

Modeling of pharmacokinetic data using nonlinear mixed effects: a paradigm shift in veterinary pharmacology

A case study with the NSAID robenacoxib in cats

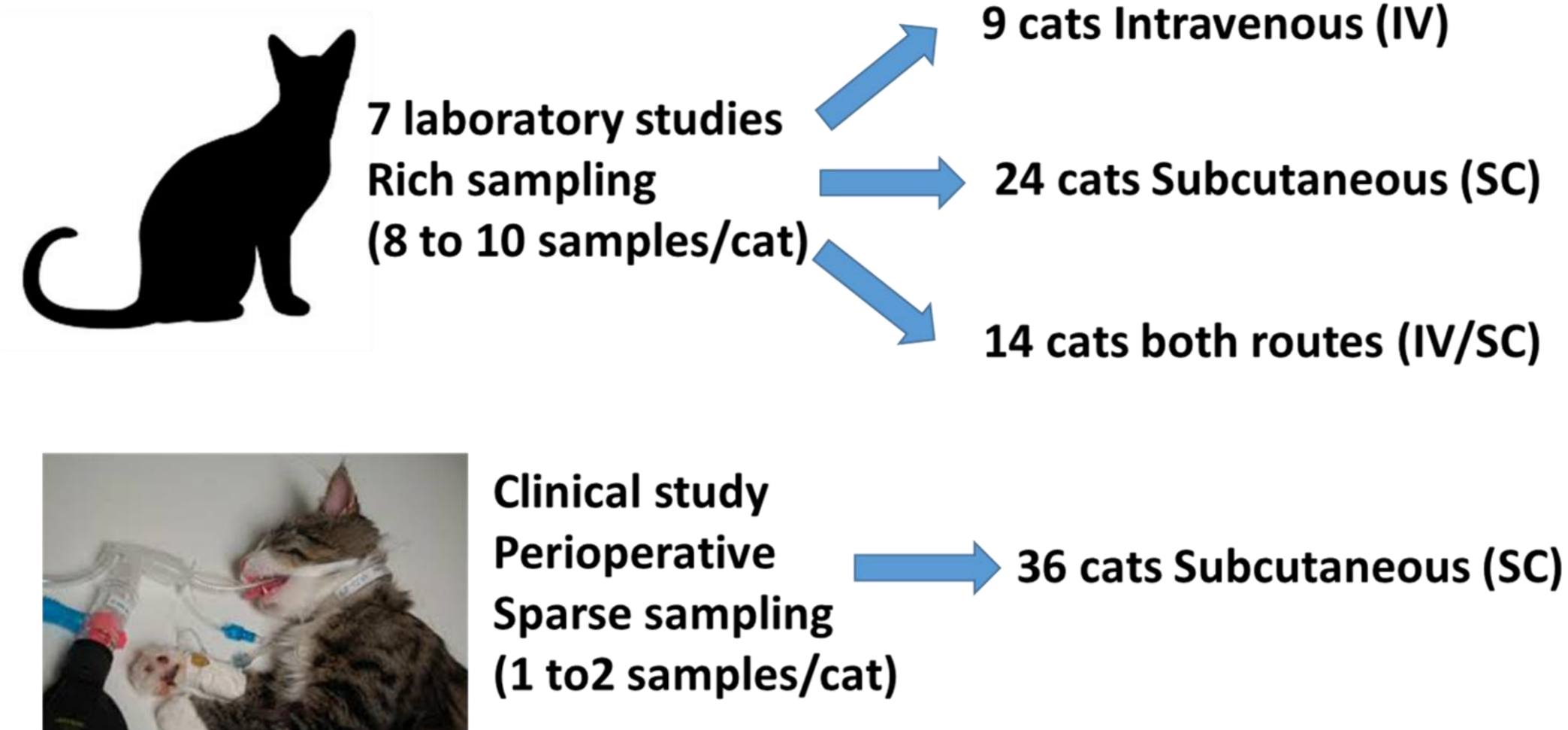
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Research Rationale

- Background:** Very often in **veterinary medicine** characterization of drugs **pharmacokinetics** is performed using a so-called **2 stages approach**, thereby limiting most of the analyses to **rich data**
- Objectives:** Model the **disposition kinetics** of **robenacoxib** in cats by **pooling data** from diverse sources in order to **leverage** the **richness** of the **intensively sampled** individuals to **inform parameter estimates** of the more **sparsely sampled** patients



Methods

- Data from 83 cats were pooled from **7 preclinical** (laboratory cats) and **1 field** (client-owned cats, perioperative sampling) **robenacoxib** PK studies
- Cats received robenacoxib **subcutaneously** (SC) and/or **intravenously** (IV). Sampling was **rich** for 47 laboratory cats and **sparse** for 36 clinical cats. The exact dose ranged from 1.6 to 2.3 mg/kg
- Data from **both routes** were modeled **simultaneously** with NLMEs in Monolix 4.3.2

Results

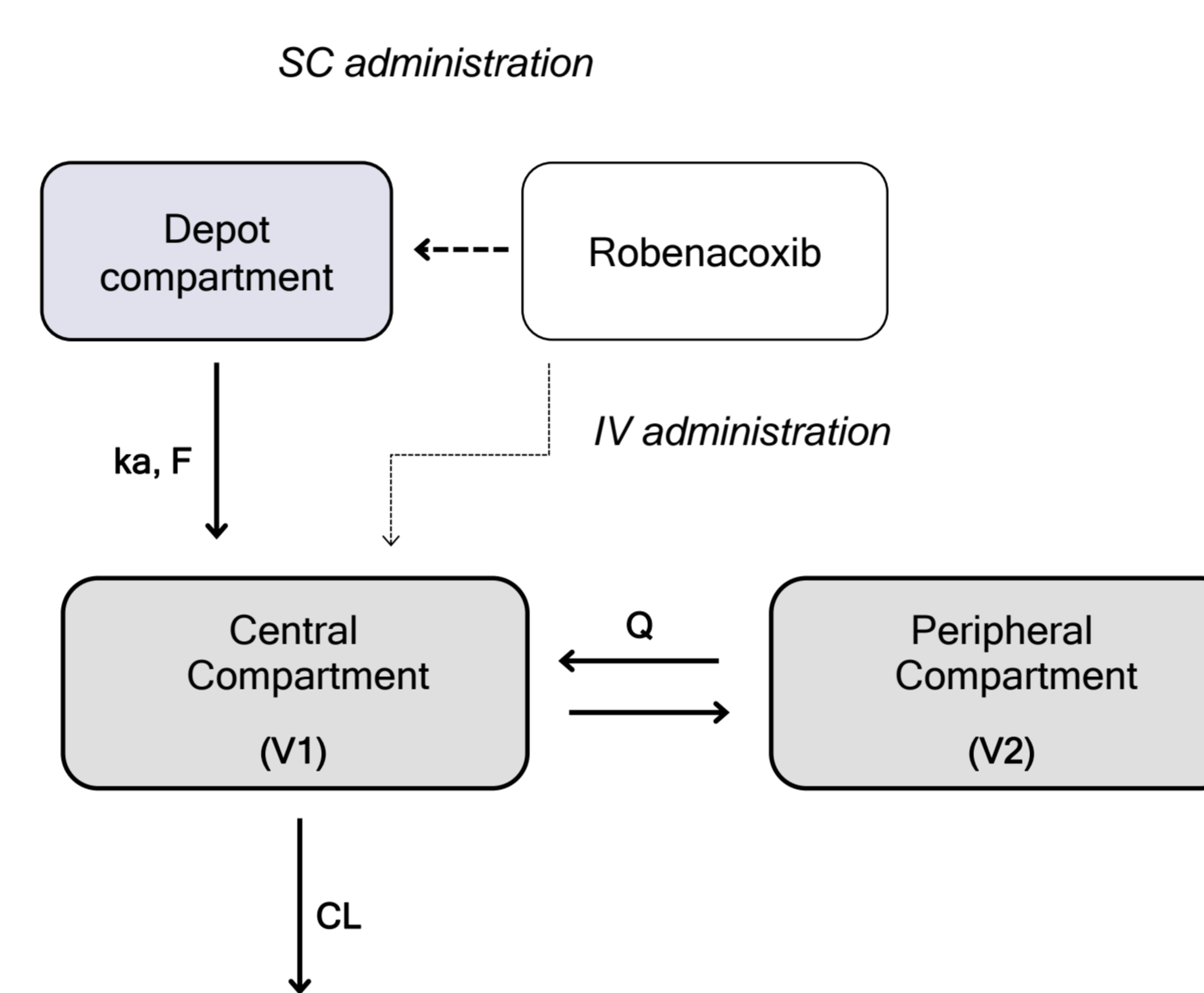
A **2-compartment mammillary** model with 1st-order absorption and elimination best described the kinetics of robenacoxib in blood. The **precision** of the final models parameters was considered **satisfactory** (RSE < 20% for most parameters)

The **total body clearance** was estimated to be **moderate** (0.50 L/kg/h) and the **global extraction ratio E** was **small** (0.06). The SC **bioavailability** was **high** (79%) and the steady state volume of distribution was 0.27 L/kg

The **absorption constant** (Ka: 0.86 h⁻¹) was **lower** than the **elimination constant** of the combined model (K10: 2.17 h⁻¹), thus confirming **flip-flop kinetics** with the SC route

None of the population characteristics was found to explain the between-subject variability observed in the present studies

Figure 1. Mathematical model of robenacoxib disposition kinetics



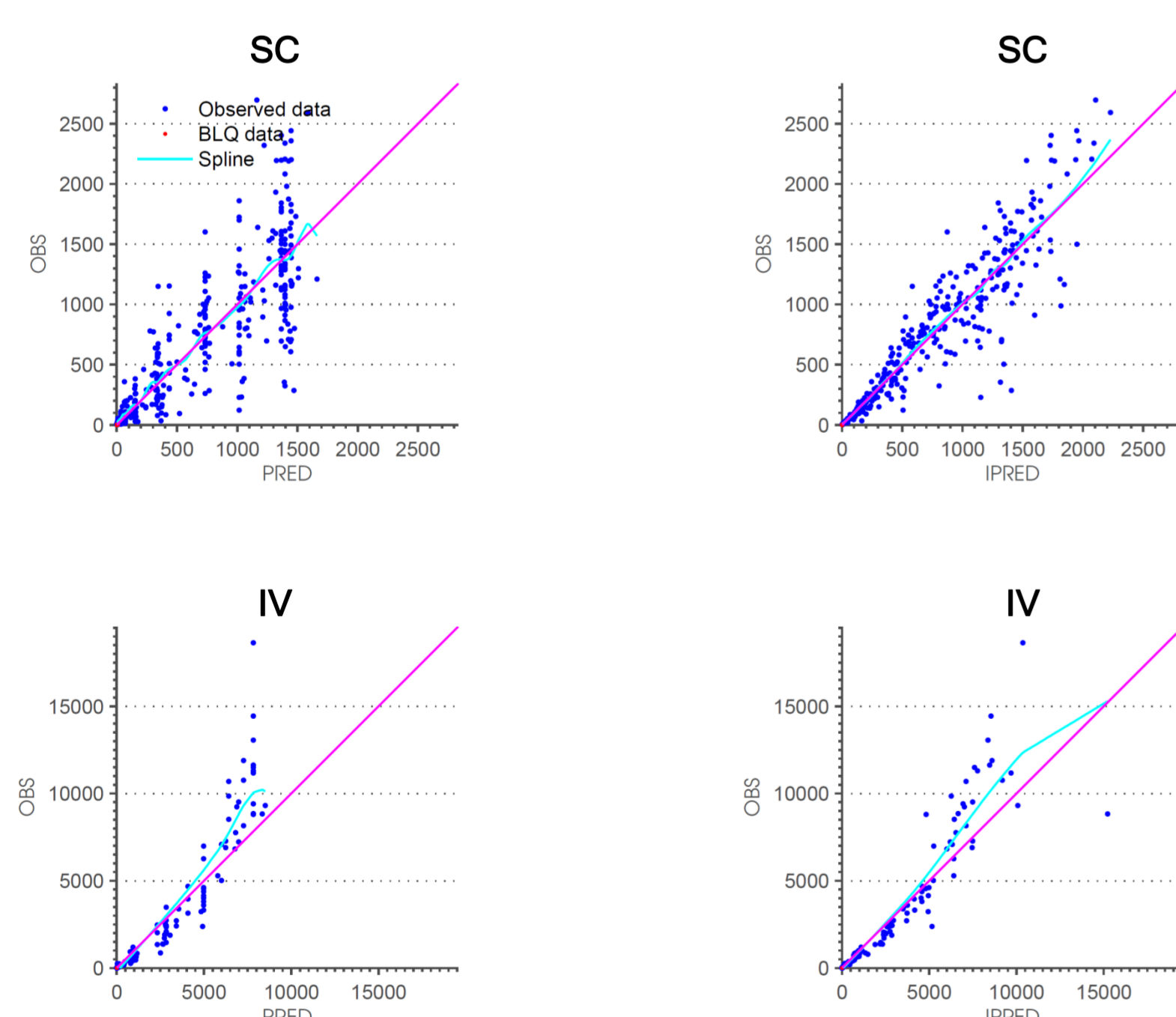
Simultaneous modeling of robenacoxib kinetics following intravenous and subcutaneous administration in cats. CL: total body clearance, V1: volume of the central compartment, Q: intercompartmental clearance, V2: volume of the peripheral compartment, ka: absorption rate constant, F: absolute bioavailability

Table 1. Parameter estimates of the population model

PK Parameter	Unit	Point estimate	RSE (%)
CL	L/kg/h	0.50	4
V1	L/kg	0.23	7
Q	L/kg/h	0.02	8
V2	L/kg	0.04	7
ka	1/h	0.86	4
F	%	79	4
ω (CL)	L/kg/h	0.15	17
ω (V1)	L/kg	0.38	14
ω (ka)	1/h	0.30	11
ω (Q)	L/kg/h	0.18	65
ω (V2)	L/kg	0.28	23
ω (F)	%	0.34	73

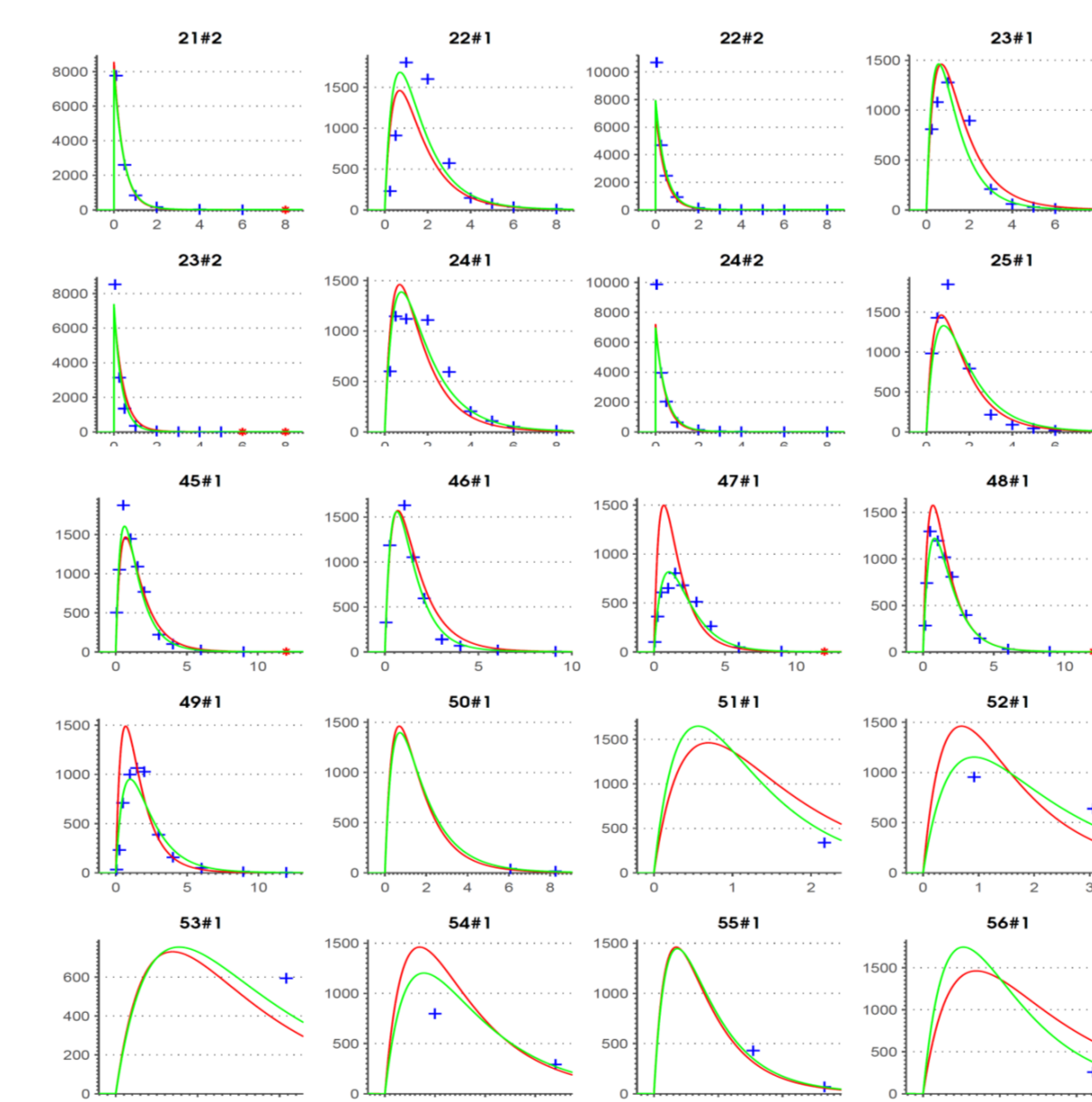
Point estimates, and relative standard error of the mean (RSE) of pharmacokinetic model parameters with their inter-individual variability. The precision of the final model parameters was considered satisfactory (RSE < 20% for most parameters)

Figure 2. Standard goodness-of-fit diagnostics



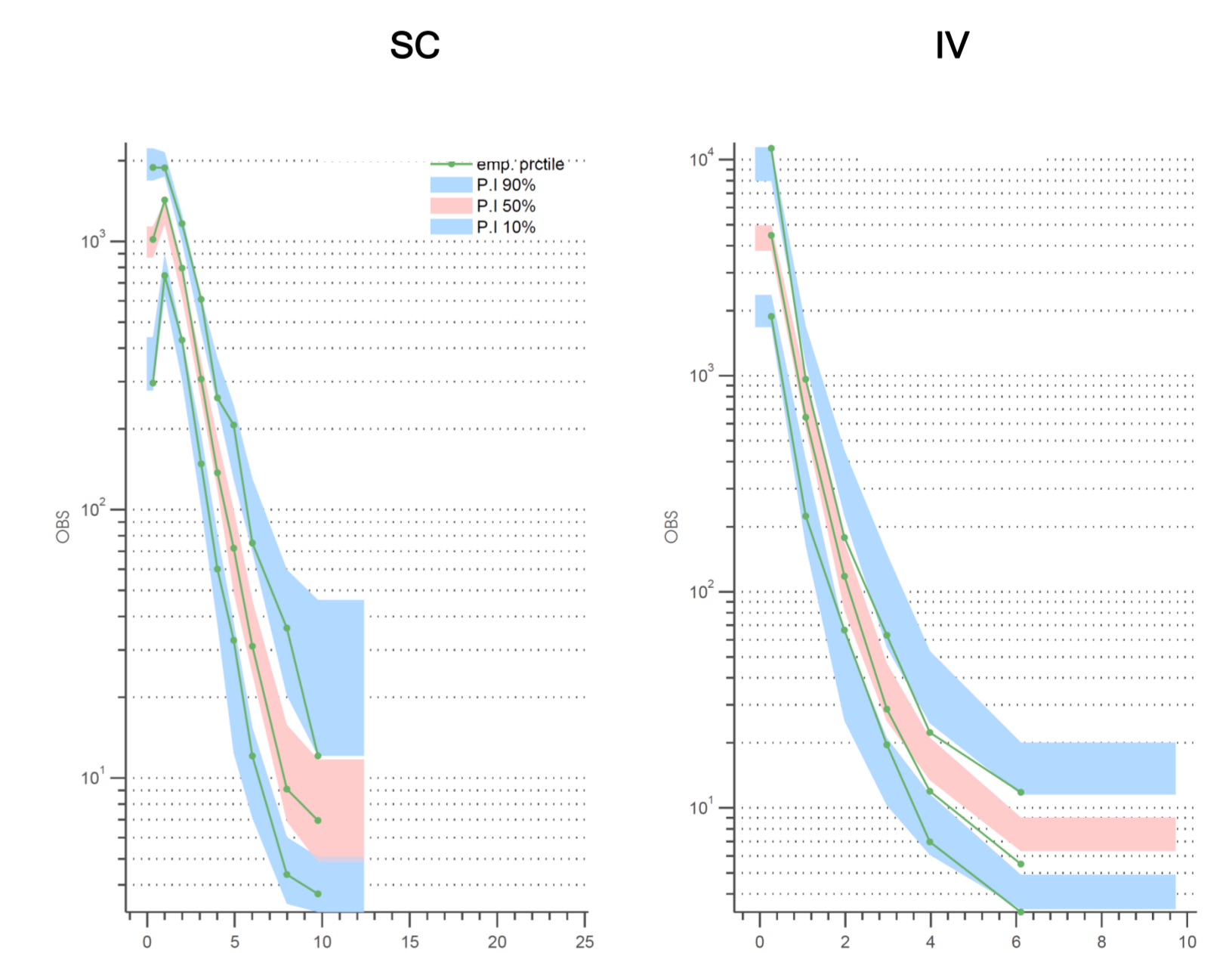
First column: population predictions vs. observations. Second column: individual predictions vs. observations. First row: subcutaneous administration. Second row: intravenous bolus. Solid pink line: identity line. Solid blue line: loess fit

Figure 3. Predictions based on individual parameters estimates



Scatter plot of observed (blue crosses) and predicted (continuous lines) robenacoxib levels (mg/mL) versus time after dose (hr). Red lines: population predictions. Green lines: individual predictions. #1: SC; #2 to IV route

Figure 4. Visual predictive checks for the final model



Visual predictive checks generated from 500 MC simulations. Green lines: 10th, median and 90th percentile of the observed data. Blue and pink area: 95% CI of the 10th, median and 90th percentile of the prediction interval

Conclusions and Perspectives



- The **population approach** allows **pooling** of data from several individuals, even from **different studies** with **different application routes** and **dosing regimens**
- Simultaneous modeling** of the IV and SC routes **unveiled the flip-flop** kinetics of robenacoxib in cats
- Estimates of robenacoxib **exposures** from **perioperative** (sparse) and **conscious** (rich) cats **did not differ** substantially
- Using **population modeling** to estimate the pharmacokinetics of **anaesthetized cats** is **new to veterinary pharmacology**

References: [1] Fink M, Letellier I, Peyrou M, Moche JP et al. Res Vet Sci, 95:580-7 (2013)
 [2] Pelligand L, King J, Toutain PL, Elliott J et al. J Vet Pharmacol Ther, 35:19-32 (2012)

Acknowledgments: The pharmacokinetic studies were conducted at the Centre de Recherche Sante Animale SA of Novartis Animal Health and at the Royal Veterinary College (UK)