

Population pharmacokinetic modelling of selexipag and its active metabolite after oral and intravenous administration in adult pulmonary arterial hypertension patients

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INTRODUCTION

Selexipag is a selective prostacyclin receptor agonist approved for use in adults with pulmonary arterial hypertension (PAH). After its oral administration, carboxylesterases in the liver and intestinal wall transform selexipag into ACT-333679, the active metabolite, and the major contributor to drug effect.¹

OBJECTIVES

- To jointly characterize the time-course of plasma concentrations of selexipag and ACT-333679, and its corresponding between subjects variability, following oral and intravenous (IV) dosing.
- To compare the model-based simulated plasma concentration-time profiles of selexipag after the administration of two different infusion rates which delivered the same total dose over a dosing interval of 12 hours.

METHODS

A total of 20 adult subjects with PAH (4 men, 16 women) were included in the AC-065A309 study, which was an open-label, cross-over, Phase 3 study assessing the safety and tolerability of switching from a stable oral to the corresponding IV dose of selexipag. A total of 261 selexipag and 263 ACT-333679 plasma concentrations were included in the population PK analysis. The PK data were analysed using non-linear mixed effect modelling approach (NONMEM®)² and the model evaluations were performed using prediction corrected visual predictive checks (pcVPC) using PsN.³

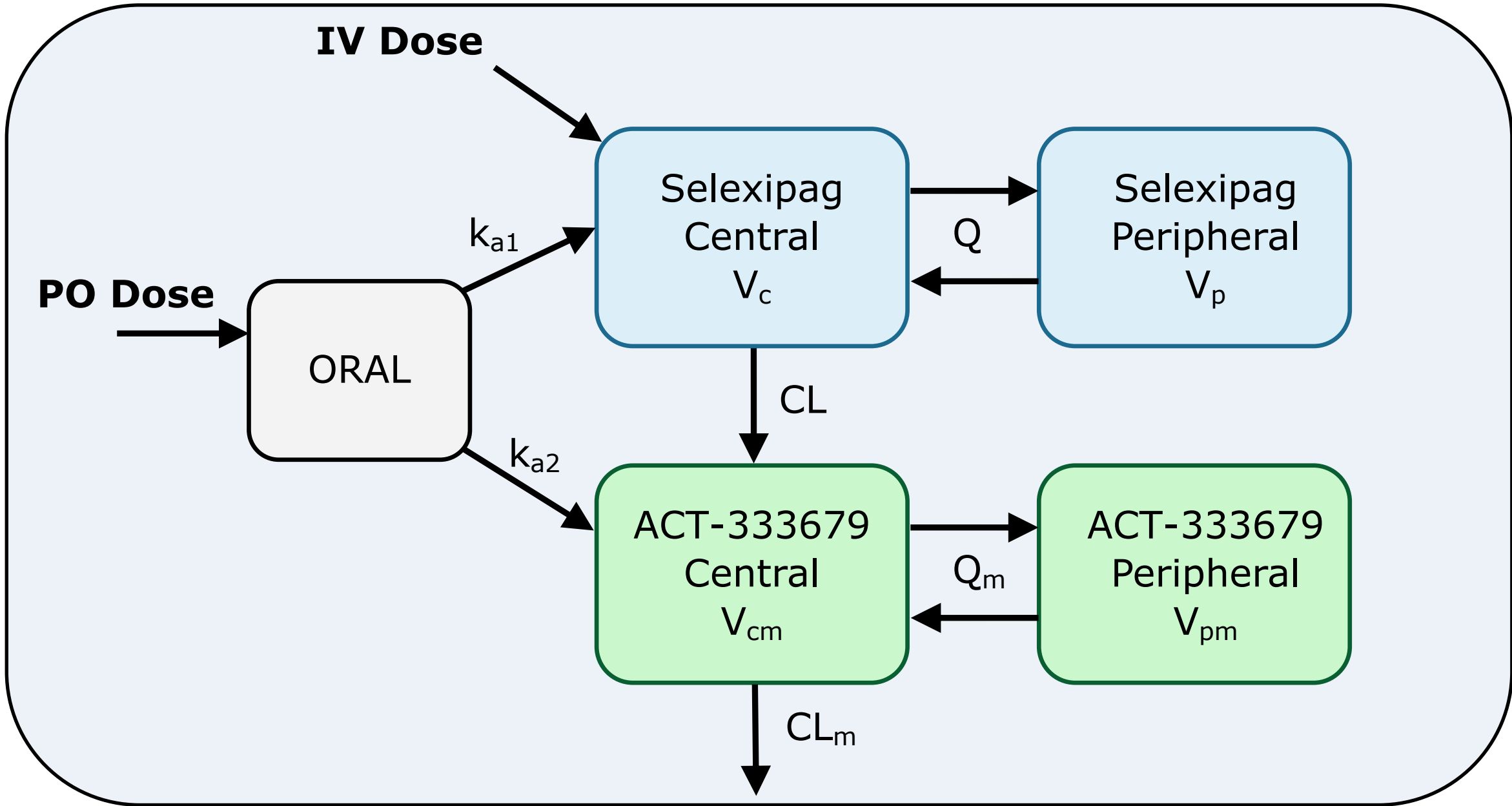


Figure 1: Schematic of the Population PK model for Selexipag and ACT-333679.

RESULTS

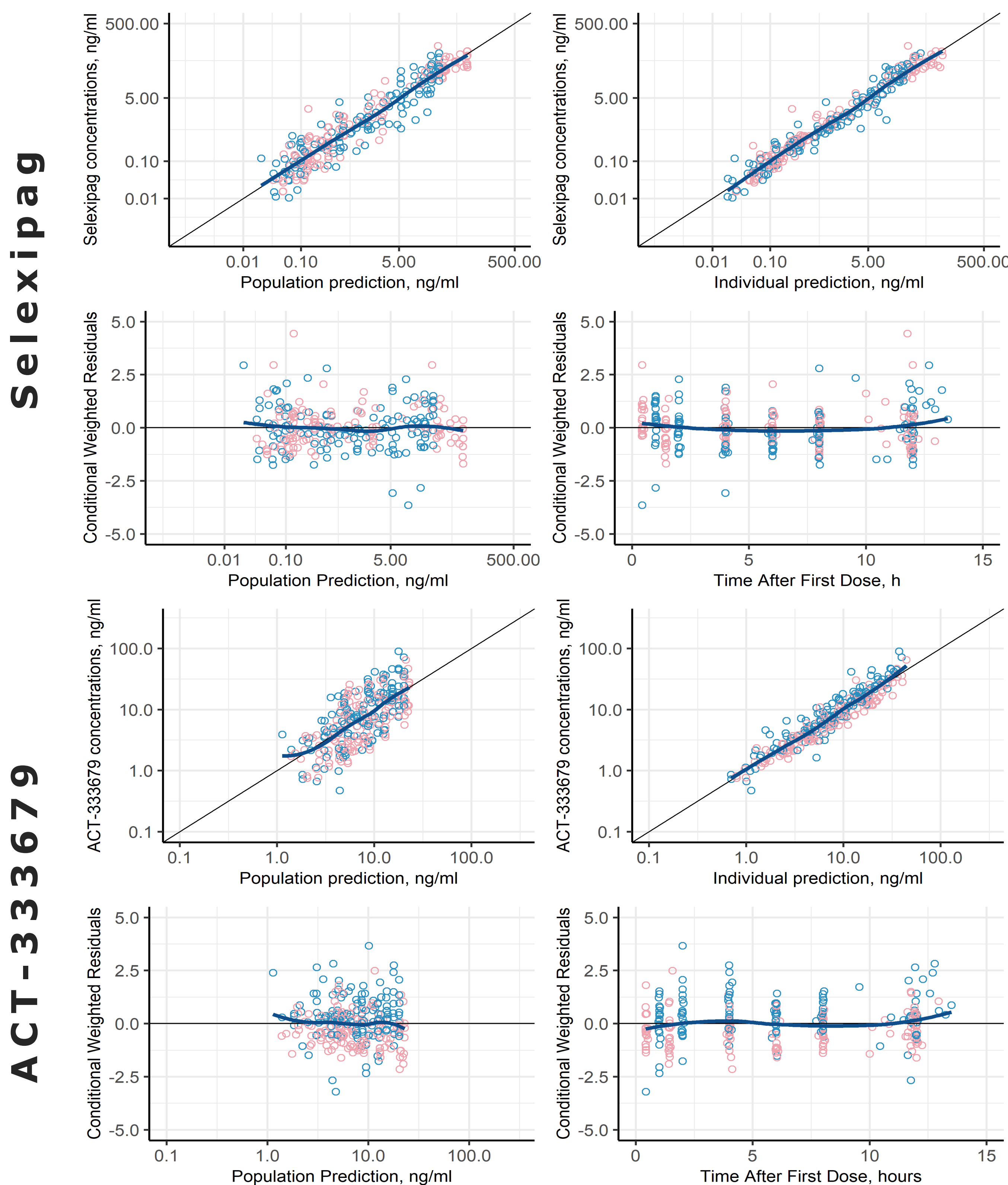


Figure 2: Goodness of fit plots for the Population PK model. Blue and pink circles represent the observations/predictions and conditional weighted residuals for PO and IV administration respectively; solid black line represents the identity line while the solid dark blue line represents the locally weighted scatterplot trend line.

RESULTS

Table 1. Parameter estimates of the Population PK Model.

Structural Model Parameters		Inter-individual Variability (IIV; CV %)	
Parameters	Estimate (RSE %)	Parameter	Estimate (RSE %)
Selexipag			
k_{a1} (h^{-1})	0.470 (13.8)	IIV k_{a1}	47.1 (73.0)
k_{a2} (h^{-1})	0.269 (12.7)	IIV k_{a2}	37.2 (62.6)
V_c (L)	10.6 (8.94)		
V_p (L)	2.40 (14.1)		
Q (L/h)	0.514 (20.4)		
CL (L/h)	14.6 (8.77)	IIV CL	23.5 (36.4)
ACT-333679			
V_{cm} (L)	26.3 (6.9)	IIV V_{cm}	56.8 (25.3)
V_{pm} (L)	1.53 (0.8)		
Q_m (L/h)	212 (4.6)		
CL_m (L/h) ^a	67.3 (4.8)	IIV CL_m	22.6 (29.2)
Residual variability (CV%)			
Selexipag	55.9 (4.92)		
ACT-333679	35.5 (4.79)		

RSE: relative standard error; CV: coefficient of variation;
^a Correlation (r^2) between CL and CL_m was determined to be 0.92 (RSE=35.2%).

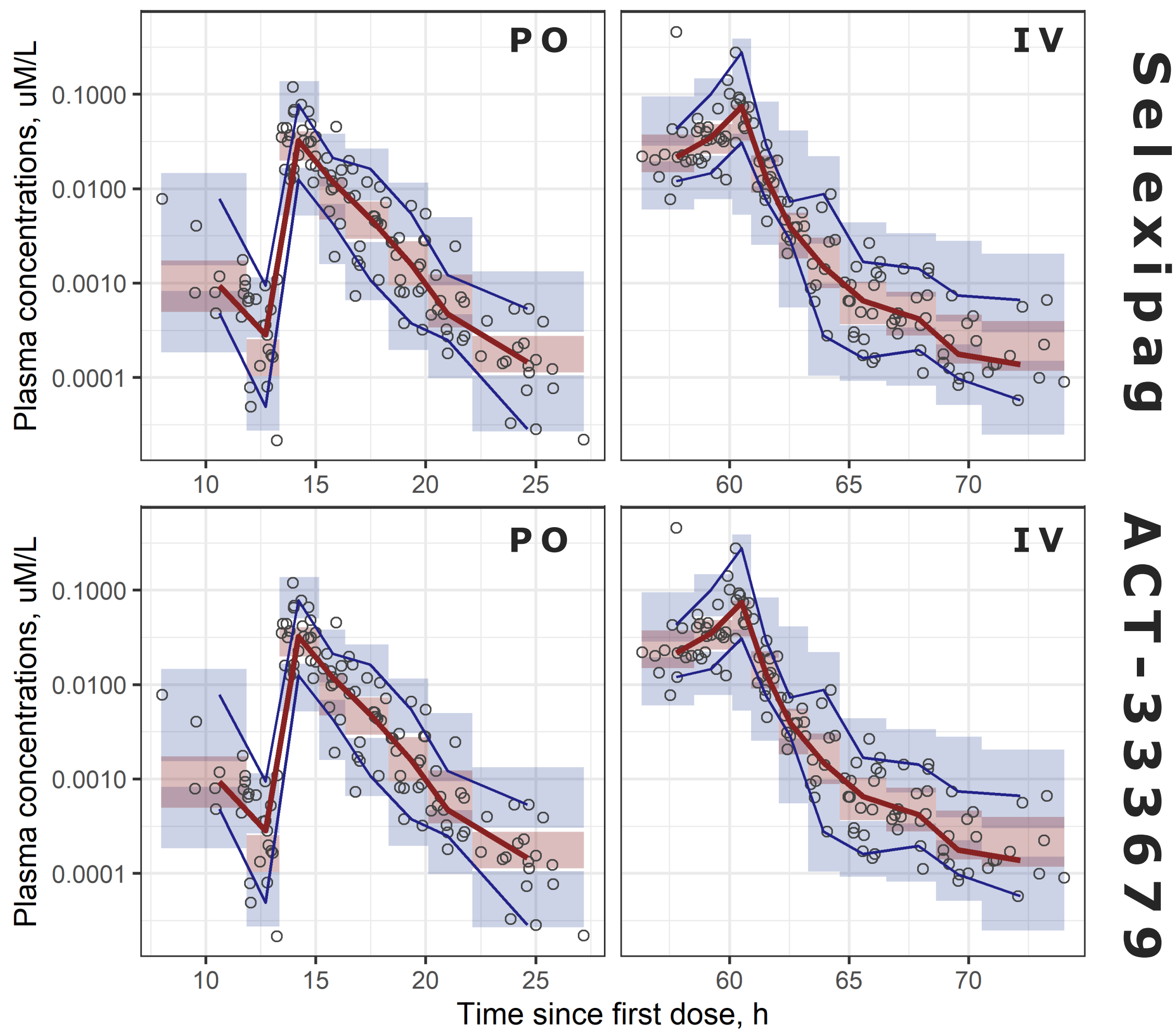


Figure 3: Prediction-corrected VPC for Selexipag and ACT-333679 stratified by the route of administration. The VPC displays the 5th, 50th and 95th percentiles of the plasma concentrations, and the 95% confidence interval for the corresponding model-based predicted percentiles computed from 100 Monte Carlo replicates.

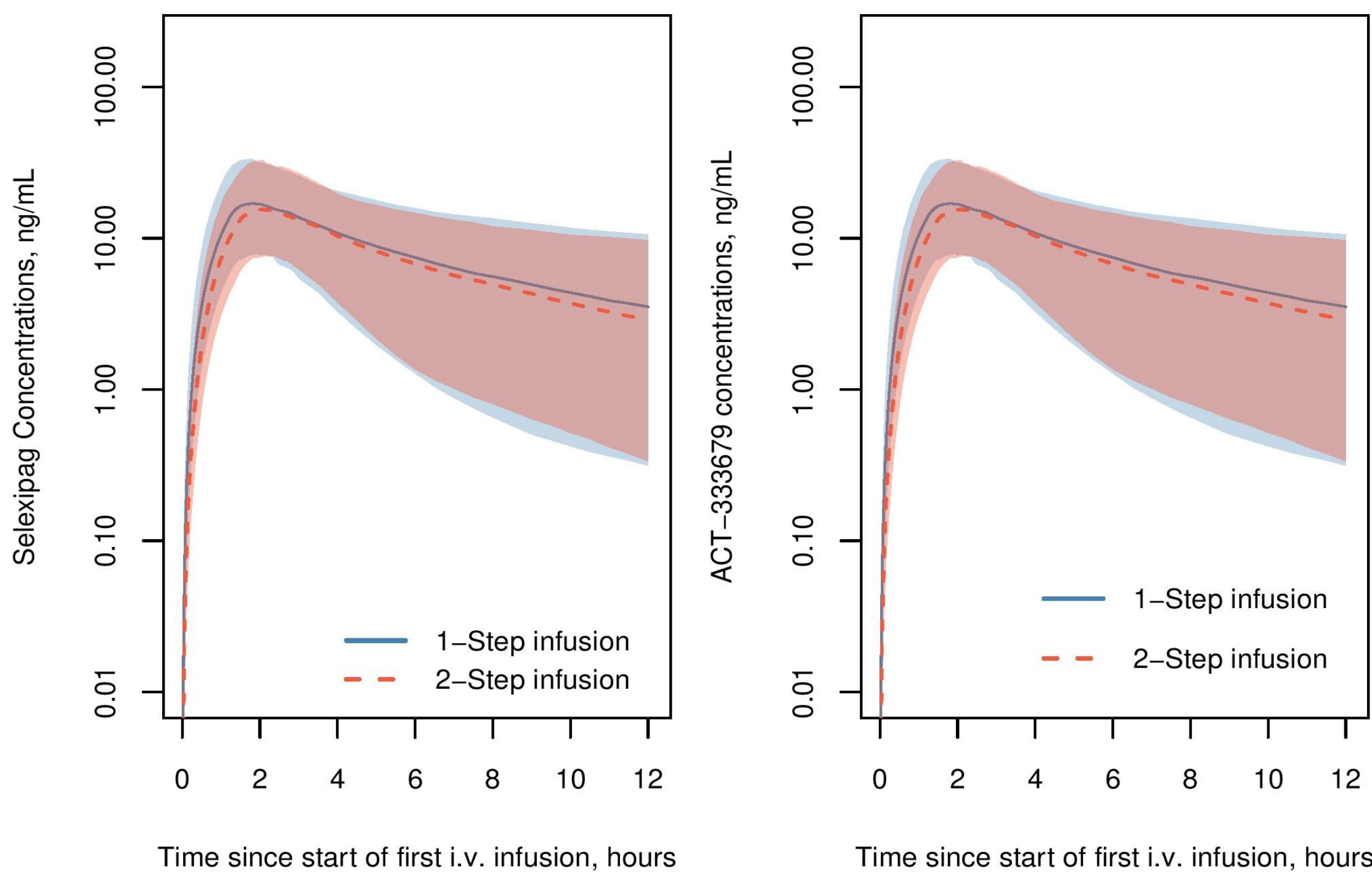


Figure 4: Model-based simulations of the PK profiles of 1-step and 2-step IV infusion rates of selexipag. The solid blue line with its associated blue shaded represents the median and the 90% prediction interval of a 1800 mg in 80 min (1-step infusion); the dashed red line with its associated red shaded represents the median and the 90% prediction interval of a 180 mg in 15 min followed by 1620 mg in 72 min rates (2-step infusion).

CONCLUSIONS

- The PK of selexipag and ACT-333679 after PO and IV administration in PAH patients was adequately described using an integrated population PK model.
- The absolute bioavailability of selexipag in PAH patients in the AC-065A309 study estimated by the population PK model was 63.6% (90% CI: 58.1 – 66.1%), which is comparable to the NCA derived value of 55.3% (90% CI: 45.8 – 66.7%).
- The fraction of selexipag metabolized to ACT-333679 is 1.25-fold higher after PO dosing, relative to IV dosing.
- Changing the IV infusion rates from a 2-step infusion to a 1-step constant rate infusion is not expected to have any relevant effect on the PK profile of selexipag and ACT-333679.

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