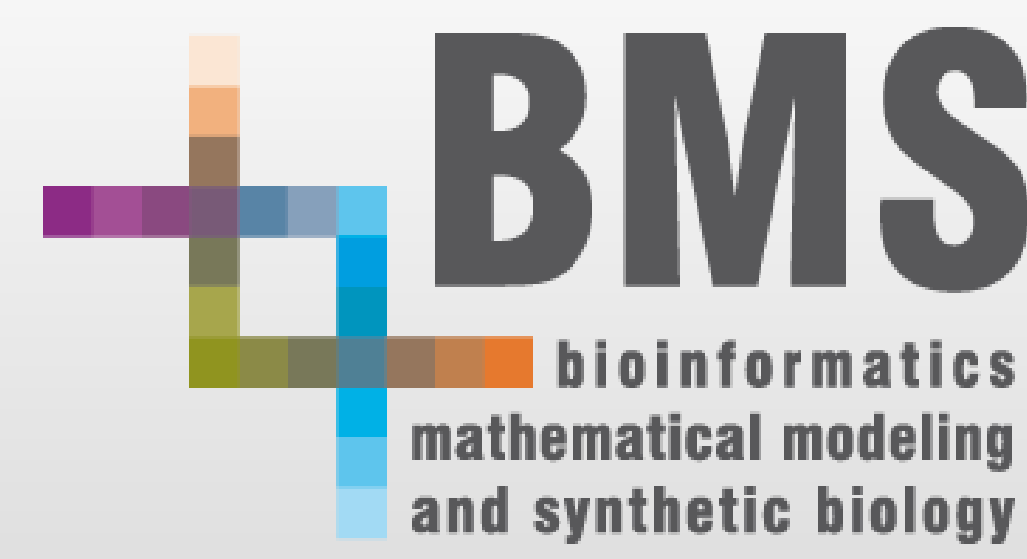




Optimal design of paediatric clinical trials: the Macitentan case study

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BACKGROUND: Macitentan is an endothelin receptor antagonist approved for the treatment of Pulmonary Arterial Hypertension (PAH) in adults, although PAH is a rare condition that can occur also in childhood [1]. For this reason, a paediatric study is mandatory. However, paediatric clinical trials can have ethical and practical restrictions that need to be considered when defining the experimental protocol, and so a design optimization is required in order to maximize the information that can be extrapolated from the collected data while minimizing the impact on patients [2].

OBJECTIVE: To optimize the paediatric clinical trial for Macitentan and its active metabolite (ACT-132577), finding the minimum number of samples per patients and an optimal sampling schedule.

METHODS:

PK model

A population pharmacokinetic model, describing the steady state kinetics of Macitentan and its active metabolite, was found in literature [3].

Individual model

$$\ln(\vartheta_j) = \ln(\vartheta_{pop}) + \eta_{\vartheta_j} \quad \eta_{\vartheta_j} \sim \log N(0, \Omega_{\vartheta})$$

Error model

$$y_{1,ij} = C_{1,ij} + (a_1 + b_1 C_{1,ij}) \varepsilon_{1,ij}$$

$$y_{2,ij} = C_{2,ij} + (a_2 + b_2 C_{2,ij}) \varepsilon_{2,ij}$$

$$\varepsilon_{1,2,ij} \sim N(0,1)$$

Allometric scaling

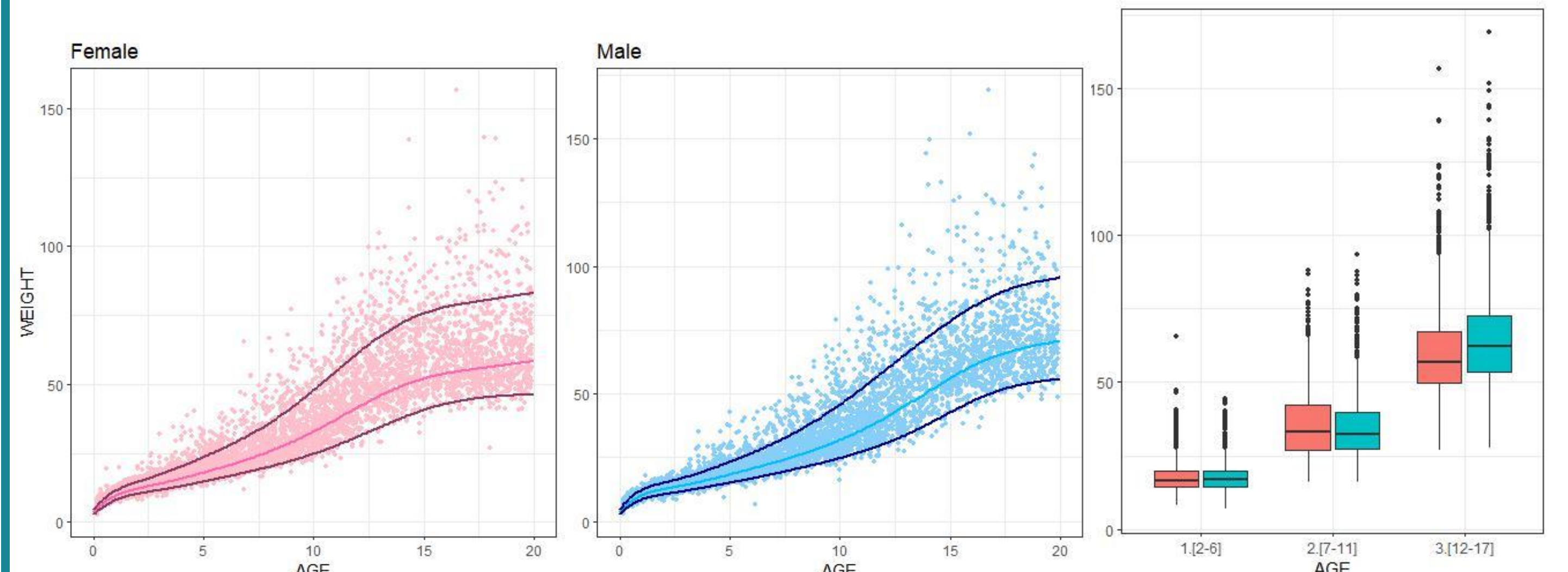
$$V_{M,j} = V_{M,pop} \left(\frac{WT_j}{70} \right)^1 \quad V_{A,j} = V_{A,pop} \left(\frac{WT_j}{70} \right)^1$$

$$CL_{1,j} = CL_{1,pop} \left(\frac{WT_j}{70} \right)^{0.75} \quad CL_{2,j} = CL_{2,pop} \left(\frac{WT_j}{70} \right)^{0.75}$$

Adults PK data were used to identify the parameter values, which were then allometrically scaled to adapt the model to a paediatric population.

Virtual paediatric population

Real data of age and weight were collected from the Third National Health and Nutrition Examination Survey (NHANES III).



A virtual population of 40 subjects, from 2 to 6 years old, was sampled and used with the scaled popPK model to simulate the administration of Macitentan.

Different doses were used for different weight ranges.

RESULTS:

Protocol optimization

- The R package PopED was used to optimize the design in terms of number of samples per subject and optimal timing schedule;
- Numbers of samples from 1 to 9 were evaluated in order to select the minimum number to obtain a certain level of precision;
- For each case, the optimal design was chosen using Ds-optimality, that is based on the Fisher's Information Matrix (FIM):

$$\vartheta = [\vartheta_1, \vartheta_2]$$

$$\vartheta_1 \text{ Unimportant parameters}$$

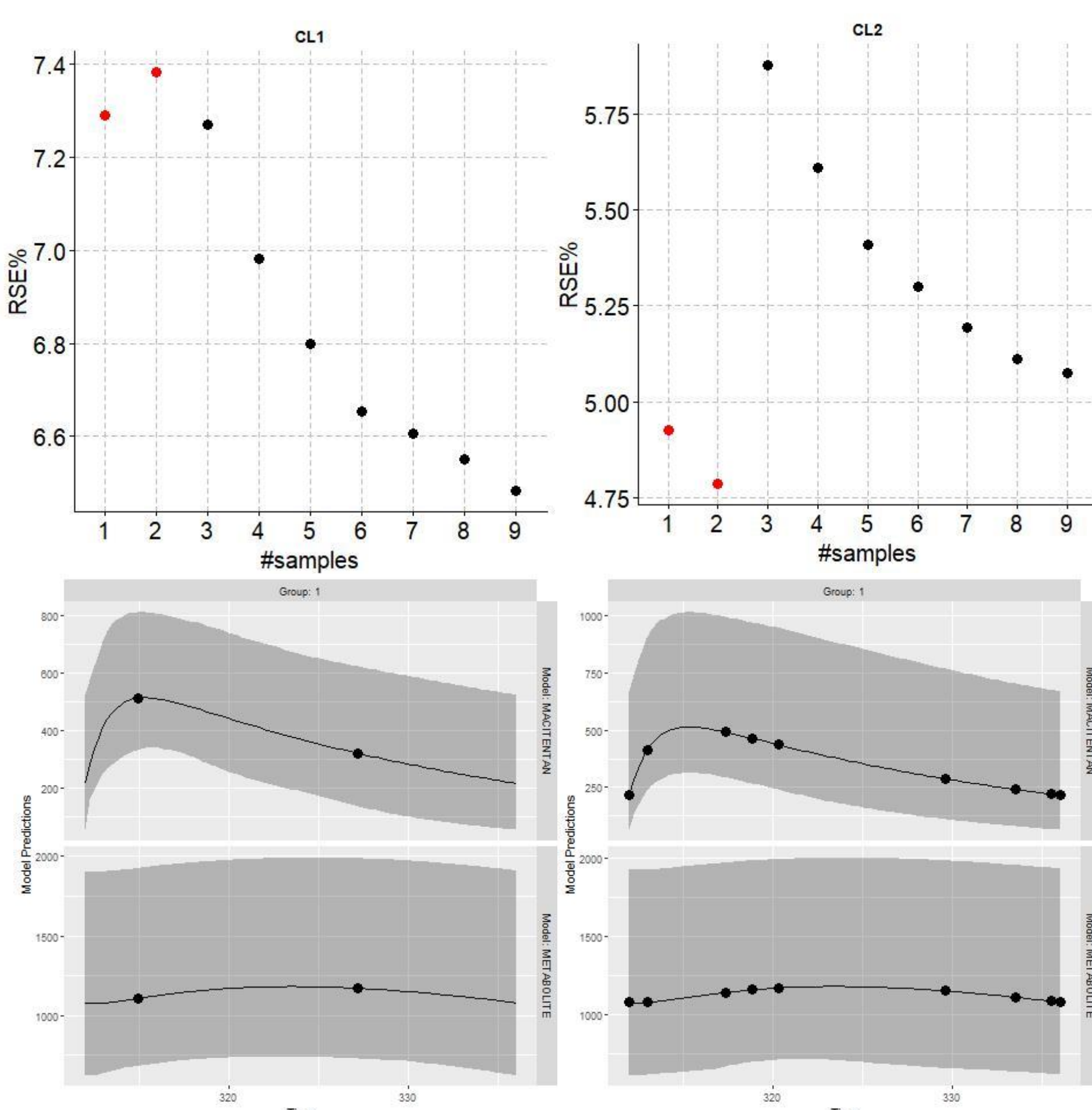
$$\vartheta_2 \text{ Important parameters}$$

$$FIM = \begin{bmatrix} FIM_{11} & FIM_{12} \\ FIM_{21} & FIM_{22} \end{bmatrix} \quad OFV = \max(\det(\frac{FIM}{FIM_{11}}))$$

- Each scenario was analysed first imposing the same schedule for both the molecules and then removing this constraint.
- To compare the scenarios, the Relative Standard Error (RSE%) was calculated for each parameter.

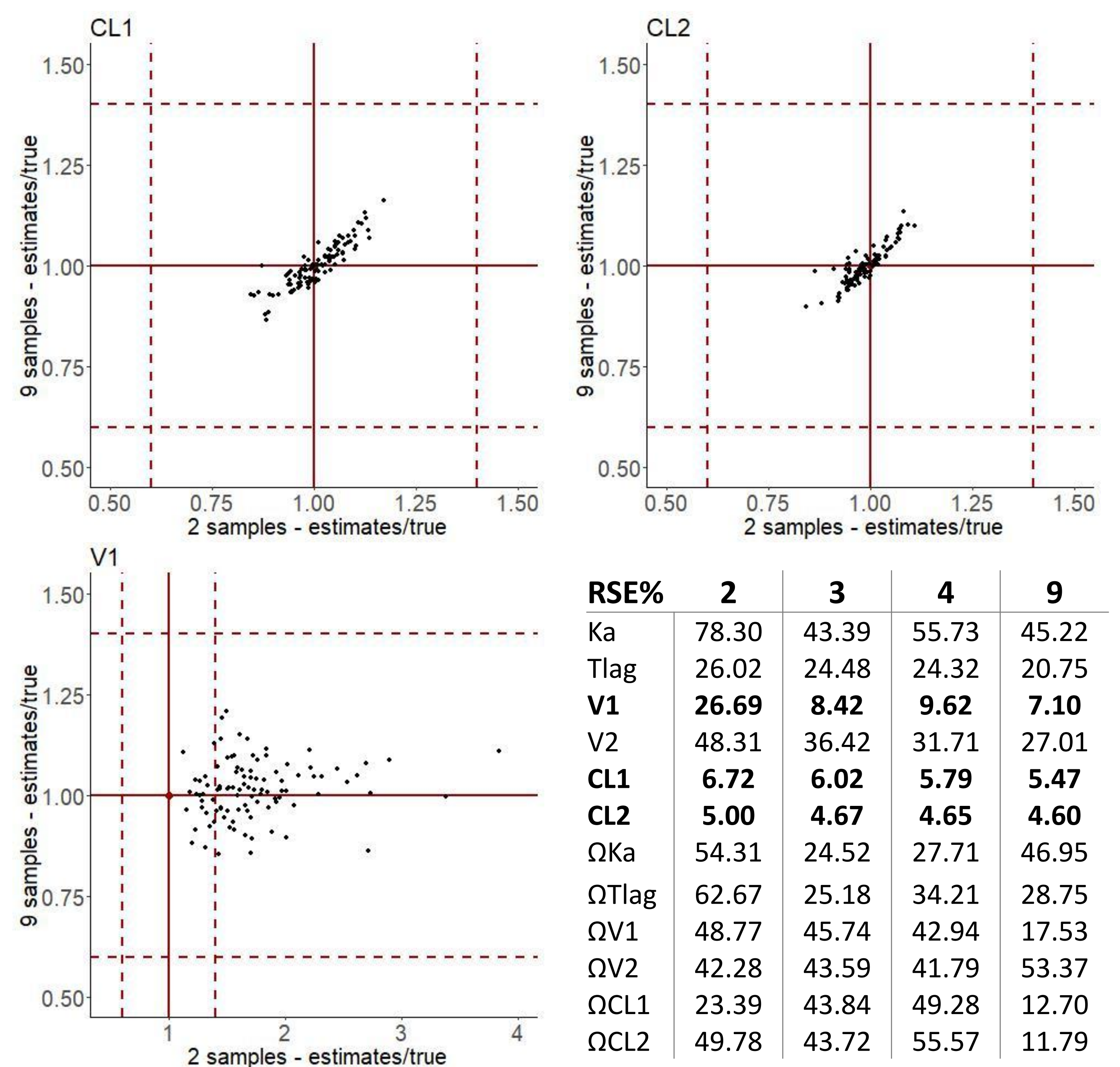
Comments:

- The showed results are referred to the scenarios with the same schedule for both the molecules;
- CL1, CL2 were selected as important parameters;
- with one and two samples PopED returned a warning (red dots);
- for all the scenarios, the estimated RSE% for CL1 and CL2 was lower than 8%;
- the optimal schedule for 2 and 9 samples is showed.



Parameter estimation

- A parameter estimation was performed with MonolixSuite2018R2 for the optimized designs of 2, 3, 4 and 9 samples, with the same schedule for both the molecules;
- 100 datasets were simulated using SimulX (package mlxR of R);
- the ratio between estimates and the true value of each parameter was calculated. A range of [0.6,1.4] was considered acceptable.



CONCLUSIONS: The optimization of the experimental protocol is an essential phase of the clinical studies, especially for paediatric populations. PopED is a useful tool to evaluate different designs, even if the user intervention remains essential to compare the results. In this work, an attempt to identify an optimal sampling schedule, with the minimum number of samples per patient, was made using PopED and testing the results in Monolix. Although these are preliminary results, they show that the Relative Standard Error of the parameter estimation is small in all the considered scenarios, especially for CL1 and CL2 – on which the sampling time optimization was performed. For some parameters, e.g. Ka and V2, is evident how the precision increases according to the number of samples. Therefore, the choice of the best number of samples per patient depends on which parameter is considered important for the trial.

REFERENCES: [1] M.G. George et Al. Pulmonary Hypertension Surveillance: United States, 2001 to 2010. Chest. 2014; 146(2): 476-495.

[2] F. Bellanti, O. Della Pasqua. Modelling and simulation as research tools in paediatric drug development. Eur J Clin Pharmacol. 2011; 67(1):75-86.

[3] A. Krause, J. Zisowsky, J. Dingemans. Modeling of pharmacokinetics, efficacy, and hemodynamic effects of macitentan in patients with pulmonary arterial hypertension. Pulm Pharmacol Ther. 2018; 49:140-146.