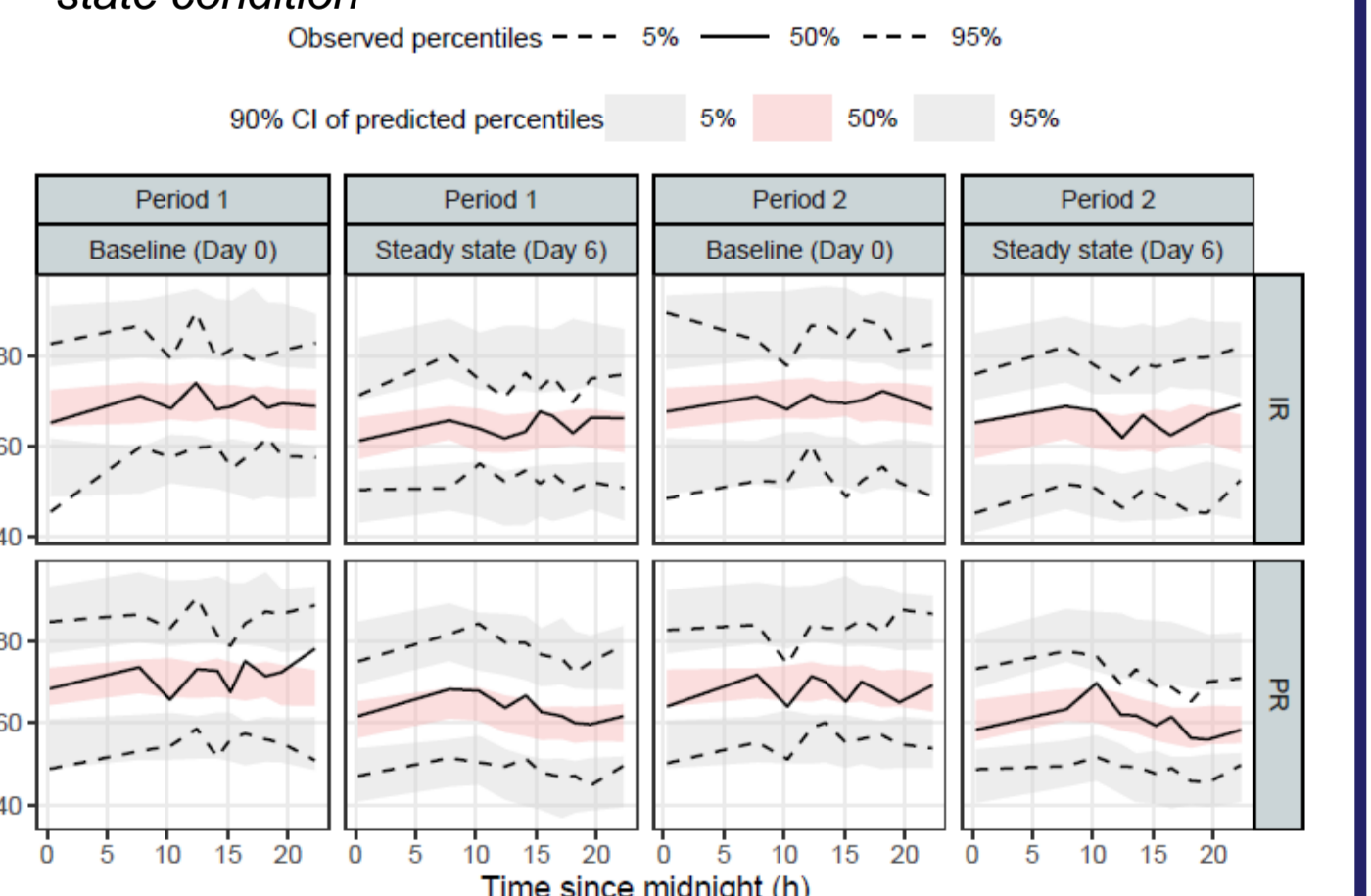
$$Treatment = E \max \cdot \frac{\frac{C_{eD}}{EC_{50D}} + \frac{C_{eM}}{EC_{50M}}}{1 + \frac{C_{eD}}{EC_{50D}} + \frac{C_{eM}}{EC_{50M}}}$$

**C<sub>eD</sub>** : concentration of ivabradine in the effect compartment driven by KE0p  
**C<sub>eM</sub>** : concentration of metabolite in the effect compartment driven by KE0m

#### PKPD model results

Run	2012	OFV	7838	Condition number	178
	Unit	Value	RSE (%)	SHR (%)	
	Baseline heart rate	(bpm)	65.6	2.90	
	24h circadian amplitude	(bpm)	1.74	12.4	
	24h circadian phase shift	(h)	11.6	9.53	
	Relative change in Baseline for female subjects		0.123	47.2	
	E <sub>max</sub>		0.307	37.3	
	EC <sub>50,p</sub>	(ng/mL)	21.3	70.0	
	EC <sub>50,m</sub>	(ng/mL)	24.0	(FIX)	
	KE0,p	(1/h)	0.190	32.5	
	KE0,m	(1/h)	0.820	(FIX)	
	Relative change in EC <sub>50p</sub> for PR		-0.370	19.7	
	IIV RUV	(CV)	0.182	21.2	7.95
	IIV Baseline heart rate	(CV)	0.107	19.9	1.48
	IIV 24h circadian phase shift	(CV)	0.366	23.1	11.5
	IOV on baseline	(CV)	0.0317	21.4	41.4
	IIV E <sub>max</sub>	(CV)	0.407	19.3	9.58
	RUV	(bpm)	4.67	4.27	0.804

Visual Predictive Check (VPC) of the PKPD model, stratified by formulation, study period, baseline values, and steady-state condition



## Conclusion

- The modeling supported the analysis of the potential deviation between formulations, through the computation of AUC<sub>0-24ss</sub> and the mean HR change from baseline over 24 hours.
- Simulations were performed based on the final parent-metabolite PK model and the final PK/PD model and allowed to support the results from the bioequivalence study between IR and PR formulation in term of PK and PD.

**This work underlines the importance of modelling and simulations for the analysis of clinical studies for development of new formulations especially in a complex setting where PD readout is impacted by an active metabolite.**