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Does size matter? : bridging and dose selection in paediatric trials

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Randomised Concentration-Controlled Trials (RCCT) in paediatric development: dealing with heterogeneity and uncertainty in pharmacokinetic trials in children

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Abstract

In paediatric pharmacology, differences in treatment response may be influenced by the effect of developmental changes and maturation on drug disposition. This leads to ambiguous relationships between dose and exposure, and therefore the choice of the appropriate dose range remains a challenge. The objective of this investigation was to assess whether an adaptive design in early clinical trials based on the paradigm variable dosing - controlled exposure can provide better dosing recommendations compared to the standard fixed dose approach. Adult AUC_{0-12} was deemed as effective exposure. In a clinical trial simulation (CTS) setting, a paediatric study ($n=128$) was simulated for abacavir. Plasma

concentrations following the current recommended dose (8 mg/kg) were taken at standard sampling times. The data were fitted with a one-compartment model that included the effect of weight on clearance and volume of distribution. Following this first dose, exposures to abacavir were calculated and doses individually adapted to reach the target exposures. A second round of simulations followed with the adapted doses and the resulting concentrations were fitted again with the same model. Exposure distributions in both condition (fixed dose and exposure-controlled) were compared, and the same was done for PK parameter estimates. Adaptive randomisation can be used to optimise dosing regimens in early paediatric research. The randomisation of patients to exposures rather than dose increases the probability of demonstrating efficacy (i.e., study power) as compared to dose-controlled trials. Furthermore, it contributes to further understanding of the role of dose on the total heterogeneity in clinical response.

8.1 Introduction

THE EFFICACY OF A PHARMACOLOGICAL TREATMENT is usually described by a function that relates the effect with the dose. However, drug concentration or exposure (e.g., AUC) are known to be better descriptors of the pharmacological effect. Yet, fixed dose protocols are considered best practice in the assessment of efficacy in clinical trials, which often results in (an unnecessarily) large variability in response. This issue is particularly important in paediatric pharmacology, where differences in treatment response may be influenced by the effect of developmental changes and maturation on drug disposition, which lead to ambiguous relationships between dose and exposure. Consequently, such uncertainty renders difficult the selection of the appropriate dose range. This issue is compounded by the lack of a widely accepted methodology for the rationale for the starting dose in a paediatric trial, given that dose escalation studies are not accepted or desirable in children. From a drug development point of view, these two points represent a major challenge for the design of a clinical study and to the interpretation of the results. Although the assessment of pharmacokinetics in children has been performed in an empirical manner and often disconnected from efficacy measurements, it should be clear that the interpretation of efficacy and safety findings may be inconclusive without pharmacokinetic data. For instance, the potential causes for the lack of efficacy or adverse events in a trial cannot be accurately explained in the absence of pharmacokinetic data. In other words, one cannot explain whether findings are due to pharmacodynamic factors (e.g., drug-target interaction) or simply because the administered amount was too low or too high.

Traditionally, drugs started to be used in children long before formal paediatric clinical studies were performed and evidence for the dose rationale had been derived from well-designed, controlled clinical trials. Paediatricians were somehow obliged (and to some extent still are) to use drugs in children in an off-label manner, extrapolating the dose from the adult regimen or simply adjusting it according to differences in body weight, age or body surface area. Despite the concerns regarding

the potential implications of such practice, no formal dose finding studies have been performed for a considerable number of drugs currently used in paediatric clinical practice. Unfortunately, one should realise that for the majority of the cases, the doses proposed in early clinical development propagate into clinical practice, irrespective of consensus about the appropriate dosing recommendation [1].

Both regulatory agencies and clinical pharmacologists recommend the use of model-based approaches for the characterisation of pharmacokinetics in children [2–6]. In a recent publication, we have emphasised the importance of a model-based approach to identify the correct dosing regimen in a paediatric population during early clinical development, especially if pharmacokinetic bridging concepts can be applied [7]. However, we have also shown that limitations exist in the approach when extrapolations are required from one population to another. Our findings make evident that parameter distributions or parameter-covariate correlations cannot be assumed comparable across age groups [8]. Such limitation imposes careful consideration about how to tackle dose selection during drug development when patient population may be staggered according to age groups and an initial estimation of the paediatric dose must be obtained by extrapolation.

Based on the aforementioned, we can therefore state that a model-based approach for the assessment of pharmacokinetics in children is necessary but not sufficient. The use of a parametric approach, whether mechanistic or not, must consider that parameter estimation uncertainty is accompanied by or coupled to model uncertainty and eventual misspecification. In these circumstances, the learning-confirming paradigm proposed by Sheiner becomes essential [9]. These concepts must be reflected on the experimental design used to support the estimation of the parameters of interest. In brief, it must be clear that uncertainty plays as an important role as heterogeneity. These two factors are interrelated and cannot be addressed by rigid experimental designs.

Here we propose the introduction of a randomised concentration-controlled trial (RCCT) design as framework for the implementation of experimental protocols in early clinical development. Using abacavir, a powerful nucleoside analog reverse transcriptase inhibitor [10] as a paradigm compound, we illustrate the principles of RCCT based on a comprehensive simulation exercise that takes into account uncertainty in parameter distributions. An adaptive design is proposed that makes use of a pharmacokinetic model built using sparse paediatric and dense adult data. This scenario reflects the situation where a formal trial is performed after the drug has been clinically used in children in an off-label manner, and therefore some paediatric pharmacokinetic data are already available to support model building.

In contrast to a randomised dose controlled trial (RDCT), where patients are randomly assigned to a predefined fixed dose, in a RCCT patients are randomly assigned to a predefined drug exposure range or value. During the study, each patient's dose is adjusted so as to bring drug exposure to the pre-specified randomisation range or value. This adjustment is normally made using an algorithm, the complexity of which may depend on the compound being studied, the population and the objectives of the study [11]. The main difference between RDCT and RCCT is that the nominal dose is allowed to vary. Despite the lack of consensus about

the advantages of RCCT over the RDCT in terms of precision and bias reduction in parameter estimates [12, 13], Monte Carlo simulations suggest that the RCCT is more efficient (in terms of sample size) than the more traditional dose-controlled trials, yielding higher statistical power [14]. If well-designed, this procedure allows one to control different source of variability in drug absorption, distribution and elimination. These features represent an appealing option for paediatric clinical trials, given the limited availability of patients for clinical trials. Unfortunately, the main criticism on the use the approach is often related to the increased workload these protocols require compared to the standard designs [15, 16].

8.2 Methods

Rationale for the target exposure

In a bridging exercise, the objective is to ensure comparable exposure between the reference and target populations. For abacavir, effective levels as expressed by the area under the concentration *vs.* time curve (AUC) are considered to be the most suitable measure of exposure. In adults, the median exposure observed showing efficacy is 6.02 mg·h/L [17]: to warrant an effective exposure to more than half of the paediatric patients, an AUC₀₋₁₂ of 7 mg·h/L was set as target exposure for the purposes of the current analysis.

Pharmacokinetic model

The pharmacokinetics of abacavir in children has been previously described according to a one-compartment model with first-order absorption and first-order elimination processes [7]. Given the availability of adult data (n=111) the analysis, which was implemented in NONMEM VI (release 1.0) [18], also demonstrated how prior information can be introduced into the estimation procedures during model building. In the final model, body weight was identified as a covariate on clearance and volume of distribution. The covariate effect was characterised by an exponential relationship, as shown in equation 8.1:

$$\theta_i = \theta \cdot \left(\frac{BW_i}{70} \right)^{EXP} \quad (8.1)$$

where θ_i is the individual parameter (CL or V), θ is the population parameter, BW_i is the individual body weight and EXP is the allometric exponent. Details of the model can be found in [7].

Clinical trial simulation

Simulations of a RCCT were performed according to an adaptive protocol design, in which patients were expected to reach the target exposure under steady-state

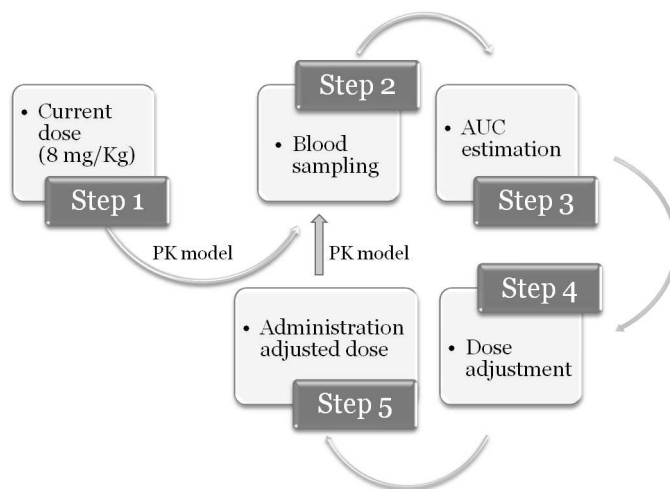


Figure 8.1: Diagram depicting protocol procedures and adaptation rules. The loop on the right-hand side (steps 2 to 5) can be virtually repeated at will

conditions. Protocol procedures include monitoring of drug concentrations at pre-defined intervals after the beginning of therapy. Based on the observed exposure at these intervals, if necessary, the total dose is adjusted using model parameter estimates, as determined by the non-linear mixed effects modelling. An overview of the protocol procedures and adaptation rules is presented in Figure 8.1.

Study population

A paediatric population with a broad range of weights and ages was simulated. Age distribution included children and adolescents from 2 to 17 years. Weight distribution was calculated according to growth charts available from the National Center for Health Statistics (http://www.cdc.gov/growthcharts/cdc_charts.htm). To ensure appropriate assessment of the covariate effect and prevent the potential confounders due to imbalance in the population, a total of 128 subjects were simulated, with the objective of obtaining 8 patients per year of age.

Dosing regimen and adjustment criteria

Patients are initially given a dose of 8 mg/kg up to a maximum of 300 mg, i.e., the recommended twice daily dose of abacavir. Based on a sparse sampling schedule, individual dose adjustment is subsequently performed with the objective of reaching the target exposure. A third monitoring step allows confirmation of the results and further dose titration if necessary. Individual doses are calculated according to the

formula:

$$\text{adjusted dose} = \frac{\text{first dose} \cdot \text{target AUC}}{\text{individual AUC}}. \quad (8.2)$$

The number of plasma samples used in the simulations reflects the number of samples in the original paediatric trial, i.e., 7 samples per patient, at 1, 2, 3, 4, 6, 8 and 12 h.

Simulation and dose adaptation procedures

Individual concentration data were simulated at pre-defined sampling times using non-linear mixed effect modelling. The simulated concentration *vs.* time profiles were subsequently analysed using the pharmacokinetic model described above. This procedure allowed individual pharmacokinetic parameters to be estimated for each patient. The dose adjustment required to achieve the pre-defined target exposure was based on the individual parameter estimates and consisted in up or down-titration relative to the starting dose. Finally, in order to explore whether clustering of exposures around target range would improve the precision of parameter estimates, the simulated concentration *vs.* time data were analysed again following the final adaptive step.

Pharmacokinetic parameter estimation

The stochastic approximation expectation maximisation (SAEM) [19] method in NONMEM VII (release 1) was used to re-fit the data. The pharmacokinetic parameters obtained after the first and second adaptation steps were compared with the values initially used to simulate the concentration *vs.* time profiles. In addition, the precision of model parameters was assessed by means of a nonparametric bootstrap procedure. 500 bootstrap samples were generated by re-sampling with replacement. These results were used to evaluate model stability and to obtain reliable confidence intervals for the parameter estimates. Each model was fitted repeatedly to the replicate bootstrap samples using the standard options in PsN [20]. The parameters estimates obtained from bootstrapping were compared with those obtained from the original data set.

Area under the concentration *vs.* time curve and target exposure.

The distribution of AUC₀₋₁₂ values observed after the first, the second and the third adaptation procedures were calculated according to the trapezoidal rule and compared to each other. Based on this distribution, the number of individuals showing an exposure to abacavir <6.02 mg·h/L was also investigated. This figure represents the proportion of individuals theoretically underexposed to abacavir and reflects therefore those patients treated with the wrong dose. Given that no

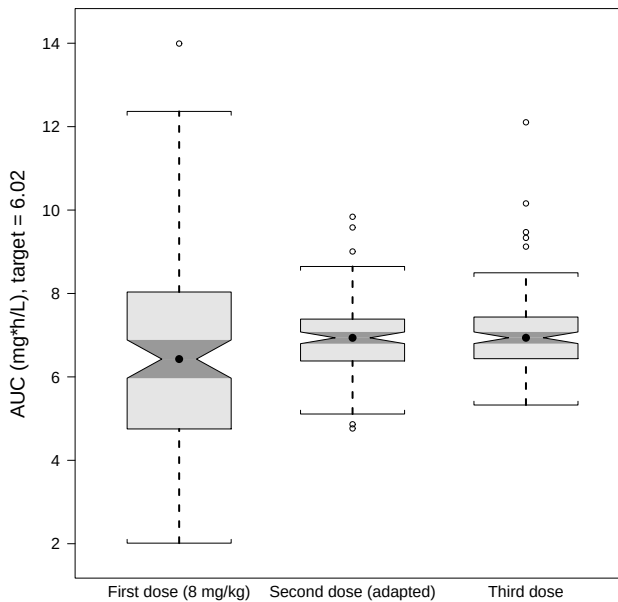


Figure 8.2: Whisker plots of the exposures distribution obtained with the different dosing protocols in the clinical trial simulation involving 128 children

clear information is available about the relationship between exposure to abacavir and toxicity, an arbitrary threshold of 10 mg·h/L was selected to indicate the level beyond which patients would potentially be overexposed. The proportion of patients trespassing this threshold was also calculated.

Finally, to demonstrate the clinical implications of the adaptative procedures in a paediatric protocol, we simulated a trial with the same 14 patients which were available for model building in the original pharmacokinetic analysis [7]. Concentration *vs.* time profiles were simulated following administration of doses individually adapted to reach the proposed target exposure. The distribution of AUC_{0-12} values obtained in the original trial was then compared with the distribution observed following dose adjustment procedures. All calculations included in the statistical and graphical analysis were performed in R [21].

8.3 Results

The AUC distribution after the initial dose level (8 mg/kg) resulted in a median exposure of 6.43 mg·h/L and 90th percentile ranging between 3.13 and 10.67 mg·h/L. 51 subjects, out of a cohort of 128 patients, showed AUC values below the effective

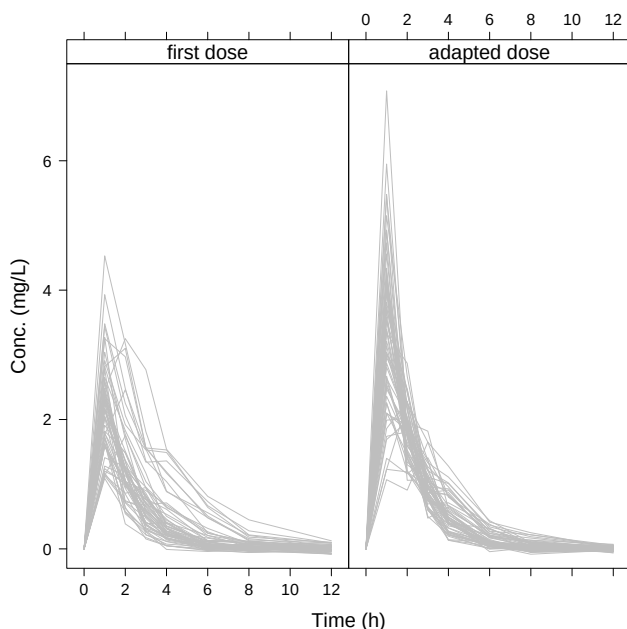


Figure 8.3: Concentration profiles of subjects receiving a sub-optimal dose as starting dose (either too low or too high, left), and the corresponding profiles after dose adjustment (right)

exposure (6.02 mg·h/L), whereas 10 of them reached an AUC higher than the arbitrary safety threshold of 10 mg·h/L. In total, this means that 61 patients (48%) received a dose that was either too low or too high. After the dose adjustment as defined by the adaptation procedures, the median exposure reached 6.94 mg·h/L, with 90th percentile ranging between 5.57 and 8.25 mg·h/L. Only 14 subjects appeared to remain below the target exposure, whilst no one showed values higher than 10 mg·h/L. The second adaptation step resulted in no changes to the median exposure, which remained the same (6.94 mg·h/L), with 90th intervals ranging between 5.75 - 8.37 mg·h/L. Despite the dose adjustment, in this occasion 14 subjects were still showing AUC levels lower than desired, whilst two subjects exceeded the safety threshold. The AUC distributions obtained after the initial dose and the consecutive dose adjustments are graphically summarised in Figure 8.2.

A summary of the implications of fixed dose *vs.* adaptive protocols on the proportion of patients achieving a pre-defined target exposure is presented in Table 8.1.

An example of the individual concentration *vs.* time course profiles for patients below and above the effective exposure is shown in Figure 8.3, including the corresponding profiles obtained after the adaptation steps.

Table 8.1: *Implications of fixed-dose vs. adaptative protocols on the proportion of patients achieving a pre-defined target exposure. In this example, 11% of the patients does not reach effective exposure despite dose adjustment procedures. These results suggest that the heterogeneity of the population (i.e., width of the parameter distribution) may play a more important role than accuracy and precision (i.e., uncertainty) in parameter estimates*

	Initial dose	1 st dose adjustment	2 nd dose adjustment
Patients underdosed (AUC <6.02 mg·h/L)	51	14	14
Patients overdosed (AUC >10.00 mg·h/L)	10	0	2
Total patients with inappropriate exposure	61 (48%)	14 (11%)	16 (12%)

In addition to the target exposure, a comparison was performed of the precision and accuracy of model parameter estimates obtained from data generated according to a fixed dose protocol *vs.* adaptive procedures in an exposure-controlled trial. In the PK analysis performed after the first dose level (8 mg/kg), the parameter estimates fell all around 5% of the true value (the value used to simulate the concentration profiles), with exception of K_a (+17.6%) and the allometric exponent on V (-10.1%). After the first adaptation of the doses the accuracy of the parameter estimates was very similar to the previous one. In this case all estimates were found to vary around 5% of the true parameter value, with the exception of V (-9.8%) and the allometric exponent on V (-20.2%). The precision of the parameters estimates was also similar in both protocols, although the RCCT showed generally lower coefficient of variations. A summary of the PK parameters obtained according to the fixed and adaptive protocol design is shown in Table 8.2.

Finally the simulation of a trial including the original 14 children in which the current dosing regimen is used (8 mg/kg) yielded a median exposure of 5.0 mg·h/L, with 90th percentile varying between 2.96 - 9.08 mg·h/L. Ten out of the 14 patients showed an AUC lower than the effective exposure, whilst one had an AUC value higher than the arbitrary safety threshold. Based on these findings, it seems that 79% of the patients were administered with a sub-optimal dose. In contrast, in the adaptive protocol median exposure raises to 6.97 mg·h/L (90th percentile: 6.38 - 12.81 mg·h/L), with no patients showing exposure levels below the effective AUC and two of them being above the safety threshold. The AUC distributions observed after each design are depicted in Figure 8.4.

8.4 Discussion

In contrast to common practice in paediatric drug development, the recent introduction of the paediatric legislation in the European Union imposes prospective

Table 8.2: *Pharmacokinetic parameters estimates for abacavir. It is evident from the re-estimation procedures using simulated data according to a fixed-dose protocol (mid column) that, although precise and accurate, pharmacokinetic parameter estimation alone does not guarantee patients achieving the desired target exposure. Parameter estimates from simulated data according to an adaptive protocol showed comparable accuracy and precision (right). In both cases, all bootstrapped data sets resulted in successful minimisation*

	Model parameters from Cella [7]	Parameter re-estimation after the initial dose		Parameter re-estimation after the adapted dose	
Parameters		mean	bootstrap mean (%CV)	mean	bootstrap mean (%CV)
<i>Fixed effects</i>					
CL (L/h)	40.6	41.5	41.2 (5.2)	42.3	42.0 (4.5)
V (L)	69.1	65.5	65.3 (5.5)	62.3	62.2 (4.3)
Ka (h ⁻¹)	3.58	4.21	4.34 (16)	3.67	3.86 (16)
Exponent on CL	0.722	0.761	0.761 (7.0)	0.745	0.744 (6.2)
Exponent on V	0.810	0.728	0.726 (7.2)	0.646	0.646 (7.0)
<i>Inter-individual variability (%)</i>					
CL	27	26	25 (17)	25	25 (15)
V	11	19	19 (24)	17	16 (20)
Ka	98	101	101 (24)	99	101 (21)
F	37	39	47 (33)	34	35 (30)
<i>Residual error (%)</i>					
ε	3.6	3.7	3.7 (10)	3.7	3.7 (10)

assessment of pharmacokinetics, pharmacodynamics, safety and efficacy of drugs prior to their approval and therapeutic use [22]. Thus far, despite the feasibility and potential advantages of model-based approaches to the design and analysis of early paediatric trials, issues such as dose selection, dose rationale and study design for paediatric indications continue to be addressed in an empirical manner. In fact, some reluctance to the use of pharmacostatistical methods (e.g., non-linear mixed effects modelling) may result in one hand from the lack of understanding of quantitative clinical pharmacology. The possibility to apply modelling and simulation as a tool to evaluate relevant clinical questions is simply beyond the working knowledge of most paediatricians and drug developers. On the other hand, there are some key conceptual issues with regard to the use of model-based approaches which are more of a scientific and statistical nature. The former refers to the predictive value of models when extrapolations are made from one population to another, given that the role of developmental growth and maturation processes vary considerably from birth to adolescence [23]. The latter refers to the assumptions regarding population heterogeneity (i.e., parameter distributions), parameter-covariate correlations and model performance (i.e., accuracy and precision of estimates) when dealing with different groups, phenotypes or clinical conditions [24]. From a statistical perspective, this means that model uncertainty and eventual misspecification must be taken into account. These considerations are vital for the use of modelling and

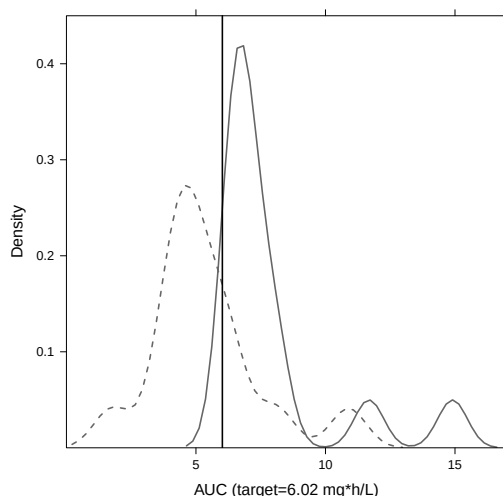


Figure 8.4: *Density plots of the exposure distribution calculated in the original 14 children after the current dose (8 mg/kg, dashed line) and the simulated exposure distribution of the same patients after dose adjustment (continuous line)*

simulation as basis for the dose rationale and overall study design in paediatric drug development.

In the current investigation we have demonstrated that some of the potential scientific and statistical limitations of non-linear hierarchical modelling can be addressed by a learning-confirming paradigm. The use of adaptive rather than fixed dose protocols enables the accurate selection of the paediatric dose. More specifically, a randomised concentration-controlled trial (RCCT) design was proposed as framework for clinical protocols in early clinical development. Using clinical trial simulations, it became clear how abacavir exposure differs between subjects when fixed doses are used, as compared to protocols in which a target exposure is defined and dose adjustments performed to ensure such a target is reached. Furthermore, our results show that despite comparable AUC values in children and adults (6.43 mg·h/L in children *vs.* 6.02 mg·h/L in adults), linear scaling of the dose according to body weight resulted in a very wide distribution of AUC values, with nearly half of the subjects lying outside the target range.

Although one could question whether a different dosing regimen would have shrunk the observed AUC distribution, the adaptation procedures did clearly affect the resulting exposure. After dose adjustment, AUC values clustered around the median value of 6.94 mg·h/L, showing a much narrower distribution. The proportion of patients with suboptimal dosing was reduced to 11%, with no patients showing exposure above the safety threshold. As anticipated, for abacavir the second adaptation step did not produce significant changes to the observed exposure

distribution. However, the possibility of multiple adaptive steps is relevant when pharmacokinetics is known to be affected by metabolic induction or time-dependent inhibition [25–28].

In addition to identifying the most appropriate dose for children and supporting the rationale for pharmacokinetic bridging studies, we have previously hypothesised that this design would also yield an increase in the statistical power of the study, allowing for a potential reduction in the number of patients as well as in the sampling frequency. Indeed, applying the same methodology to 14 children, who were included in the original clinical trials used to develop the pharmacokinetic model, yielded comparable results. Adaptive procedures allow shrinkage of the observed exposure distribution around the target range irrespective of study size. From a clinical perspective, this means less patients will be potentially under or overdosed.

Another statistical aspect addressed by our investigation was the gain in precision and accuracy of parameter estimates [11], suggesting superiority of RCCT over fixed dose protocols. The accuracy of pharmacokinetic parameters estimates for abacavir was comparable across protocols (i.e., fixed *vs.* adaptive dose), whilst parameter precision appeared to be only slightly higher after dose adjustment, as indicated by the coefficients of variation obtained by bootstrapping.

Finally, it should be noted that the use of simulation scenarios allowed clear, systematic evaluation of the implications of dose selection in a clinical trial. Irrespective of the primary objective of a clinical protocol (i.e., pharmacokinetic bridging or efficacy), one needs to understand that the larger the heterogeneity in the target population the larger the proportion of subjects deviating from the central tendency (e.g., median, mean or target range). It is clear from our results that fixed-dose protocols lead to a considerable proportion of patients beyond a desirable target range. In adult populations, this dispersion is often a reflection of the underlying biological processes and can be expressed as random effects (i.e., inter-individual variability) in parameters such as clearance and volume of distribution. In contrast, in paediatric populations the variability has an additional time-variant component, which is associated with developmental growth and maturation processes. Depending on the experimental protocol design (e.g. treatment duration, dose level), these time-variant components are confounded by factors such as disease condition or demographic characteristics (e.g. ethnic differences). As such they cannot be disregarded and must be captured either as fixed or random effects in a model. However, accurate model selection and characterisation of parameter-covariate correlations may not be achieved based solely on inferential methods. Confirmatory evidence (data) from the population of interest is also required, which may not be available at the beginning of a clinical development programme with novel compounds.

It can be concluded that defining the dose rationale for children based on extrapolation or interpolation procedures is unlikely to ensure optimal dosing regimen at the individual patient level. Adaptive procedures are required to tackle the uncertainty in model structure (i.e., model misspecification), discriminating it from the uncertainty in parameter estimates (i.e., heterogeneity). The availability

of such data allow formal assessment of dose and dosing regimen requirements for a fixed-dose protocol, which then can be used in subsequent confirmatory trials. Despite the challenges associated with the implementation of adaptive protocols, these considerations are essential in early clinical drug development. The advantages of a randomised concentration-controlled trial largely exceed the practical drawbacks attributed to it, i.e., it ensures the child's right to receive the right dose.

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