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Clinical trial simulations in paediatric oncology: A feasibility study from the Innovative Therapies for Children with Cancer Consortium

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Abstract ***Introduction:*** Paediatric dose-finding studies are challenging to perform due to ethical reasons, the limited number of available patients and restricted number of blood samples. In certain cases, the adult pharmacokinetic (PK) exposure can be used as target for dose finding in paediatrics. The aim of this study was to investigate the performance of a paediatric phase I dose-finding clinical trial *in silico*.

Methods: Using an adult pharmacokinetic model, clinical trial simulations were performed to determine the power of a proposed clinical trial design. Power was defined as the fraction of 1000 trials with an area under the plasma concentration–time curve at steady-state ($AUC_{0\text{-}24,SS}$) within ±20% of the adult geometric mean $AUC_{0\text{-}24,SS}$. Different scenarios were compared to optimise the design of the trial. To show the potential of this framework for similar compounds, the current simulation method was also evaluated with adult and paediatric data from literature on sunitinib.

Results: At the starting dose of 300 mg/m^2, the power of the trial design was 66.9%. Power did not improve by dose escalation to 350 mg/m^2 (65.3%). Power increased to 78.9% with inclusion of 10 patients per trial. Paediatric sunitinib PK data were adequately predicted from adult

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data with a mean prediction error of 1.80%.
Conclusion: The performance of PK-based clinical trials in paediatrics can be predicted and optimised through PK modelling and simulation. Application of this approach enables clinical trials in paediatrics to be performed as efficiently as possible while protecting the child from unnecessary harm.

1. Introduction

The development of new anticancer drugs that are safe and effective in the paediatric population is of great importance [1]. The main aim of phase I trials is to define the safe and appropriate dose for subsequent evaluation of efficacy in further clinical trials [2]. The most important variables in the design of a paediatric phase I and pharmacokinetic trial are the starting dose, the number of required blood samples and a convenient sampling schedule [3].

It is widely accepted that pharmacokinetics (PK) as well as pharmacodynamics (PD) must play a more important role in early clinical trial design [4,5]. The International Conference on Harmonisation guideline E11 and the European Medicines Agency guideline, describing the role of PK in the development of medicinal products in the paediatric population, both emphasise on the use of adult data for modelling and simulation to guide paediatric clinical trial designs [6,7].

Predictions regarding the optimal number of samples, sampling time points and patient numbers in order to perform an efficient and successful clinical trial can be obtained by a modelling and simulation approach [8–10]. One of the advantages of paediatric drug development is that clinical trials in general start with extensive existing knowledge on clinical pharmacology of the drug in adults. This also means that different scenarios can be explored before enrolling paediatric patients into a clinical trial. With previously developed PK models the expected exposure and associated variability can be simulated. However, no phase I clinical trial simulations have been reported regarding paediatric oncology hitherto [11,12].

In paediatrics, chronic myelogenous leukaemia (CML) is a rare disease, accounting for about 3% of all paediatric malignancies, with an approximate annual incidence of 1 per million children. CML is a haematopoietic stem cell disease and is characterised by a constitutive activation of the breakpoint cluster region–Abelson leukaemia virus (BCR-ABL) fusion protein [13]. Bosutinib is a multitargeting tyrosine kinase inhibitor (TKI), which is active against BCR-ABL mutations [14]. To date, bosutinib has not been used in the treatment of paediatric CML. As bosutinib may represent an additional therapeutic option for paediatric CML, a phase I/II study was designed to evaluate bosutinib in children and adolescents as part of a Paediatric Investigational Plan (EudraCT number 2015-002916-34). The aim of the current study was to evaluate the paediatric phase I trial design *in silico*, which may also serve as a proof of concept for other trials in paediatric oncology. Therefore, the developed simulation framework was applied to existing adult and paediatric data for another TKI (sunitinib) to show the potential applicability of this approach.

2. Methods

An Innovative Therapies for Children with Cancer (ITCC) consortium's paediatric phase I/II clinical trial has been designed for dose finding of bosutinib administered orally in paediatric patients with CML. The previously observed exposure in adult CML patients treated with the approved dose of 500 mg bosutinib once daily (OD) served as a target for dose finding in children. The recommended phase II dose (RP2D) was defined in the protocol as the dose which results in a 24-h area under the plasma concentration–time curve at steady-state ($AUC_{0\text{-}24,SS}$) within ±20% of the geometric mean $AUC_{0\text{-}24,SS}$ that was found in adults (3640 h*ng/ml) and was considered safe (no dose-limiting toxicities (DLTs) in six patients or one DLT in ten patients) [15].

The protocol stated six time points for blood withdrawal: pre-dose and 1, 3, 6, 8 and 24 h post dose at day 14 after start of treatment (i.e. steady-state). Furthermore, three dose levels (250 mg/m^2, 300 mg/m^2 and 350 mg/m^2) were predefined, with 300 mg/m^2 (max. 500 mg) as the starting dose based on body surface area (BSA) scaling from the 500 mg adult dose. The design of the simulation study to evaluate this study design is depicted in Fig. 1.

2.1. Paediatric pharmacokinetic simulations

A population PK model has previously been developed using a pooled PK dataset from three clinical trials of adult patients with Philadelphia chromosome positive chronic phase (Ph + CP) CML and solid tumours treated with bosutinib by Hsyu *et al.* [15]. Paediatric bosutinib PK

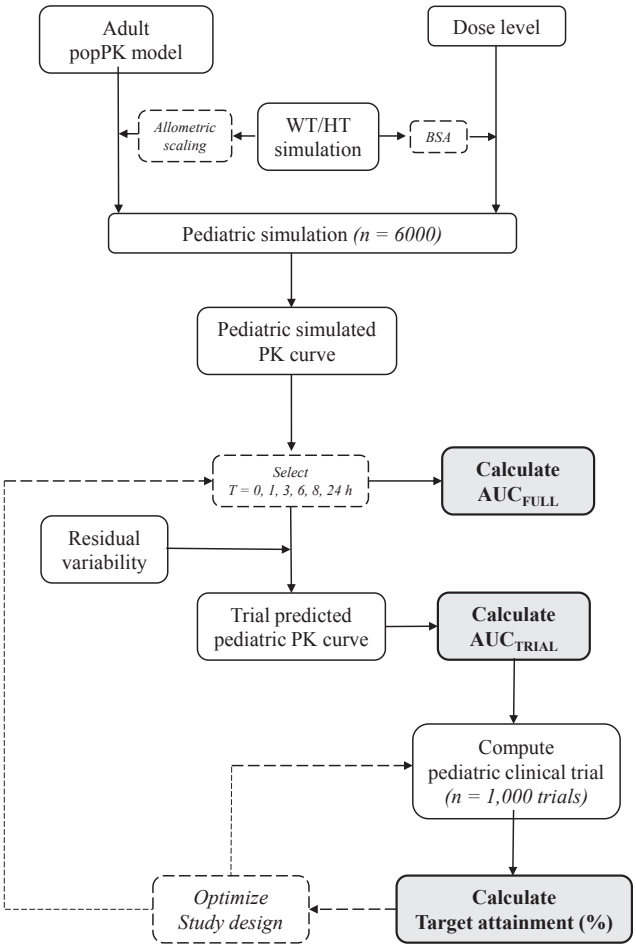

Fig. 1. Flowchart representing the steps of the simulation method.

parameters ($CL_{\text{pediatric}}$, $Q_{\text{pediatric}}$, $V1_{\text{pediatric}}$ and $V2_{\text{pediatric}}$) were described using an allometric model, with power coefficients of 0.75 for clearance parameters and 1.0 for distribution parameters (Equations (1)–(4)) [16,17].

$$CL_{paediatric} = CL_{adult} \times \left(\frac{BW}{70}\right)^{0.75} \times \exp\left(\eta_{i,BSV,CL}\right) \quad (1)$$

$$Q_{paediatric} = Q_{adult} \times \left(\frac{BW}{70}\right)^{0.75} \quad (2)$$

$$V1_{paediatric} = V1_{adult} \times \left(\frac{BW}{70}\right)^{1} \times \exp\left(\eta_{i,BSV,V1}\right) \quad (3)$$

$$V2_{paediatric} = V2_{adult} \times \left(\frac{BW}{70}\right)^{1} \times \exp\left(\eta_{i,BSV,V2}\right) \quad (4)$$

Where CL_{adult}, Q_{adult}, $V1_{\text{adult}}$ and $V2_{\text{adult}}$ are the parameter estimates in an adult with a body weight of 70 kg. BW is the simulated individual paediatric body weight and $\eta_{i,BSV}$ represents the between-subject variability (BSV), distributed following N $(0,\omega^2)$ per parameter. To generate individual values for the BSV for every parameter, stochastic simulations with random sampling from a multivariate distribution were performed [18]. The covariance matrix from the developed PK model was used to perform these simulations [15]. This stochastic simulation method was also applied for the simulation of a realistic body weight and height distribution, as suggested in literature [19]. A dataset with matching body weights and heights from a clinical trial with paediatric patients with acute lymphoblastic leukaemia (ALL) was available and used for this calculation (EudraCT number 2009-014037-25). With these simulated body weights and heights, the corresponding BSA was calculated per individual by the Mosteller formula, as indicated in the clinical trial protocol [20]. Subsequently, BSA-normalised doses were calculated. Doses that exceeded the maximum once-daily adult flat dose, i.e. 400 mg, 500 mg and 600 mg, respectively, were adjusted to the corresponding maximum adult dose.

2.2. Clinical trial simulations

A total dataset of 6000 different paediatric patients was simulated in order to generate 1000 virtual clinical trials, consisting of six paediatric patients per clinical trial. This was separately performed for the three- dose levels. With the input parameters, the full plasma concentration–time curve was simulated per patient steady-state after repeated oral dosing. For this PK curve, bosutinib plasma concentrations were simulated every 30 min during a 24-h dosing interval. Subsequently, the predicted trial PK curve was generated by selecting the concentrations at the proposed trial sample time points. These simulated concentrations were transformed to predicted observations at these time points taking the combined proportional and additive residual error model from the previously described bosutinib PK model into account, again by stochastic simulation from a multivariate normal distribution [15]. The $AUC_{0\text{-}24,SS}$ was calculated by non-compartmental analysis from each individual's simulated full PK profile and predicted trial PK profile, according to the clinical trial protocol. The maximum concentration at steady-state ($C_{max,SS}$) was determined as the highest concentration during the dose interval.

The power of the clinical trial design was defined as the fraction of 1000 clinical trials, consisting of six paediatric patients each, with a geometric mean $AUC_{0\text{-}24,SS}$ within the target range of 2912–4368 h*ng/ml (±20% of the adult geometric mean $AUC_{0\text{-}24,SS}$). Subsequently, simulations were performed to optimise the clinical trial design in order to improve the power of the clinical study design. Adjusted sampling schedules and a different number of patients per simulated

trial were tested. For the simulation with ten patients per clinical trial, a total of 10,000 paediatric patients was simulated.

2.3. External evaluation

The simulation framework was also evaluated using an adult PK model and paediatric PK data of the anti-cancer drug sunitinib derived from literature [21,22]. In this paediatric phase I trial, eight patients were treated with 15 mg/m^{2}sunitinib once daily. Pediatric predicted AUCs from zero to 48 h ($AUC_{0\text{-}48}$) were calculated and compared with the reported phase I results.

Bias was described by the mean prediction error (MPE%) which was calculated for the paediatric predicted trial sunitinib $AUC_{0\text{-}48}$ versus sunitinib $AUC_{0\text{-}48}$ observed in the paediatric phase I trial, as depicted by Equation (5) [23].

$$MPE\% = \left(\frac{(AUC_{est} - AUC_{obs})}{AUC_{obs}}\right) \times 100\% \quad (5)$$

Where AUC_{obs} is the observed sunitinib $AUC_{0\text{-}48}$ and AUC_{est} is the predicted trial sunitinib $AUC_{0\text{-}48}$.

2.4. Software

All PK simulations and calculations were performed with R (version 3.3.1), using the differential equation-solving R-package deSolve [24].

3. Results

3.1. Paediatric pharmacokinetic simulations

The simulated PK profiles for the three dose levels are depicted in Fig. 2. With increasing dose, the $C_{max,SS}$ and exposure increased as expected (Table 1). Large variability in $C_{max,SS}$ and $AUC_{0\text{-}24,SS}$ between patients was observed, this variability was similar across the three dose levels. In addition, Fig. 3 shows the uniformity of the AUCs across the paediatric body weight ranges.

3.2. Clinical trial simulations

Table 1 summarises the results of the clinical trial simulations. At the starting dose of 300 mg/m^2, the power to show target attainment was 66.9%, 25.9% of the trials showed an exposure below and 7.2% above the target range (Table 1). The mean exposure on this dose level was predicted to be slightly lower than the mean exposure in adults (3442 h*ng/mlversus 3640 h*ng/ml). However, the next higher protocol- defined dose level showed a slightly higher exposure than with the adult standard dose (4045 h*ng/mlversus 3640 h*ng/ml) and, consequently, the power of this dose level was similar (65.3% with 28.0% of trials below and 6.7% above the

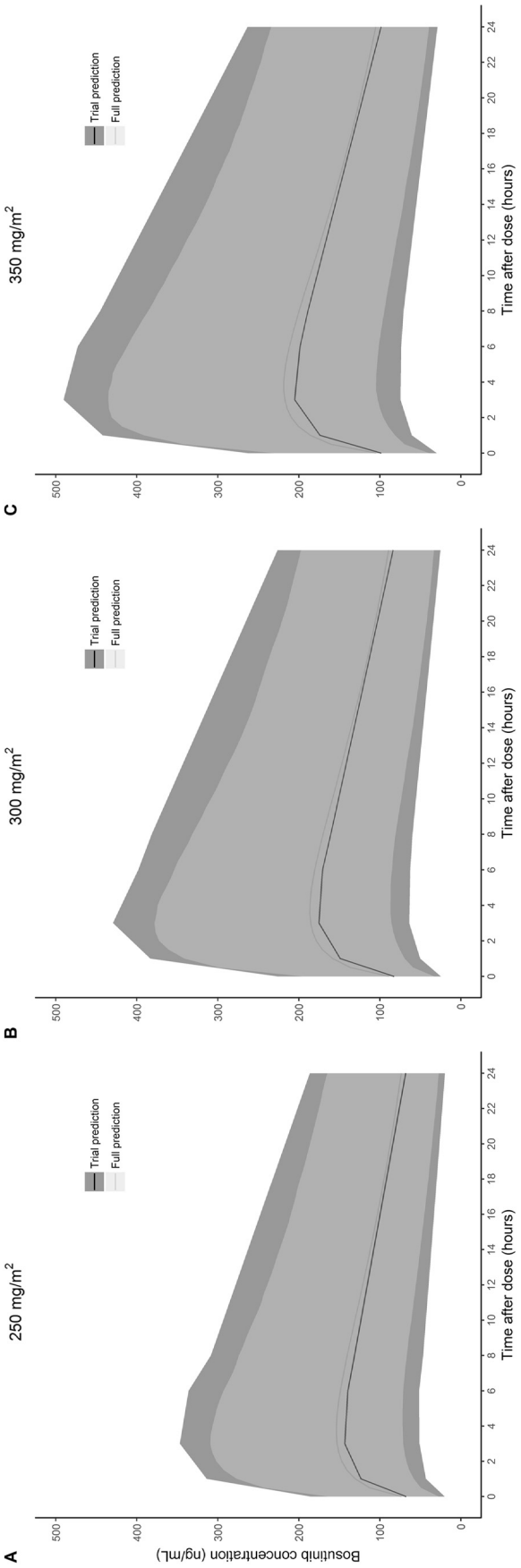

Fig. 2. **Simulated plasma concentration–time profile of the bosutinib concentrations in paediatrics at steady-state.** The different panels represent the three dose levels. Solid lines represent the geometric mean concentrations; the shaded areas represent the 5th–95th percentiles of the simulated concentrations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

Table 1
$AUC_{0\text{-}24,SS}$, $C_{max,SS}$ and target attainment of bosutinib in paediatrics.

	250 mg/m^2	300 mg/m^2	350 mg/m^2
$C_{max,SS}$ (ng/ml)[a]			
Full prediction	159.7 (45.18)	193.7 (44.77)	227.4 (43.70)
Trial prediction	192.9 (48.33)	234.6 (49.11)	274.7 (47.01)
$AUC_{0\text{-}24,SS}$ (h*ng/ml)[a]			
Full prediction	2838 (44.37)	3442 (44.68)	4045 (43.57)
Trial prediction	2719 (48.65)	3316 (48.92)	3894 (46.99)
Power n = 6 (%)[b]			
Successful trials	34.8	66.9	65.3
Below target	64.2	25.9	6.7
Above target	1.0	7.2	28.0
Power n = 10 (%)[b]			
Successful trials	33.9	78.9	75.3
Below target	66.1	17.9	2.5
Above target	0	3.2	22.2

[a] $C_{max,SS}$ Maximum concentration; $AUC_{0\text{-}24,SS}$ 24-h area under the plasma concentration–time curve. Geometric mean and coefficient of variation (CV%) of n = 6000 simulated patients per dose.

[b] Percentage successful trials out of 1000 trials consisting of 6–10 patients based on the $AUC_{0\text{-}24,SS}$ target interval (±20% of 3640 h*ng/ml) by the different dose levels and percentage of trials with an $AUC_{0\text{-}24,SS}$ below or above the target range.

target range). As expected, the protocol-defined dose level of 250 mg/m^2 once daily shows a considerably lower power (34.8%), due to underexposure.

3.3. Study design optimisation

Based on these simulation results, the dose that best approached the target $AUC_{0\text{-}24,SS}$ with the proposed clinical trial design was calculated as 325 mg/m^2. The power with this intermediate dose level was 70.4%. Subsequently, different sampling designs with more or less samples and different time points were tested at this intermediate dose level (Table 2). The sampling schedules with more sample points during 24 h showed similar power compared to each other and to the original trial design (schedule I versus IV and V). With the addition of one sample point in the absorption phase the power was 72.3%, addition of a sample point in the elimination phase resulted in a power of 71.2%. Likewise, fewer samples and samples collected at different time points only marginally reduced power (70.4% versus 72.0% and 67.1%, schedule I versus II and VI). Removal of the blood sample at 8 h post dose resulted in similar power compared to the original sample schedule (70.4% versus 69.4%, schedule I versus III).The different sample schedules were also applied to the proposed clinical trial starting dose (i.e. 300 mg/m^2) with similar results. Increasing the number of patients to ten patients per trial resulted in an increased power of 81.1% with the intermediate dose and a power of 78.9% with the proposed starting dose.

3.4. External evaluation

Simulation of the paediatric $AUC_{0\text{-}48}$ of sunitinib showed that the predictions were in good agreement with the observed values in the paediatric phase I trial (Fig. 4). The median predicted trial $AUC_{0\text{-}48}$ was 500.8 h*ng/ml (range 210.5–671.2 h*ng/ml) and the corresponding observed median $AUC_{0\text{-}48}$ in the paediatric clinical trial was 492.0 (range 247–1111) [22]. The bias between the predicted trial $AUC_{0\text{-}48}$ and observed $AUC_{0\text{-}48}$ (MPE%) was 1.80%.

4. Discussion

Paediatric dose-finding studies of targeted agents are very difficult to perform. First, for ethical reasons, the number of patients treated at low doses should be minimal to prevent undertreatment. Second, the number of patients fulfilling the inclusion and exclusion criteria is usually low because of the rarity of malignancies in paediatric patients. Third, the number of blood samples to be collected should be as low as reasonably possible [4,25,26]. A thorough *a priori* evaluation of a proposed trial design could aid in the optimisation of the design. We successfully performed an *in silico* evaluation of a proposed trial design for a dose-finding study of bosutinib in paediatric patients with CML.

It has been extensively advocated in literature that PK should be better integrated in paediatric drug development [6,7,27]. Paoletti *et al.* found that the paediatric RP2D ranged between 90% and 130% of the BSA-adjusted approved dose in adults for 70% of 25 paediatric phase I trials that investigated molecularly targeted agents [5]. In addition, 63% of the patients did not receive an optimal dose. Suggesting early-phase clinical trials validating PK, PD and efficacy findings from adults while controlling for toxicity appears to be an alternative to accelerate drug development in paediatric oncology. However, PK characteristics of a drug may differ between age groups due to the heterogeneity of many anatomical and physiological maturation processes, in particular in young children [28]. It is essential that these changes are considered to ensure appropriate trial rationales and dosing schedules among all age ranges.

Population pharmacokinetic model-based simulations were performed to determine an optimal clinical trial design based on the likelihood of achieving an *a priori* established PK target. As this paediatric phase I trial is the first paediatric trial for bosutinib, no information regarding the exposure–efficacy relationship in paediatric patients with CML was available. Thus, the geometric mean $AUC_{0\text{-}24,SS}$ observed in adult patients was chosen as paediatric PK target for the

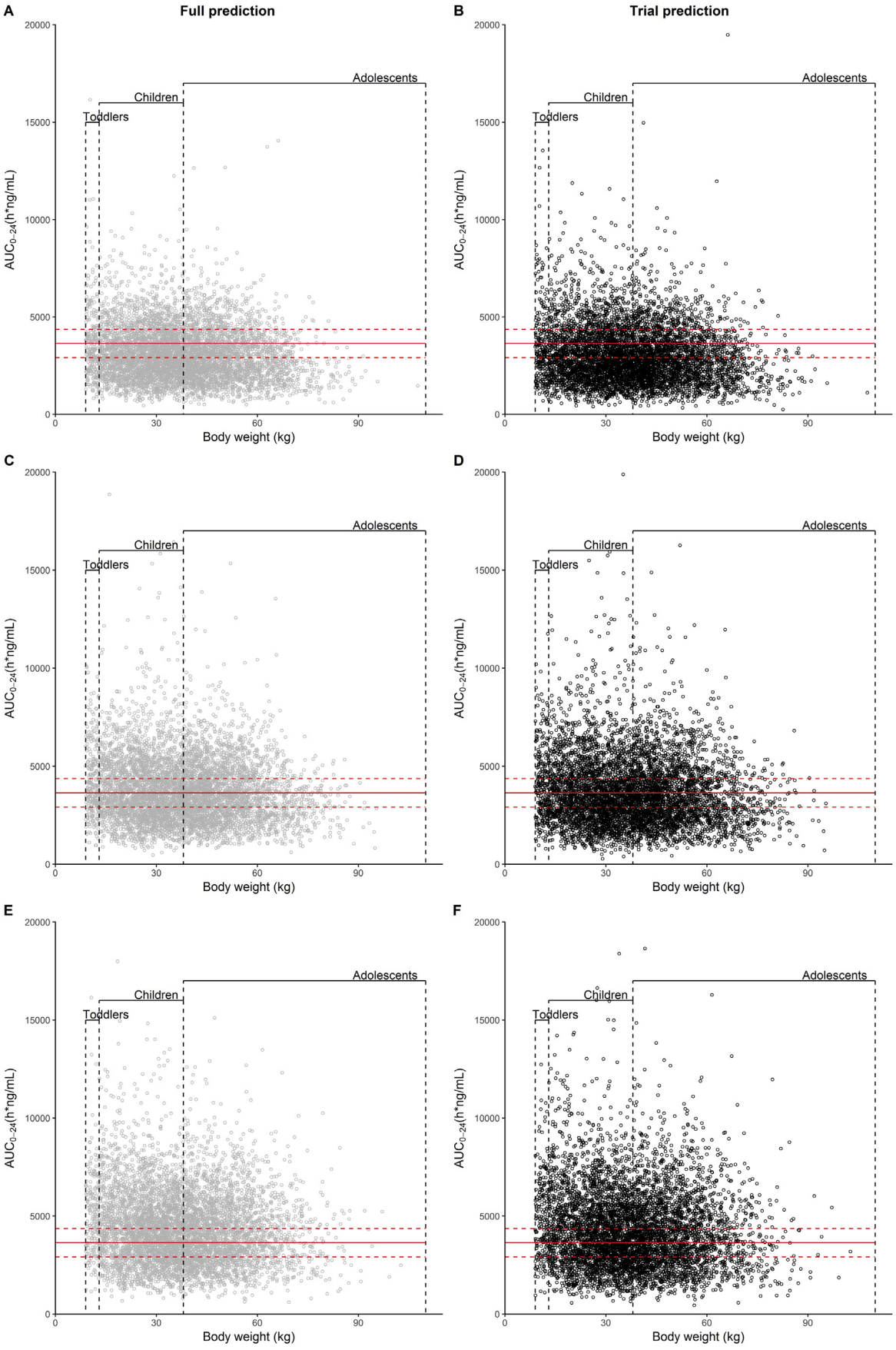

Fig. 3. **Distribution of the simulated paediatric $AUC_{0\text{-}24,SS}$ versus body weight for the three different dose levels (n = 6000 per dose level)**. Panel A and B represent dose level 250 mg/m^2, panel C and D represent dose level 300 mg/m^2 and panel E and F represent dose level 350 mg/m^2. Expected body weight ranges for infants, preschool children, children and adolescents are indicated. The red dashed lines represent the $AUC_{0\text{-}24,SS}$ target area and the red solid line represents the adult geometric mean $AUC_{0\text{-}24,SS}$ in patients with CML. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 2
Predicted trial $AUC_{0\text{-}24,SS}$ and target attainment for alternative sampling scenarios.

	I[c]	II[d]	III[e]	IV[f]	V[g]	VI[h]	VII[i]
325 mg/m²							
Predicted trial $AUC_{0\text{-}24,SS}$[a]	3605	3540	3551	3621	3641	3384	3610
Power (%)[b]	70.4	72.0	69.4	72.3	71.2	67.1	81.1
300 mg/m²							
Predicted trial $AUC_{0\text{-}24,SS}$[a]	3316	3220	3250	3312	3337	3107	3340
Power (%)[b]	66.9	61.2	64.8	67.5	67.7	57.9	78.9

$AUC_{0\text{-}24,SS}$, 24-h area under the plasma concentration–time curve (h*ng/ml).
[a] Geometric mean.
[b] Percentage successful trials based on the $AUC_{0\text{-}24,SS}$ target interval (±20% of 3640 h*ng/ml).
[c] Sample at T = 0, T = 1, T = 3, T = 6, T = 8, T = 24 h after dose (original sample schedule).
[d] Sample at T = 0, T = 1, T = 2, T = 5, T = 24 h after dose.
[e] Sample at T = 0, T = 1, T = 3, T = 6, T = 24 h after dose.
[f] Sample at T = 0, T = 1, T = 2, T = 3, T = 6, T = 8, T = 24 h after dose.
[g] Sample at T = 0, T = 1, T = 3, T = 6, T = 8, T = 12, T = 24 h after dose.
[h] Sample at T = 0, T = 1, T = 3, T = 12, T = 24 h after dose.
[i] Ten patients per trial with original sample schedule.

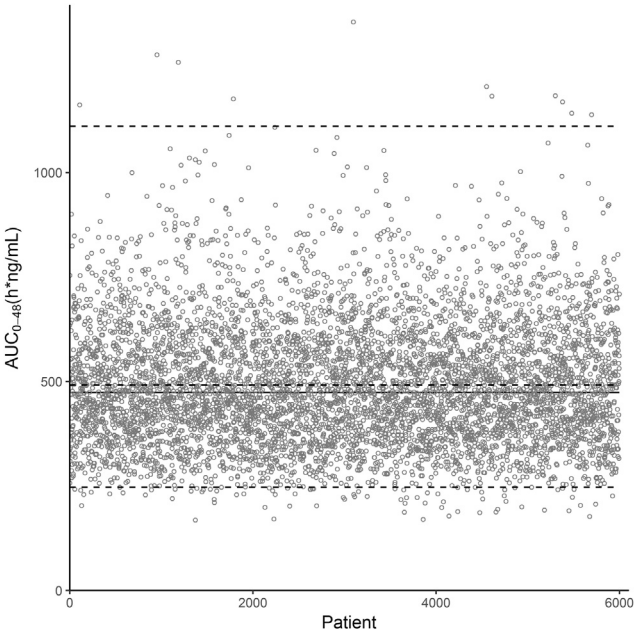

Fig. 4. **Distribution of the predicted trial sunitinib paediatric $AUC_{0\text{-}48}$.** The dashed lines represent the range and median $AUC_{0\text{-}48}$ observed in paediatric patients and the solid line represents the paediatric median predicted trial $AUC_{0\text{-}48}$ (n = 6000).

clinical trial in this simulation study. The simulated full $AUC_{0\text{-}24,SS}$ values were higher than the predicted trial $AUC_{0\text{-}24,SS}$ at the three dose levels, which means that the true exposure is underestimated by the proposed sampling schedule. This can be explained by the use of non-compartmental method for calculation of the AUC. The power increased with increasing dose, with exception of the highest dose level. The power did not improve substantially with lessor more samples or adapted sampling times. With carefully chosen sampling times, the power remained the same when only five sample time points were included instead of the original 6 time points. The clinical trial simulation consisting of ten paediatric patients per trial showed an increased power of 81.1%. This is a plausible scenario since the trial will be extended to ten patients if one DLT is observed in the first 6 patients. To assess whether the clinical trial simulation produces meaningful results, we also performed this simulation on a published dataset of sunitinib in adults and children. Results of this simulation showed that the PK of sunitinib in children could be adequately predicted on a population level from a PK model based on adult data only.

To date, only few studies have been published in the setting of paediatric clinical trial simulation that included PK. Mouksassi *et al.* presented a clinical trial simulation method in paediatric patients using an adult population PK model [29]. The scaled adult model included a maturation function of the glomerular filtration rate in addition to allometric scaling. Bosutinib is mainly metabolised by CYP3A isoenzymes into inactive metabolites [14]. The maturation of cytochrome P450 3A4 (CYP3A4) is assumed to be complete at 1 year of age [30,31]. A maturation factor for CYP3A was not considered for this simulation because the clinical trial only includes patients older than 1 year of age. Moreover, CML is extremely rare in younger children and it is expected that the majority of included children will be even >10 years of age. Stockmann *et al.* and Reif *et al.* provide a usable method to design a paediatric clinical trial in a large group of paediatric patients based on adequate statistical power [32,33]. Translation of this clinical trial simulation method to paediatric oncology is not applicable because of the rarity of malignancies in paediatrics.

In conclusion, a simulation method has been developed for the prediction of bosutinib PK in paediatrics. Simulations revealed that the power of a clinical trial design can be predicted and optimised for various clinical trial designs. The developed simulation method will be further validated as part of the pharmacometric analysis of the bosutinib paediatric clinical trial.

Conflict of interest statement

None declared.

Sources of support

None.

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