

Clinical Trial Simulation of a Phase I Paediatric Oncology Study using Simulo.



Quentin Leirens, Belén Valenzuela, Andreas Lindauer, Ruben Faelens, Per Olsson Gisleskog, Daniel Röshammar.
SGS Exprimio NV, Mechelen, Belgium.

Background

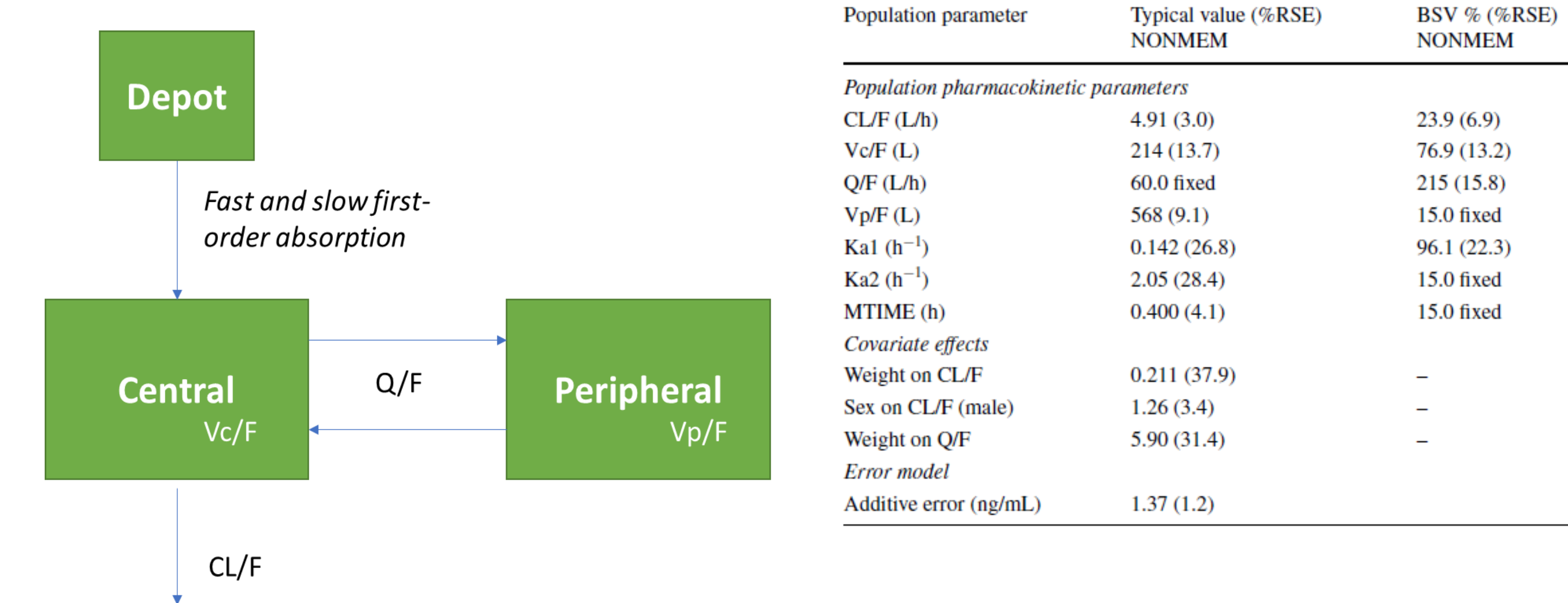
- The main challenge during oncology drug development in the paediatric population is to improve the clinical development process making it faster to have access to safer and more effective treatments.
- Regulatory agencies advocate the use of modelling and simulation of the available adult data to guide paediatric clinical trial designs.
- One of the most intuitive and user-friendly software for performing clinical trial simulations is Simulo [1].

Objectives

- To show Simulo’s capabilities for simulating a paediatric phase I oncology clinical trial with the aim to predict a dose level that likely provides a similar exposure range as in adults.
- For this illustrative clinical trial simulation example, we selected to predict the potential outcome of an ongoing study [2] with trametinib, a MEK inhibitor approved in adult population for the treatment of V600E or V600K BRAF mutation-positive melanoma.

Methods

- A previously developed population pharmacokinetic (PK) model for trametinib in adult patients [3] was implemented in Simulo.
- Simulations of the paediatric population were performed using the adult PK model, allometric scaling, and paediatric body weights sampled from the NHANES database.



- Figure 1.** Schematic and typical values of the adult PK model [3].
- In total, 18000 different paediatric patients were simulated: 3 dose levels (0.0125, 0.025, and 0.040 mg/kg) x 6 patients x 1000 virtual clinical trials.
 - The percentage of “successful” trials under each dose level was defined as the proportion of virtual trials with exposure related parameters ($AUC_{0-24,ss}$, $C_{min,ss}$, and $C_{max,ss}$) within the corresponding adult geometric mean value $\pm 20\%$ (ranges: 296 to 444 ng·h/mL for $AUC_{0-24,ss}$, 9.68 to 14.52 ng/mL for $C_{min,ss}$, and 17.76 to 26.64 ng/mL for $C_{max,ss}$).

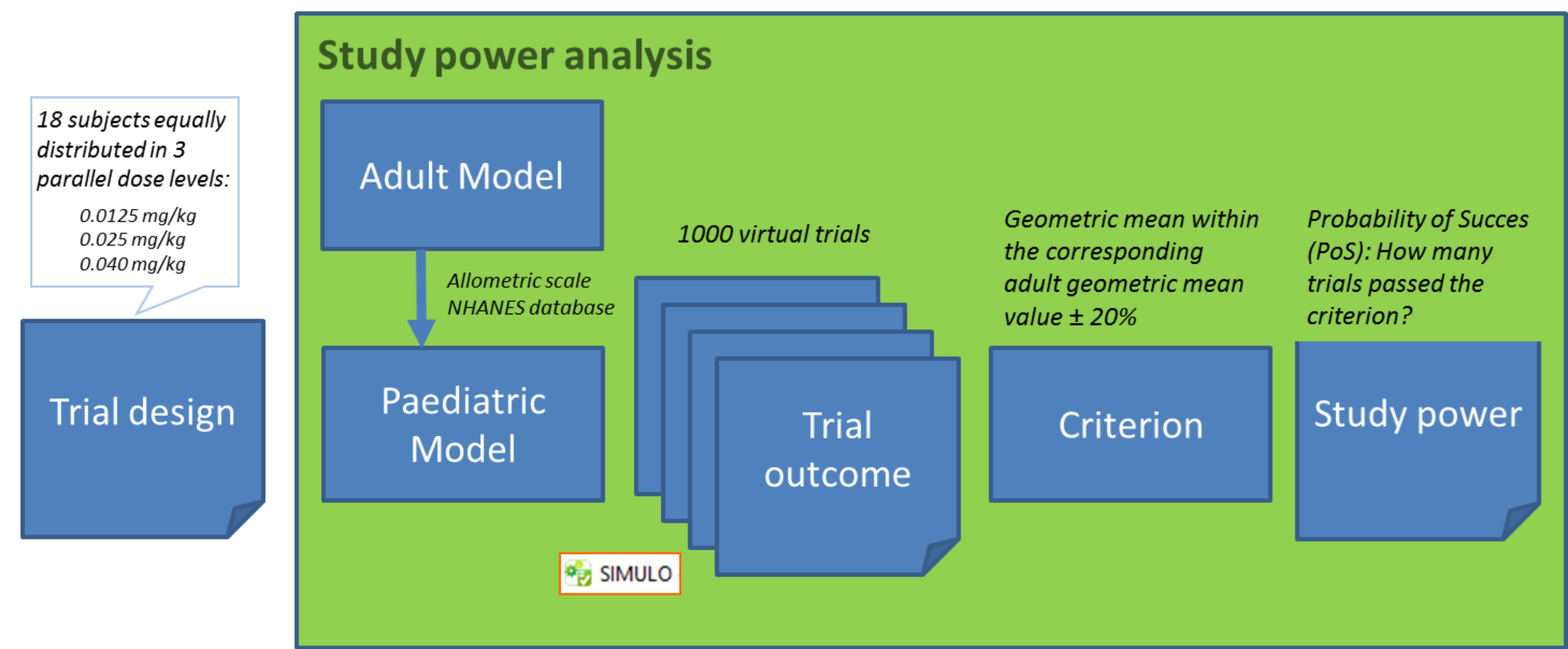


Figure 2. Simulation framework for the study power analysis. Simulo acts as a central component.

REFERENCES

[1] Leirens Q, Faelens R, Gisleskog PO, et al. PAGE 26 2017. Abstr 7331 [\[www.page-meeting.org/?abstract=7331\]](https://www.page-meeting.org/?abstract=7331).
[2] Study to investigate safety, pharmacokinetic (PK), pharmacodynamic (PD) and clinical activity of trametinib in subjects with cancer or plexiform neurofibromas and trametinib in combination with dabrafenib in subjects with cancers harboring V600 mutations. <https://clinicaltrials.gov/ct2/show/NCT02124772>.
[3] Ouellet D, Kassir N, Chiu J, et al. Population pharmacokinetics and exposure-response of trametinib, a MEK inhibitor, in patients with BRAF V600 mutation-positive melanoma. Cancer Chemother Pharmacol (2016) 77(4): 807-17.
[4] Infante, Jeffrey R et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase1 dose-escalation trial. The Lancet Oncology , Volume 13 , Issue 8 , 773 – 781.

Results

- The model is nicely structured in the Simulo interface.

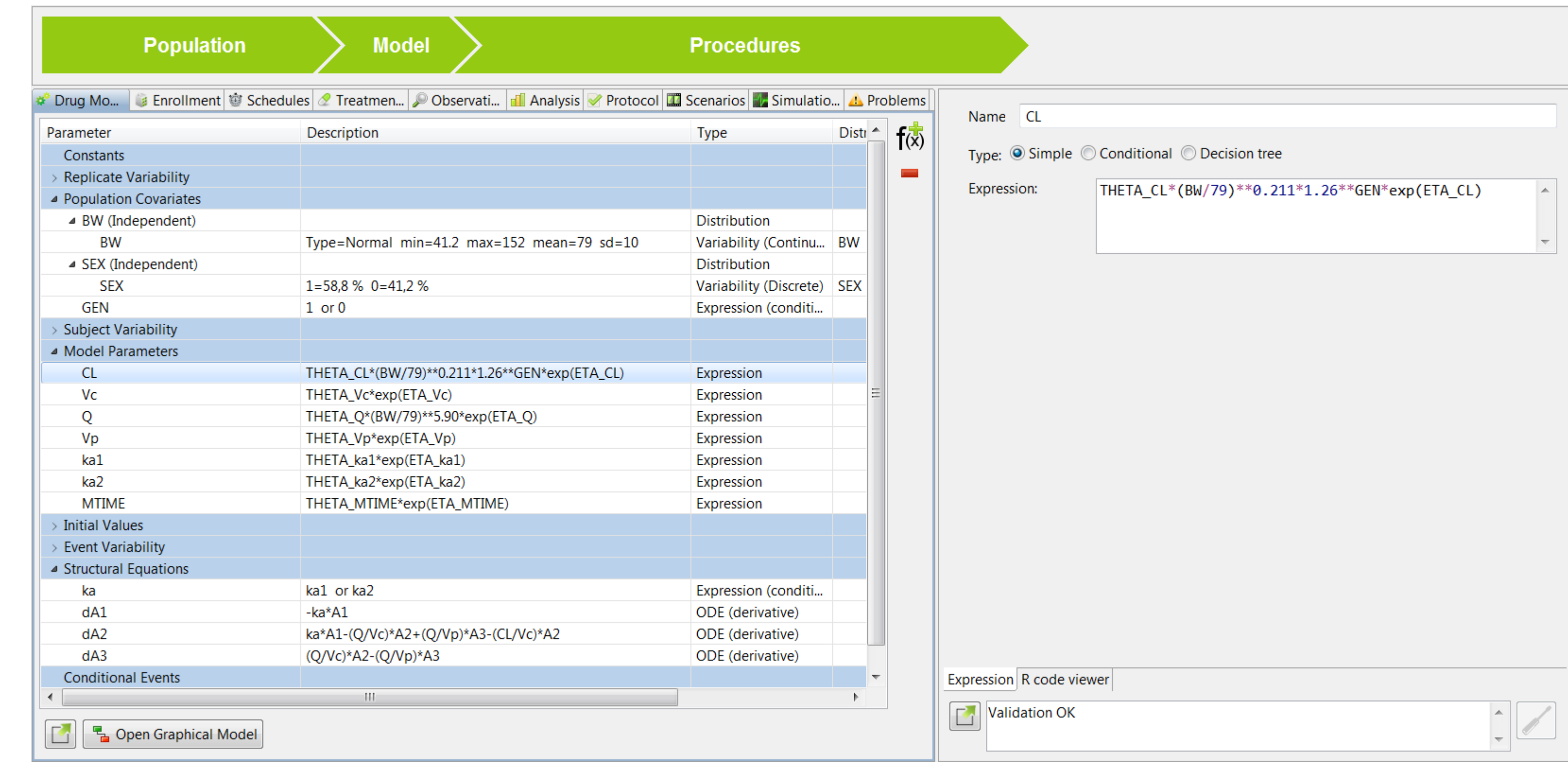
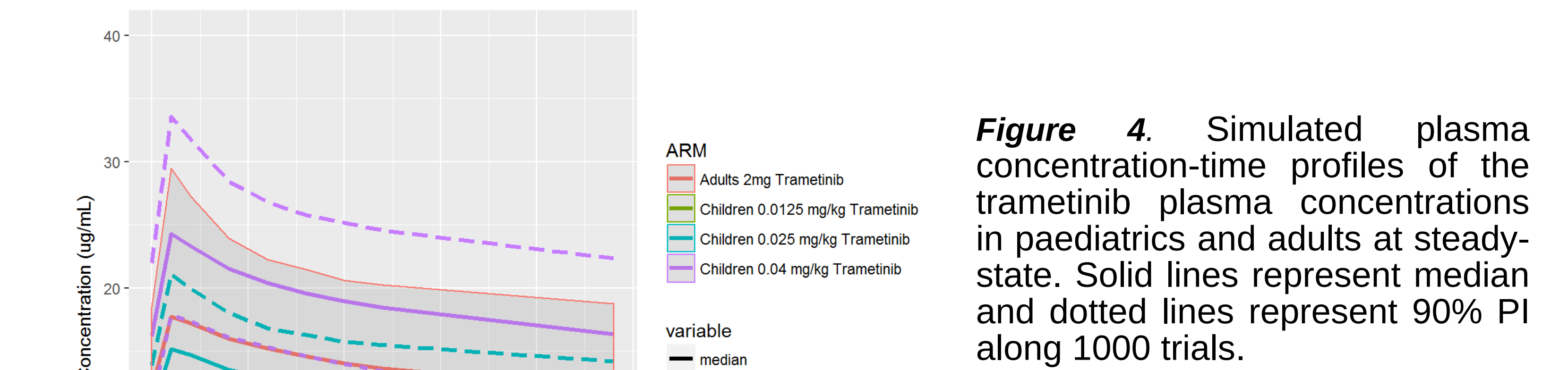


Figure 3. Screenshot of Simulo’s pharmacokinetic model and parameter definition window.

- PK paediatric profiles of each dose level can be compared with the adult one.



- Figure 4.** Simulated plasma concentration-time profiles of the trametinib plasma concentrations in paediatrics and adults at steady-state. Solid lines represent median and dotted lines represent 90% PI along 1000 trials.
- At the lowest dose of 0.0125 mg/kg, 100% of the simulated clinical trials were below the exposure targets for all three metrics.
 - With the intermediate dose level, 23% of the simulated clinical trials had a $C_{min,ss} \geq 10$ ng/mL (trough plasma concentration that has been found to be associated with progression free survival in an adult exposure-response analysis).
 - For the highest dose level (0.040 mg/kg), an $AUC_{0-24,ss}$ above the upper limit was found in 42% of virtual trials and more than 44% would have $C_{min,ss} \geq 14.52$ ng/mL.

	AUC			Cmax			Cmin		
	PoS (%)	Below (%)	Above (%)	PoS (%)	Below (%)	Above (%)	PoS (%)	Below (%)	Above (%)
0.0125 mg/kg Trametinib	0	100	0	0	100	0	0	100	0
0.025 mg/kg Trametinib	31.3	68.7	0	21.4	78.6	0	22.5	77.5	0
0.04 mg/kg Trametinib	58	0	42	81.3	0	18.7	54.5	1.3	44.2

Table 1. Study power analysis results using the criterion adult geometric mean value $\pm 20\%$. PoS: percentage of success.

- It can also look at a different criterion: how many of the 6 patients are within the 90% PI of the adult distribution of $AUC_{0-24,ss}$, $C_{max,ss}$ and $C_{min,ss}$ reference ranges, respectively.

	AUC	Cmax	Cmin
0.0125 mg/kg Trametinib	0%	0%	0%
0.025 mg/kg Trametinib	29.3%	30.7%	45.2%
0.04 mg/kg Trametinib	4.4%	16.1%	8.2%

	6/6	5/6	4/6
0.0125 mg/kg Trametinib	0%	0%	0%
0.025 mg/kg Trametinib	14.5%	30.5%	33.6%
0.04 mg/kg Trametinib	2%	9.7%	24.7%

Table 2. Study power analysis results using the criterion 6 out of 6 patients are within the 90% PI of the adult distribution of $AUC_{0-24,ss}$, $C_{max,ss}$ or $C_{min,ss}$

Table 3. Study power analysis results investigating how many of the 6 patients are within the 90% PI of all the 3 adult distributions of $AUC_{0-24,ss}$, $C_{max,ss}$ or $C_{min,ss}$

Conclusions

- Application of modelling and simulation using the previous knowledge from adult populations can help to explore different scenarios before enrolling paediatric patients into phase I clinical trials in order to avoid treatment with ineffective dose levels and to define the most convenient dose in a faster way.
- Other parameters like the number of children to be enrolled, different dosing strategies (flat dosing or tier-based dosing), can be also easily simulated using Simulo.