Use of an integrated modelling and simulation approach to develop a simplified peginterferon alfa-2a dosing regimen for children with hepatitis C

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Peginterferon alfa-2a and ribavirin are approved for chronic hepatitis C treatment in patients aged ≥ 5 years.
- Since BSA is known to impact on the pharmacokinetics of this drug, paediatric dosing is calculated based upon this parameter.
- To potentially reduce possible risk of dosing errors using an individualized calculation, a simplified dosing regimen is needed.

WHAT THIS STUDY ADDS

- A modelling and simulation approach was applied to propose a simplified dosing regimen intended to mimic the individualized calculation employed in paediatric clinical trials.
- The simplified dosing regimen is expected to reduce the burden of dosing calculations for patients and caregivers while providing an appropriate range of exposures that are effective and safe.

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AIM

The aim of the study was to simplify the dosing regimen of peginterferon alfa-2a in paediatric patients with chronic hepatitis C.

METHODS

A population pharmacokinetic (PK) model was developed using PK data from 14 children aged 2–8 years and 402 adults. Simulations were produced to identify a simplified dosing regimen that would provide exposures similar to those observed in the paediatric clinical trials and in the range known to be safe/efficacious in adults. Model predictions were evaluated against observed adult and paediatric data to reinforce confidence of the proposed dosing regimen.

RESULTS

The final model was a two compartment model with a zero order resorption process. Covariates included a linear influence of body surface area (BSA) on apparent oral clearance (CL/F) and a linear influence of body weight on apparent volume of distribution of the central compartment (V_1/F). A simplified dosing regimen was developed which is expected to provide exposures in children aged ≥ 5 years similar to the dosing formula used in the paediatric clinical trial and within the range that is safe/efficacious in adults. This simplified regimen is approved in the EU and in other countries for the treatment of chronic hepatitis C in treatment-naïve children/adolescents aged ≥ 5 years in combination with ribavirin.

CONCLUSION

Pre-existing adult PK data were combined with relatively limited paediatric PK data to develop a PK model able to predict exposure in both populations adequately. This provided increased confidence in characterizing PK in children and helped in the development of a simplified dosing regimen of peginterferon alfa-2a in paediatric patients.

Introduction

Hepatitis C is an infection of the liver caused by the hepatitis C virus (HCV). The World Health Organization estimates that about 150 million people are infected with HCV and more than 350 000 people die from HCV-related liver diseases each year [1]. However, available information regarding the incidence and prevalence of HCV infection in children is limited. Prevalence estimates in healthy children and adolescents (under 20 years of age) range from 0% to 0.9% [2]. Population-based surveys in the United States have estimated that the prevalence of anti-HCV antibodies in children ranges from 0.2% for those 6 to 12 years of age to 0.4% for those 12 to 19 years of age [3]. The main routes of HCV infection in children are through blood products and vertical transmission. Since the introduction of routine HCV testing of the blood supply in the United States and Europe in the early 1990s, the vast majority of new infections in countries where blood testing is routinely performed are through mother-to-child transmission.

The current standard of care for paediatric patients infected with HCV includes the combination of pegylated interferon (PegIFN) and ribavirin (RBV) [4]. PegIFN alfa-2a (40 KD) (Pegasys®) and RBV (Copegus®) are approved for treatment of chronic hepatitis C in patients 5 years and older. PegIFN alfa-2a (40 KD) consists of a 40 KD branched polyethylene glycol moiety attached to interferon alfa-2a. The pharmacokinetics (PK) of PegIFN alfa-2a in adults has been described previously [5]. Briefly, attachment of this large, branched (40 KD), pegylated moiety to interferon alfa-2a creates a much larger molecule that undergoes sustained absorption from the subcutaneous tissue, restricted distribution and reduced renal clearance as compared with conventional interferon [5, 6]. Overall, this results in sustained serum concentrations throughout the course of a week, allowing for a once weekly dosing regimen. Following subcutaneous administration, PegIFN alfa-2a is absorbed slowly with a median $t_{\max}$ of approximately 78 h. The terminal half-life is approximately 160 h, resulting in an approximate two-fold accumulation with multiple dosing of a 180 µg dose given once weekly [7].

Two clinical trials (a PK study [8]) and PEDS-C [9]) have been performed evaluating PegIFN alfa-2a as monotherapy or in combination with RBV in children with chronic HCV infection [8, 9]. The dose of PegIFN alfa-2a utilized in the two clinical studies was derived by adjusting the recommended adult dose by the child's body surface area (BSA). BSA was used instead of body weight because normalizing the dose based on BSA provides similar plasma concentrations in adults and in children for drugs with small (<0.3 l kg⁻¹) volumes of distribution [10]. The volume of distribution of PegIFN alfa-2a in healthy adults is approximately 9 l [11] or approximately 0.13 l kg⁻¹ for a 70 kg person, so BSA was considered to be a more appropriate scaling factor than body weight. In adults, PegIFN alfa-2a is administered by subcutaneous injection once

a week at a dose of 180 µg. The average BSA of adults is 1.73 m². Therefore, the paediatric dose was obtained by multiplying the BSA of a child in m² by the µg m⁻² dose for an average adult (180 µg 1.73 m⁻²). The results of the PEDS-C study [9] support the use of the formula-based dose calculation of PegIFN alfa-2a for the treatment of chronic hepatitis C in children.

However, this regimen requires the caregiver to calculate an exact dose for each patient based upon the child's BSA. To reduce potentially the risk of dosing errors it is desirable to simplify the dosing regimen for patients and caregivers by providing a dosing recommendation consisting of several 'fixed' doses for given ranges of BSA. The objective of this analysis was to leverage our existing understanding of the PK of PegIFN alfa-2a in adults to supplement the limited information collected in children by using a population PK modelling approach. This allowed us to perform PK simulations of PegIFN alfa-2a with increased confidence and allowed for development of a simplified dosing recommendation for PegIFN alfa-2a in paediatric patients with chronic HCV infection.

Methods

An integrated population PK model was developed using paediatric PegIFN alfa-2a PK data available from a clinical trial in 14 HCV-infected children between 2 and 8 years of age [8] and adult PK data obtained from approximately 402 adult patients enrolled in six previous clinical trials ([12], unpublished data on file, Hoffmann-La Roche Inc., Nutley, NJ, USA). Thus, the complete dataset comprised a total of 143 paediatric and 4020 adult PK observations. All study protocols were approved by the institutional review boards of the participating centres, and informed consent was obtained from all patients or, in the case of children, the parent or legal guardian.

The paediatric PK study [8] was an open label, multicentre, pilot trial in which 14 patients aged 2–8 years were treated with PegIFN alfa-2a monotherapy for 48 weeks at a dose of 180 µg 1.73 m⁻² × BSA of the child. The results of this study have been reported previously [8]. Blood samples for PK assessment were collected during week 1 and week 24 pre-dose (0 h) and at 24, 96 and 168 h after administration of PegIFN alfa-2a to evaluate single dose and steady-state parameters. The PK samples at 24 and 96 h post-dose were included to capture the $C_{\max}$ and the sample collected at 168 h to capture the C_{trough} . Additional pre-dose (trough) samples were collected at weeks 4, 8, 12, 40 and 48. The limited sampling in these children was considered adequate for the purposes of the study because the pharmacokinetic profile of PegIFN alfa-2a is relatively flat over a dosing interval with a peak-to-trough ratio of only 1.5 to 2.0 [5].

Data from six studies in adults with chronic hepatitis C were combined with data from the paediatric study

described above. Patients enrolled in these phase II or III studies received PegIFN alfa-2a alone at dosages ranging from 45 to 270 µg once weekly or at a dosage of 180 µg once weekly in combination with RBV. The sampling schemes varied across the six adult studies but generally were more intensive than the scheme in the paediatric trial. In order to characterize fully the single dose and steady-state (week 48) PK parameters in adults, samples were collected after the first and last doses of PegIFN alfa-2a as follows: pre-dose (0) and then 15, 30 and 45 min post-dose and 1, 2, 3, 5, 7, 24, 48, 72, 96 and 168 h post-dose. Additional pre-dose samples were collected during treatment weeks 4 to 44 to characterize C_{trough} .

In all studies, serum concentrations of PegIFN alfa-2a were measured by a quantitative sandwich immunoassay (ELISA) using two monoclonal antibodies that recognize different epitopes. The assay range in human serum is 62.5 to 2000 pg ml⁻¹, with a lower limit of quantitation of 125 pg ml⁻¹.

A two part modelling approach was employed. In the first part the paediatric PK data were analyzed separately to ensure an accurate description of the PK without an undue influence of the adult data. This analysis was performed using non-linear mixed effects modelling (NONMEM), version 7.1.0 [13]. During model development, different structural models were tested to fit the data, including one or two compartment models with zero order or first order absorption. Models were evaluated and selected on the basis of goodness of fit and stability. Further assessment and comparison used the likelihood ratio test and reviewed changes in the objective function value (OFV) between models. Improvement in model fit was determined by chi-square distribution, with the degree of freedom corresponding to the number of additional parameters from one model to the other (for one DF, $\text{DOFV} < 3.84 = P < 0.05$). Inter-individual variability was assessed on all PK parameters with exponential variability models. Patient characteristics were investigated in the base model including weight and BSA. The relevant covariates were incorporated into the model, and tested for their significance. Model improvement was assessed according to the goodness of fit diagnostics. The results of the final model using the first order (FO) method were re-run using the first order conditional estimation (FOCE) method.

In the second part, data from the paediatric study were combined with data from the adult studies in order to evaluate further the modelling approach and reinforce confidence in the model. The same structural model was used for the combined dataset but the parameters were re-estimated. The accuracy of the model was evaluated graphically by examining *post hoc* predictions of exposure in the two populations.

The *post hoc* PK parameters obtained from the final model were subsequently used to perform simulations evaluating alternative dosing schemes with the aim of identifying a simplified regimen. These simulations used 'fixed' doses of PegIFN alfa-2a for discrete ranges of BSA

in children that would provide PegIFN alfa-2a exposure similar to those obtained with the dosing formula used in the paediatric clinical trials. The main parameters used in the simulation included clearance and its estimated variability, as well as the BSA distribution in the target population. The simulated values of $\text{AUC}(0,\tau)$ in paediatric patients were compared with the values of $\text{AUC}(0,\tau)$ in adults with a $\text{BSA} \leq 1.73 \text{ m}^2$, at the currently approved dose of 180 µg once per week, estimated by non-compartmental PK analysis from six previously conducted clinical trials ([12], unpublished data on file, Hoffmann-La Roche Inc., Nutley, NJ, USA).

Simulations were performed using S-PLUS version 7 for Windows (Insightful Corp, Seattle, WA, USA). More than 1000 subjects (10 per BSA value with increments of 0.1 m²) were simulated over the entire range of BSA by sampling from the CL/F distribution predicted from BSA, and the inter-individual variability observed in the paediatric PK study. Subsequently, exposure values were derived using the formula: $\text{AUC}(0,\tau) = \text{weekly PegIFN alfa-2a dose} / \text{CL/F}$. The BSA break-points were iteratively adapted, taking into consideration the feasibility and practicality of graduations on the planned pre-filled syringes. The range of BSA evaluated was determined using standardized WHO MGRS growth charts [16] for children aged 2–20 years. The lower limit of 0.71 m² is estimated from the lowest 5th percentile of height and weight for a 5-year-old child. The lower limit of 5 years of age was selected because this is the lowest age for which PegIFN alfa-2a based therapy is currently approved for treatment of children infected with HCV [17, 18].

Since the adult PegIFN alfa-2a label allows for up to three step-wise dose reductions during therapy in order to manage laboratory abnormalities, simulations were also performed to evaluate the impact of similar dose reductions in paediatric patients. Each reduction results in a 25% decrease in dose (e.g. in adults this three step reduction protocol corresponds to a decrease from 180 µg to 135, 90 and 45 µg). Since PegIFN alfa-2a exhibits linear PK [14, 15], $\text{AUC}(0,\tau)$ for each level of dose modification was estimated by a simple dose adjustment. Simulations were performed and *post hoc* predictions of $\text{AUC}(0,\tau)$ in paediatric patients were compared with predicted $\text{AUC}(0,\tau)$ values for each dose reduction in adults with a $\text{BSA} \leq 1.73 \text{ m}^2$.

Results

Paediatric population PK modelling

After model selection process based on goodness-of-fit examination, the final model developed to describe the population PK of PegIFN alfa-2a in young children was a two compartment model with a zero order resorption process. A combined proportional and residual error model was found to be most appropriate.

With regards to the covariate investigation, a linear influence of BSA on CL/F and a linear influence of body weight on V_1/F were included as covariates in the model. Inspection of the different goodness-of-fit plots shows that the model provided an adequate description of the data, although some low concentrations were over-predicted by the model.

Integrated paediatric/adult population PK modelling

The population PK parameters of the paediatric model were re-estimated after combining the paediatric and adult data. The goodness-of-fit plots presented in Figure 1 show a reasonable agreement between the predicted and the observed data. With the exception of a few

Figure 1

Goodness-of-fit plots of the predictions vs. the observations. Scatterplot overlapped with a smoothing function [solid line] compared with the identity [dashed line] for (A) the overall population and (B) split for adults vs. paediatrics

observations which are over-predicted there were no specific trends in the weighted residuals vs. prediction and time for the paediatric and adult population.

The model parameters from the integrated paediatric-adult model are similar to those from the paediatric model with the exception of central volume of distribution being two times higher compared with the paediatric model. However, this difference has no impact on the population goodness-of-fit plot for the paediatric dataset. Due to some stability issues, the between-subject variability on the inter-compartmental rate constant, K_{21} , was fixed to 0. A between-subject variability has been estimated on the second inter-compartmental rate constant, K_{12} (Table 1).

The effects of BSA on CL/F and of BW on V_1/F were found to be very similar in the paediatric and integrated paediatric-adult models. Figure 2 illustrates the relationship between CL/F and BSA across the entire studied BSA range.

To evaluate the predictive performance of the paediatric-adult model, prediction-corrected Visual Predictive Checks (pcVPC) were performed simulating 200 studies. These pcVPC were stratified by study and are represented in Supplemental Figure 1 for the paediatric PK study. The pcVPC compare the 5th and 95th (dashed lines) and the 50th (solid line) percentiles of the observed values, normalized using the individual model prediction rescaled by the average prediction in the bin, with the confidence intervals (shaded areas) around each of these percentiles derived from the simulations normalized using the same rule. The large confidence interval observed in the paediatric pcVPC is due to the small sample size ($n = 14$). Despite some under-prediction of the

between-subject variability, the pcVPC plots show that the model is able to reproduce adequately the mean and inter-individual variability of the PK profiles in the paediatric population. Similar outcomes were evident in the adult population (not shown). The model was therefore considered as qualified for simulations in the two populations.

The *post hoc* predicted individual CL/F values ranged from 6.6 ml h⁻¹ to 35.5 ml h⁻¹ over the BSA range of 0.61 to 1.30 m². These values resulted in *post hoc* predicted steady-state C_{trough} concentrations of PegIFN alfa-2a ranging from 9 to 39 ng ml⁻¹ and *post hoc* predicted values of AUC(0,τ) at week 24 of 1604 to 9232 ng·h ml⁻¹ h (mean 5667 and SD ± 2165 ng·h ml⁻¹ h). The mean *post hoc* AUC(0,τ) from the paediatric population PK analysis (5667 ng·h ml⁻¹ h) was 25% to 70% higher than the AUC(0,τ) values in adult patients assigned to receive a 180 µg weekly dose of PegIFN alfa-2a in historic studies (range of mean values, 3334 ng·h ml⁻¹ h to 4348 ng·h ml⁻¹ h [[12], unpublished data on file, Hoffmann-La Roche Inc., Nutley, NJ, USA]). The highest AUC(0,τ) in the 14 children (9232 ng·h ml⁻¹ h) was close to but below the highest AUC(0,τ) observed in adults (11 125 ng·h ml⁻¹) treated with a weekly dose of 180 µg. Mean C_{trough} at week 48 was approximately 20 ng ml⁻¹ in children and 16 ng ml⁻¹ in adults. This dosing formula was used in a subsequent larger paediatric clinical study, [9] which established that the regimen was safe and efficacious in children with chronic HCV infection.

With the goal of minimizing potential dosing errors, this regimen was modified to create BSA categories that have a good overlap with the formula-based dosing

Table 1

Parameter estimates for the paediatric model and the paediatric-adult model

Parameters	Paediatric model estimate (SE%)	Paediatric-adult model estimate (SE%)
Structural model		
TVCL* (l h ⁻¹)	0.0120 (6)	0.0121 (6)
TVV ₁ † (l)	0.990 (10)	2.30 (11)
K_{12} (h ⁻¹)	0.0174 (11)	0.00107 (36)
K_{21} (h ⁻¹)	0.00248 (14)	0.00162 (27)
BSA_CL*	2.20 (14)	2.22 (10)
BW_V ₁ †	0.0716 (28)	0.0866 (12)
Statistical model		
BSV on TVCL*	19 (43)	36 (21)
BSV on TVV ₁ †	35 (78)	51 (37)
BSV on K_{21}	93 (61)	–
BSV on K_{12}	–	170 (20)
Proportional error (%)	26 (41)	25 (13)
Additive error (ng ml ⁻¹)	3742 (68)	1148 (49)

K_{12} and K_{21} are inter-compartmental rate constants. The residual error is modelled as a combined proportional and additive error model.

BSV, between subject variability expressed in percentage; CL, apparent oral clearance; V_1 , volume of distribution; V_1/F , apparent volume of distribution of the central compartment.

CL/F = TVCL(1 + BSA_CL*(BSA – 0.75)) + V_1/F = TVV₁*(1 + BW_V₁*(BW – 19.1))

Figure 2

Relationship between BSA and CL/F over the studied BSA range: paediatric patients = circles, adults = triangles, * combined model, • Children from combined model — Adults from combined model

regimen ($180 \mu\text{g} \times \text{BSA}/1.73$) used in the pivotal paediatric clinical trial [9]. Deviations in dosages occurred in the pivotal trial despite the use of a formula to calculate exact doses for each patient because of graduations in the scale on the syringe. In addition, despite using a standard dose of $180 \mu\text{g}$ in adult patients, some deviations

from an ideal dose occur because of variation in the BSA of adults relative to the average BSA of 1.73 m^2 . The proposed BSA categories for paediatric patients were compared with the individualized doses used in the paediatric trials and to adult doses after normalization to each patient's BSA. The recommended guidance resulted in doses that are approximately 20% higher or lower than that resulting from formula-based dosing used in the paediatric and adult clinical trials (Figure 3). Since PegIFN alfa-2a has a well-established efficacy and safety profile and a relatively wide therapeutic margin [19] the simplified dosing regimen based on BSA categories would, in principal, reduce the chance of dosing errors involving calculations while ensuring exposure comparable with that achieved in the paediatric and adult trials in which the efficacy and safety of PegIFN alfa-2a were established.

Simulations to evaluate simplified dosing regimen

The proposed simplified dosing regimen and associated predicted exposure determined from the simulations for paediatric patients are presented in Table 2. Also

Figure 3

Comparison of predicted exposure to Peg-IFN alfa-2a using the simplified BSA category-based dose regimen with predicted exposures in the paediatric pivotal clinical trial using a formula-based dose regimen and predicted exposures in adults in six clinical trials who received a fixed dose of $180 \mu\text{g}$ normalized to each patient's BSA. The percent deviation on the Y-axis indicates the deviation relative to a formula-based calculation. ^a BSA categories correspond to those shown in Table 1 and are included in the EU label for PegIFN alfa-2a. ^b BSA categories correspond to individualized doses used in the pivotal paediatric trials [8, 9]. The categories correspond to graduations on the syringe used to administer the drug. ^c Range of exposures in adults given a fixed dose of $180 \mu\text{g}$ normalized to each patient's BSA. The horizontal dotted lines indicate deviations greater than or less than 20% from an ideal dose of $180 \mu\text{g}$ 1.73 m^{-2} .

Table 2

Simplified PegIFN alfa-2a BSA-based dosing regimen

BSA range (m ²)	Starting dose (µg)	Simulated AUC Median [5 th –95 th percentile]	% of patients below the minimum AUC in children	% of patients above the maximum AUC in children
0.71–0.74	65	5830 [4281–7816]	1	4
0.75–1.08	90	5571 [3670–8500]	7	6
1.09–1.51	135	5156 [3560–7450]	9	1
>1.51	180	5132 [3680–7089]	7	1

shown are the percentages of patients predicted to exceed the range of observed AUC values in children. The scatter plots in Supplemental Figure 2 show the individual predictions of exposure for each level of dose modification in children, as compared with adults and illustrate that exposure in children with the simplified dose modification scheme can be expected to be similar to that in adults who receive the corresponding degree of dose reduction.

Discussion

Population PK modelling and simulation have been used to examine the potential for a simplified PegIFN alfa-2a dosing regimen for paediatric patients with chronic HCV infection. A population PK model was developed based on data from a pilot PK study in children and a larger set of adult PK data was used to validate the model. The final model to describe PegIFN alfa-2a PK consisted of two disposition compartments with a zero order resorption process. Based on the examination of the goodness-of-fit plots, a first order absorption model was not considered the most appropriate model to use. This could have been because of limited information in the database describing the absorption phase. A linear influence of BSA on CL/F and a linear influence of body weight on V_1/F were the two covariates included in the model.

A clear limitation of this analysis is the small number of paediatric patients and the relatively sparse PK data available for the population PK analysis. However, this is often the situation when collecting data in young children. Although the model was developed from a limited dataset, inspection of the goodness-of-fit plots, the precisely determined parameter estimates and the moderate residual variability reveals that the model is a fairly good description of the data. Confidence in this model was reinforced by re-estimating the population parameters after combining the paediatric and adult data. The diagnostic plots show a good description of both paediatric and adult data. Additionally, visual inspection of Figure 2 reinforces confidence that the model has adequately characterized the relationship between BSA and predicted PegIFN alfa-2a clearance,

as the model trend line crosses not only through the observations from the paediatric study but also through the centre of the observed data in adults.

An alternative approach to using the paediatric data to first define the structural model to describe the pharmacokinetics of PegIFN alfa 2a, followed by incorporation of the adult data, could have been to do the reverse, i.e. first define the structural model using robust data available from adult studies and then to add the paediatric data to the database. Such an approach would allow more confidence in the form of the structural model. However, the simpler approach adopted in the present analysis has enabled the goals of the analysis to be met, and has yielded a structural model that describes the data relatively well according to all the diagnostic procedures used.

The model was judged adequate to perform simulations of various dosing scenarios and dose reduction schemes using a simplified, fixed dose regimen based on categories of BSA in children. The simulations indicate that the dosing regimen in Table 2 can be expected to provide PegIFN alfa-2a exposure in children that is similar to that achieved with the dosing formula used in the paediatric clinical trial, and within the range shown to be safe and efficacious in adults. In addition, this BSA-category-based dosing regimen is simpler and therefore may reduce the potential risk of dosing errors than the formula-based dosing regimen.

In order to provide accurate dosing for paediatric patients, as well as to minimize drug wastage at lower doses, a 90 µg pre-filled syringe with six graduations (90, 65, 45, 30, 20 and 10 µg) has been developed for use in countries where PegIFN alfa-2a is currently approved for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older in combination with RBV.

In summary, PK modelling and simulation has been used to support a BSA category-based PegIFN alfa-2a dosing regimen for paediatric patients with chronic hepatitis C. This BSA-category-based regimen is being evaluated, with some modifications, in clinical trials of the pharmacokinetics, efficacy and safety of PegIFN alfa-2a in paediatric patients with chronic hepatitis B virus (HBV) infection. The modifications were made to allow for dosing in 3-year-old children in contrast to the dose regimen developed for children with HCV infection aged 5 years and older.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare Barbara Brennan and Navita Mallalieu are employees and shareholders of Hoffmann-La Roche, Inc., Cynthia Wat is an employee and shareholder of Roche Products Ltd, Michael McKenna was an employee of Roche Products Ltd at the time of the study, Annabelle Lemenuel-Diot is an employee and shareholder of F. Hoffmann-La Roche Ltd, Jonathan Solsky is an ex-employee of Hoffmann-La Roche Inc, Eric Snoeck is principal consultant of SGS Exprimio NV and is a compensated Hoffmann-La Roche consultant.

Contributions

BB: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

AL-D: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

ES: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

MM: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

JS: Critical revision of the manuscript for important intellectual content.

CW: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding.

NM: Study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1

Prediction-corrected visual predictive checks (pcVPC) comparing the predicted concentration–time data from the paediatric model vs. the paediatric-adult model. Shaded areas represent the 90% CI of the prediction corrected median, 5th and 95th percentile of the simulation, the black lines represent the prediction corrected median (solid line), 5th and 95th percentile (dashed lines) of the observed data

Figure S2

Individual predictions of exposure across a range of BSA in children as compared with adults (black diamonds) when using a simplified dosing regimen; (A) starting dose, (B) first-level reduction, (C) second-level reduction and (D) third-level reduction. Each reduction corresponds with a 25% decrease of the preceding dose. AUC = area under the serum concentration–time curve; BSA = body surface area