Clinical Trial Simulations in Paediatric Oncology: A Feasibility Study with Bosutinib in Paediatric CML

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Introduction

Paediatric dose finding studies are very difficult to perform due to ethical reasons, the limited number of available patients and the limitation in the number of blood withdrawals.(2) Phase I trials in paediatrics in general start with knowledge about the recommended phase II dose, safety and pharmacokinetics (PK) of the investigated drug in adults. In certain cases, the adult PK exposure can be used as target for dose finding in paediatrics.

Objective

Investigate the power of a paediatric phase I trial to show similar PK exposure as observed in adults

Methods

- Adult population PK parameters allometrically scaled to paediatric values.(2)
- Individual pediatric body weights, doses and PK curves simulated.
- Clinical trial simulation with proposed trial design.
  - 6 paediatric patients and 6 sample time-point: pre-dose, 1, 3, 6, 8 ,24 hours post-dose).
- Power = the fraction of 1000 trials with a geometric mean $AUC_{0-24,SS}$ within 2912 – 4368 h*ng/mL (±20% of the adult $AUC_{0-24,SS}$).
- Additional simulations to optimize the design of the paediatric trial.
- All simulations were performed with R (version 3.3.1, package deSolve).

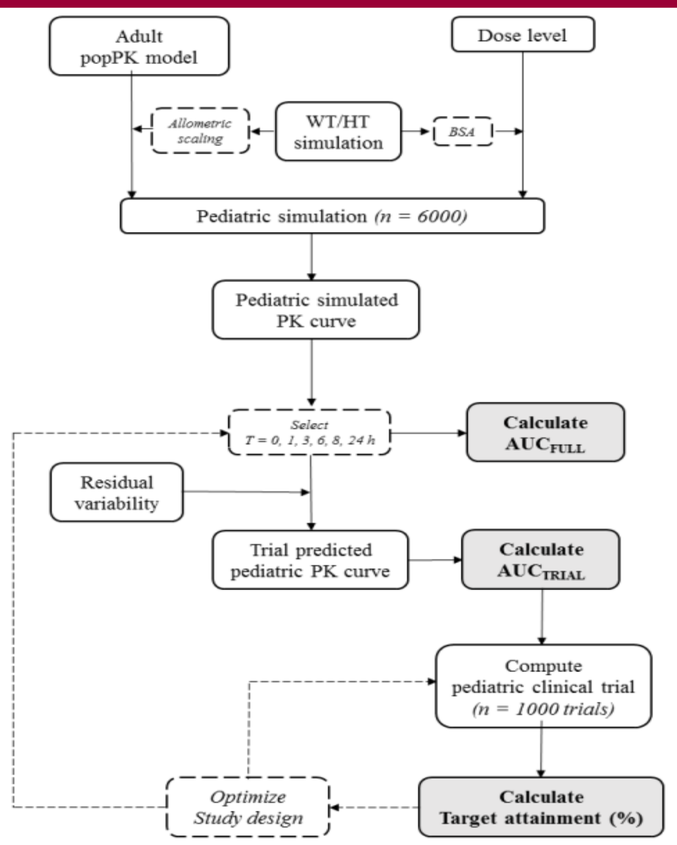

Fig 1. Flowchart representing the steps of the simulation method.

Results

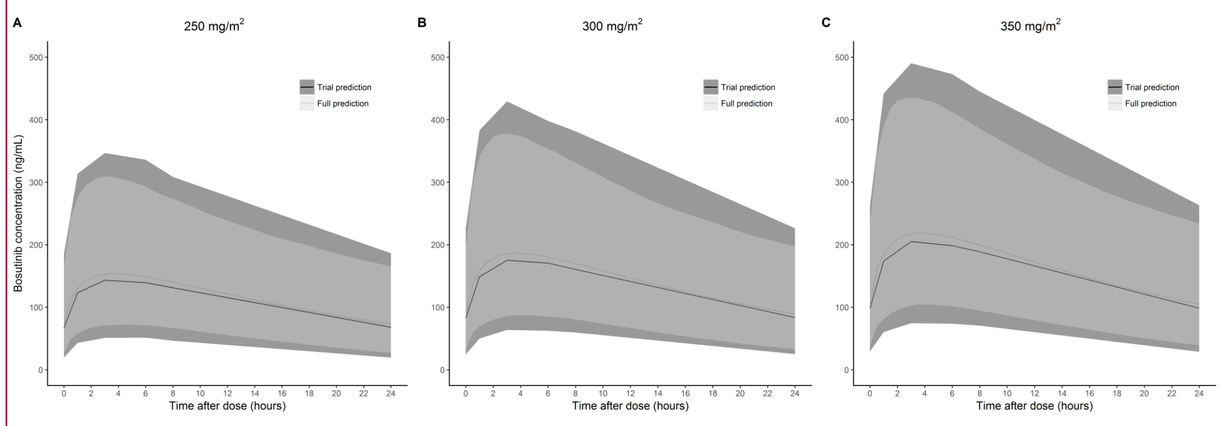

Fig 2. Predicted plasma concentration-time profile of bosutinib in paediatrics at steady-state. Solid lines represent the geometric mean concentrations; the shaded areas represent the 5th – 95th percentiles of the simulated concentrations (n=6000 per dose level).

- Increasing exposure with increasing dose.
- Large variability in plasma concentrations between patients, similar variability across the three dose levels.
- Under prediction of plasma concentration by sampling schedule.

Table 1. Predicted $AUC_{0-24,SS}$ and power of bosutinib in pediatrics.

	250 mg/m²	300 mg/m²	350 mg/m²
$AUC_{0-24,SS}$ (h*ng/mL)			
Full prediction (%CV)	2838 (44.4)	3442 (44.7)	4045 (43.6)
Trial prediction (%CV)	2719 (48.7)	3316 (48.9)	3894 (46.9)
Power (%)	34.8	66.9	65.3
Below target (%)	64.2	25.9	6.7
Above target (%)	1.0	7.2	28.0

- Addition of 1 sample to the sample schedule did not improve the power of the design.
  - Addition in absorption phase: power = 67.5%
  - Addition in elimination phase: power = 67.9%
- Removal of 1 sample did not worsen the power of the design.
  - Removal in absorption phase: power = 64.8%
  - Removal in elimination phase: power = 57.9%
- 10 patients per trial: power = 78.9%

Conclusion

- The power of a paediatric clinical trial can be predicted and optimized using the described simulation method.
- With this method, clinical trials in paediatrics can be performed as efficient as possible while protecting the child from unnecessary harm.

References

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Disclosure

None