Population pharmacokinetics and dosing recommendations for the use of deferiprone in children younger than 6 years of age

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What is already known about this subject

- Deferiprone pharmacokinetics has been characterised in adults and adolescents
- After oral administration, deferiprone is rapidly and well absorbed, and plasma levels show peak concentrations within 1 hour of administration
- Essentially no pharmacokinetic information is available in children below 6 years of age despite the long clinical experience with this iron chelator

What this study adds

- The pharmacokinetics of deferiprone has been characterised in children below 6 years of age after administration of single oral doses.
- Body weight is a covariate on clearance and volume of distribution across the paediatric population.
- The approved dosing regimen for deferiprone yields exposure in children comparable to that observed in adults and adolescents.
- A dosing regimen of 25 mg/kg t.i.d. is recommended in children below 6 years, with the possibility of titration up to 33.3 mg/kg t.i.d.

Table of links

TARGETS
Iron

LIGANDS
deferiprone

These Tables of Links list key voltage-gate ion channels and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 (Alexander et al., 2015)

Abstract

Aims: Despite long clinical experience with deferiprone, there is limited information on its pharmacokinetics in children < 6 years of age. Here we assess the impact of developmental growth on the pharmacokinetics of deferiprone in this population using a population approach. Based on pharmacokinetic bridging concepts, we also evaluate whether the recommended doses yield appropriate systemic exposure in this group of patients.

Methods: Data from a study in which 18 paediatric patients were enrolled were available for the purposes of this analysis. Patients were randomised to three deferiprone dose levels (8.3, 16.7 and 33.3 mg/kg). Blood samples were collected according to an optimised sampling scheme in which each patient contributed to a maximum of five samples. A population pharmacokinetic model was developed using NONMEM v.7.2. Model selection criteria were based on graphical and statistical summaries.

Results: A one-compartment model with first-order absorption and first-order elimination best described the pharmacokinetics of deferiprone. Drug disposition parameters were affected by body weight, with both clearance and volume increasing allometrically with size. Simulation scenarios show that comparable systemic exposure (AUC) is achieved in children

and adults after similar dose levels in mg/kg, with median (5-95th quantiles) AUC values respectively of 340.6 (223.2-520.0) and 318.5 (200.4-499.0) µmol/L*h at 75 mg/kg/day and 453.7 (297.3-693.0) and 424.2 (266.9-664.0) at 100 mg/kg/day t.i.d. doses.

Conclusions: Based on the current findings, a dosing regimen of 25 mg/kg t.i.d. is recommended in children below 6 years of age, with the possibility of titration up to 33.3 mg/kg t.i.d.

Introduction

Patients with haemoglobinopathies, such as β-thalassaemia or sickle cell disease, affecting the ability to synthesize haemoglobin may require life-long blood transfusion therapy to survive. This chronic intervention results in a series of potential complications, with iron overload being an inevitable consequence within a few years. Chelation therapy is therefore required to prevent potentially fatal iron-related complications. In most cases, the disease is diagnosed within the first year of life and blood transfusion regimen is started immediately after diagnosis. Chelation therapy is subsequently initiated when serum ferritin levels reach a threshold of about 1000 µg/L, which occurs on average about 1 year after the start of blood transfusions (1–5). Deferiprone is a hydroxypyridinone, which was authorised in Europe in 1999 for the treatment of iron overload in patients with β-thalassaemia major when deferoxamine is contraindicated or inadequate. The recommended dose of deferiprone is 75 mg/kg/day given as t.i.d. regimen; the dose can be increased up to 100 mg/kg/day, if necessary. When administered orally, deferiprone is rapidly and well absorbed. Plasma levels show peak concentrations (Cmax) within 1 hour of administration. Food reduces its absorption rate without much of an effect on the overall

exposure to the drug. In patients with β-thalassaemia, the administration of deferiprone at doses of 37.5 mg/kg twice-daily yields Cmax of 34.6 mg/L and area under the plasma concentration-time curve (AUC) of 137.5 mg/L • h (6,7). On the other hand, peak serum concentrations were 17.53 mg/L and 11.82 mg/L in fasting and fed states, respectively after a dose of 25 mg/kg (8). Deferiprone is for the most part inactivated by glucuronidation (>85%) and more than 90% of the drug is cleared from plasma within 6 hours of ingestion, with an elimination half-life of 1 to 2.5 hours in patients affected by β-thalassaemia (5,6,9–16). The chelating effect of deferiprone results from the formation of a 3:1 complex with iron, which is eliminated mainly through the kidneys, as is the free parent drug.

Despite the extensive clinical experience with deferiprone, PK data in children are sparse, and there is effectively no data in children under 6 years of age. To cover this gap, deferiprone was included in the list of priority prepared by the PDCO-EMA. The main objective of this analysis is to appropriately characterise the systemic exposure to deferiprone in paediatric patients aged less than 6 years using a model-based approach and to assess the effect of demographic and physiological factors on the drug's pharmacokinetics. Furthermore, it is our endeavour to identify the dose levels yielding drug exposure comparable to adults.

Methods

Clinical Study

This experimental and modelling study is a multi-centre, randomised, single blind, single dose PK study to evaluate the pharmacokinetics of deferiprone in children aged less than 6 years affected by transfusion-dependent haemoglobinopathies.

The pharmacokinetics of deferiprone was evaluated using data collected from the DEEP-1 Pharmacokinetic Study (EudraCT, 2012-000658-67, clinicaltrial.gov reference number: NCT01740713), in which enrolled patients were randomised to one of three dose levels (8.3, 16.7 and 33.3 mg/kg). Deferiprone was administered as a single oral dose (80 mg/ml solution). This study was sponsored and performed by the DEEP Consortium (www.deep.cvbf.net) according to an approved PIP (EMEA-001126-PIP01-10). Patients undergoing a chronic transfusion program (receiving at least 150 ml/kg/year of packed red blood cells) and, if naïve to any chelation therapy, having ferritin levels > 800 ng/ml were considered eligible for the study. In addition, amongst other criteria, patients with Hb levels less than 8 g/dl, abnormal liver function, and severe heart dysfunction secondary to iron overload or serum creatinine levels above the upper normal level were excluded from the study. The study protocol was approved by national Ethics Committees and parental consent was obtained for patients' enrolment. All experimental procedures were performed in accordance to good clinical practice guidelines and to the 1964 Helsinki declaration and its later amendments. In brief, 18 children aged less than 6 years (9 males and 9 females) who had received the active medication were included in the analysis. Recruitment of up to 30 patients was provided for by protocol to ensure a minimum sample size of 18 evaluable subjects. In practice, the use of nonlinear mixed-effects modelling allowed completing the study with the data of the first 18 evaluable subjects by providing accurate and precise estimates of the main parameters of interest. Blood samples (2 ml) for the evaluation of DPF concentrations were collected according to WHO guidelines, with total blood volume collected per patient not exceeding the maximum recommended values. A matrix was used for sampling purposes, including one pre-dose sample and the following sampling times after dosing: 0.167, 0.25, 0.333, 0.67, 0.83, 0.916, 1.083, 1.167, 1.25, 1.416, 4.5, 5.5, 6, 7 and

8 hours. A maximum of 5 post-dose samples were collected per subject according to 3 different sampling schemes derived from an optimal design analysis previously performed by our group (unpublished results). Blood samples were drawn by peripheral venous catheter following discard of 2 ml of blood; catheters were filled with saline (i.e., saline lock) between sampling times. Samples were collected in citrate tubes and maintained at 4 °C in water and ice until centrifugation; a maximum interval of 1 hour was allowed between sample collection and centrifugation. Samples were then centrifuged at 2000 x g for 10 minutes at 4 °C and plasma was thereafter transferred into a cryo-vial and stored at -80 °C until analysis.

Bioanalysis

Deferiprone plasma concentrations were analysed by the laboratory of the Division of Pharmacology (Leiden, the Netherlands) using a validated method previously developed by ApoPharma (Toronto, Canada) consisting of high performance liquid chromatography with UV detection (HPLC-UV) without internal standard (17). Extraction of deferiprone from supernatant was performed after precipitation of plasma proteins by trichloroacetic acid (TCA - 15%) and centrifugation at 10,000 g for 20 minutes at 4 ^{o}C. The analytical column used for the analysis was a Hamilton PRP-1 and separation of the chromatogram of interest was achieved using an isocratic mobile phase (pH 7.0). Mean retention time for deferiprone was 5.945 min (standard deviation: 0.087 min). The analytical range was between 3.13 and 800 μM (equivalent to 0.43 to 111 μg/ml) and an R^2 value > 0.98 was used as acceptance criterion for the calibration curve. The lower limit of quantification (LLOQ) was 0.238 μM (equivalent to 0.033 μg/ml). Inter- and Intra-day accuracy and precision were always below 6 %, except for the inter-day precision at 3.13 μM which was found to be 10.7 %.

Pharmacokinetic modelling

Nonlinear mixed effects modelling was performed in NONMEM version 7.2 (Icon Development Solutions, USA). Model building criteria included: (i) successful minimisation, (ii) standard error of estimates, (iii) number of significant digits, (iv) termination of the covariance step, (v) correlation between model parameters and (vi) acceptable gradients at the last iteration.

Fixed and random effects were introduced into the model in a stepwise manner. Inter-individual variability in pharmacokinetic parameters was assumed to be log-normally distributed. A parameter value of an individual *i* (post hoc value) is therefore given by the following equation:

$\theta_i = \theta TV * e^{\eta i}$

in which θTV is the typical value of the parameter in the population and η_i is assumed to be a random variable with zero mean and variance ω^2. Residual variability, which comprises measurement and model error, was described with a proportional error model. This means for the j^{th} observed concentration of the i^{th} individual, the relation Y_{ij}:

$Y_{ij} = F_{ij} + \varepsilon_{ij} * W$

where F_{ij} is the predicted concentration and ε_{ij} the random variable with mean zero and variance σ^2. W is a proportional weighing factor for ε.

Goodness of fit was assessed by graphical methods, including population and individual predicted vs. observed concentrations, conditional weighted residual vs. observed concentrations and time, correlation matrix for fixed vs. random effects, correlation matrix between parameters and covariates and normalised predictive distribution error (NPDE) (18,19). Comparison of hierarchical models was based on the likelihood ratio test. A

superior model was also expected to reduce inter-subject variability terms and/or residual error terms.

With the objective of increasing the stability of the model and reducing the uncertainty around the parameters of interest, the use of the Normal-Inverse Wishart Prior (NWPRI) approach was used in NONMEM (20) to test the impact on the estimates of the fixed and random effects in the pharmacokinetic model under development. Primary PK parameters estimated with a previously developed model in adults (21) were used as prior information for the pharmacokinetic analysis of deferiprone in the target population.

Covariate analysis

Continuous and categorical covariates were tested during the analysis. The relationship between individual PK parameters (post-hoc or conditional estimates) and covariates was explored by graphical methods (plot of each covariate vs. each individual parameter). Relevant demographic covariates (body weight, height, age and gender) were entered one by one into the population model (univariate analysis). After all significant covariates had been entered into the model (forward selection), each covariate was removed (backward elimination), one at a time. The model was run again and the objective function recorded. The likelihood ratio test was used to assess whether the difference in the objective function between the base model and the full (more complex) model was significant. The difference in – 2Log likelihood (DOBJF) between the base and the full model is approximately χ^2 distributed, with degrees of freedom equal to the difference in number of parameters between the two hierarchical models. Because of the exploratory nature of this investigation, for univariate analyses, additional parameters leading to a decrease in the objective function of 3.84 was considered significant (p<0.05). During the final steps of the

model building, only the covariates which resulted in a difference of objective function of at least 7.88 (p<0.005) were kept in the final model.

Model validation

The validation of the final pharmacokinetic model was based on graphical and statistical methods, including visual predictive checks (18). Given the importance of the validation procedures for the subsequent use of a model for simulation purposes, in this study we have included a wide range of diagnostic methods to assess the accuracy of the parameter estimates and the predictive performance of the model (19). Bootstrap was used to identify bias, stability and accuracy of the parameter estimates (standard errors and confidence intervals). The bootstrap procedures were performed in PsN v3.5.3 (University of Uppsala, Sweden) (22), which automatically generates a series of new data sets by sampling individuals with replacement from the original data pool, fitting the model to each new data set. Subsequently, parameter estimates were used to simulate plasma concentrations in subjects with similar demographic characteristics, dosing regimens and sampling scheme as in the original clinical studies. Mirror plots were also generated to evaluate the variance-covariance structure of the parameters in the model, which is reflected by the degree of similarity between the original fit and the pattern obtained from the fitting of the simulated data sets using the final pharmacokinetic model.

PK bridging and dosing recommendations

To optimise the deferiprone dosing regimen in the target population, simulations were performed to achieve systemic exposure values similar to the adult reference population (21). Simulations were carried out to explore how differences in demographic covariates

might affect steady-state exposure to deferiprone treatment. Sampling frequency and times were based on a serial sampling scheme for the purposes of estimating AUC, Cmax and Css over the dosing interval. Integration of the concentration time data was applied according to the trapezoidal rule to ensure realistic estimates of variability. The adequacy of the simulated dosing regimens was assessed graphically by determining the fraction of the paediatric population reaching systemic exposure comparable to the target value based on PKPD reference in adults.

A study including a one week treatment according to a t.i.d. regimen was chosen for the simulation. Each scenario consisted of 1000 simulations. Two dosing regimens were simulated in both populations: 75 and 100 mg/kg/day as three daily doses of 25 and 33.3 mg/kg respectively. The pharmacokinetic parameters of interest (AUC, Cmax and Css) were measured after administration of the first dose on day 7.

A pharmacokinetic model developed in adult healthy volunteers (21) was used to simulate deferiprone exposure in the reference population. A population of 100 subjects (50 males and 50 females) with a body weight distribution of mean 55 and sd 7.5 kg was used to characterise a standard adult thalassaemic population.

The final PK model developed during this analysis was used to simulate deferiprone exposure in the population of interest. A population of 100 subjects (50 males and 50 females) with a body weight distribution of mean 16 and sd 2.0 kg was used to characterise a standard thalassaemic population of children below 6 years of age.

Results

Population Pharmacokinetic Modelling

Data from 18 evaluable children (9 males and 9 females) were used for the pharmacokinetic analysis. Patients were randomised to 3 dose levels (8.3, 16.7 and 33.3 mg/kg) with 6 patients assigned to each group. 16 patients were diagnosed with β-thalassaemia major and 2 with thalassodrepanocytosis. Median (range) body weight, height and age of the children were respectively 15.8 (11-22.5) kg, 99.2 (83-117) cm and 3.4 (1.2-5.9) years. An overview of the baseline demographic characteristics is presented in table 1.

The pharmacokinetics of deferiprone after oral administration to paediatric patients was described by a one-compartment open model with first-order absorption and elimination processes. The absorption rate constant (Ka) represents a first order process. The disposition processes includes (apparent) clearance (CL/F) and (apparent) volume of distribution (V/F).

Between subject variability (BSV) was tested on each parameter, and was included in the final model on CL/F and V/F. An omega block was implemented in the estimation of BSV for CL/F and V/F, accounting for the expected correlation between these two parameters. The inclusion of the omega block significantly decreased the OBJF.

Different error models were tested to characterise residual variability; e.g., additive, proportional, exponential, combined, etc. The proportional error model provided the best results and was kept to describe the residual variability.

The use of the Normal-Inverse Wishart Prior (NWPRI) approach was used in NONMEM to estimate the fixed effect on the PK parameter Ka and the BSV for CL/F and V/F. The use of a prior allowed a better description of the data, reducing significantly the uncertainty around the parameters above mentioned. The prior information was derived from a population PK

analysis performed in healthy adults receiving deferiprone as a 100 mg/ml solution (21). The following values were used for the different parameters: 8.2 h^{-1} for Ka with an uncertainty of 4.02; 0.057 (23.8%) variation on CL/F and 0.0278 (16.6%) variation on V/F with an omega block of 0.0345. 54 degrees of freedom were chosen for the prior on the BSV parameters given that 55 individuals were used for the final population PK model in the healthy adults.

During covariate model selection, after a visual explorative analysis of the correlations between covariates and model parameters, the effect of weight, height, gender, and age was tested on the different parameters. The inclusion of body weight on CL/F and V/F according to fixed allometric scaling (23) led to the highest improvement in the model fitting and allowed a better description of the data, increasing the model performance. The exponent was fixed to 0.75 and 1 for CL/F and V/F respectively. The final parameter estimates are summarised in table 2.

A bootstrap analysis was performed to assess model stability. The mean parameter estimates from the bootstrap analysis were found to be in close agreement with the final model estimates, and the CV values were found to be all below 15%, indicating that the final estimates are indeed reliable. Results of the bootstrap analysis can also be found in Table 2.

Internal model validation diagnostics were satisfactory. Individual predicted profiles and goodness-of-fit plots revealed that the model provides an adequate and non-biased description of the data, as shown in Figures 1 and S1. In addition, NPDE summaries (Figure S2) show that the discrepancy between predicted and observed values can be assumed to be normally distributed. The predictive performance of the model in subsequent simulations was deemed critical to achieve the objective of our analysis. To this purpose, visual predictive checks were therefore used to assess whether the variance and covariance

structures have been well characterised (Figure 2). Overall these diagnostic techniques confirm that the final model is suitable for the purposes of data simulation.

PK bridging and dosing recommendations

The results of the simulations are shown in Figures 3 and 4 and Table 3. A similar exposure is achieved in adults and children in terms of AUC and Css when receiving the current recommended dosing regimen; with median (5-95th quantiles) AUC values respectively of 340.6 (223.2-520) and 318.5 (200.4-499) μmol/L*h at 75 mg/kg/day and 453.7 (297.3-693) and 424.2 (266.9-664) at 100 mg/kg/day t.i.d. doses. The simulation generated a 29% increase in Cmax in children when compared to the adult population.

The performance of an individualised dosing regimen was tested on the target population, but the results show that it does not change significantly the exposure in children when compared to the non-individualised one (at 75 mg/kg/day); not shown here.

Results suggest that the currently approved dosing regimen for the adult population is suitable also for children below 6 years of age in order to achieve a similar and effective exposure.

Discussion

In spite of the changes in legislation for the approval of new medicines for children, the dose rationale for many of the drugs currently approved for paediatric diseases remains unsupported or relies upon weak empirical evidence. Accurate dosing recommendations are critical for the implementation of concepts such as personalised medicines and essential for

the advancement of therapeutics in children. In this context, model-based approaches can be critical for therapeutic decisions when limited evidence is available. This is certainly the case for rare diseases such as haemoglobinopathies, especially when considering young paediatric patients, where practical and ethical constraints make paediatric clinical investigation a true challenge (24,25).

The need for better understanding of the pharmacokinetics, efficacy and safety in the paediatric population led to the establishment of the DEEP consortium (www.deep.cvbf.net). Within this project, a model-based approach has been used to overcome the specific challenge to explore the implications of potential pharmacokinetic differences and ensure adequate dosage in the <6 years of age group. Supporting evidence for the dose rationale was deemed critical before progressing with the evaluation of efficacy and safety in this group of patients. More specifically, the lack of experimental data available on the paediatric use of deferiprone, and in particular deferiprone pharmacokinetics in this group of patients, hampered our ability to assess whether doses used in adults, adjusted linearly for differences in body weight (i.e., doses in mg/kg) produce comparable exposure across the two populations.

There should be little doubt about the therapeutic relevance of defining the appropriate starting dose and dosing regimen for chronic interventions, as in the case or iron chelating agents for the management of iron overload in transfusion-dependent haemoglobinopathies. Modelling and simulation (M&S) techniques have become an invaluable tool for the evaluation of the dose rationale and personalisation of dosing regimens for subgroups of patients and special populations, allowing the characterisation and quantification of the contribution of different sources of variability to an agent's overall pharmacokinetic properties, reducing at the same time the experimental burden on such a

vulnerable population (26–28). In addition, M&S techniques can be used in conjunction with other advanced statistical concepts to optimise protocol design, increasing the quality of the information gathered. Two concrete advantages of the approach include the reduction in the number of patients required and the use of sparse blood sampling. Here we have shown the implementation of these concepts in the design, conduct and analysis of a clinical study. Our results clearly show the importance of establishing the dose rationale before evaluating the efficacy and safety of deferiprone in paediatric patients affected by transfusion-dependent haemoglobinopathies.

Pharmacokinetic modelling

The pharmacokinetics of deferiprone after oral administration to paediatric patients was successfully characterised by a model-based approach. As shown in the results section a one-compartment open model with first-order absorption and elimination processes described satisfactorily the PK profile of the drug under investigation, allowing precise and accurate characterisation of the main PK parameters of interest (Table 2). Body weight was found to be a significant predictor of changes in the distribution and elimination processes of the drug; the relationship with CL/F and V/F was described by fixed allometric scaling. Furthermore, the use of prior information in the adult population allowed a more stable characterisation of the absorption profile, showing once more how M&S techniques can overcome the limited evidence generated in the clinical study. Of note is the fact that the use of a dosing regimen based on mg/kg deferiprone did produce comparable systemic levels, despite the nonlinear (allometric) relationship between body weight and clearance. There are a number of possible reasons that may explain our findings. In fact, previous publications have shown linear correlation between dose, body weight and clearance for

biologicals and some small molecules. In general, such a linear correlation is likely to occur for drugs with small volumes of distribution, which correspond to the drug distribution in plasma and lymph (e.g., warfarin) or total body water (e.g. theophylline). By contrast, deferiprone shows a relatively large apparent volume of distribution (i.e., approximately 1.12 L/kg), but these values could well be the consequence of the 3:1 ratio for deferiprone-iron complex formation, rather than due to distribution beyond total body water (29-30).

Dosing recommendations

Given that paediatric patients are likely to initiate chelation therapy approximately after one year from the start of blood transfusions, the use of chelating agents is not clinically justified before 1.5-2 years of age. The therapeutic context in which deferiprone should be used in this patient population has therefore been accurately captured by the pharmacokinetic modelling approach here. It can be assumed that differences in drug disposition are determined by the effect of size (body weight). The impact of metabolic maturation at the start of chelation therapy can be considered minor.

The availability of a population pharmacokinetic model in children allows bridging concepts to applied, enabling the assessment of the dosing requirements to achieve drug levels which correspond to the efficacious exposure in adults. Using the pharmacokinetic parameter estimates from the current study and from a model developed previously in adults (21), simulations were performed to demonstrate how exposure to deferiprone in children below 6 years of age compares to drug levels in the adult patient population after administration of the currently recommended dosing regimen.

As shown in Figures 3 and 4, AUC and Css distributions are comparable at 75 mg/kg/day and 100 mg/kg/day respectively, whereas an increase in peak concentrations (Cmax) is predicted

in children. This increase is most probably due to differences in the volume of distribution between the two groups, and is expected to have limited clinical implications. Overall exposure (AUC and Css) is the determinant of the response, and changes in Cmax are not expected to modify the safety profile of the drug. This is confirmed in literature where previous studies in children exposed to a 100 mg/kg/day dosing regimen have safety profiles similar to those reported in adults (31–33).

In conclusion, based on these findings, a dosing regimen of 25 mg/kg t.i.d. (75 mg/kg/day) is recommended for children younger than 6 years of age, with the possibility of titration up to 33.3 mg/kg t.i.d. (100 mg/kg/day), if necessary. It is worth mentioning that this dose will be used to conduct an efficacy-safety comparative phase III study and will be adopted in future SmPC modifications.

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Conflict of interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: F.B. had financial support from the DEEP consortium (sponsored by the European

Union); no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Table and figure legends

Table 1: Baseline and demographic characteristics of the pharmacokinetic analysis population.

N=18	**Mean**	**SD**
Weight (kg)	16.08	3.18
Height (cm)	98.95	9.16
Age (year)	3.62	1.33

Table 2: Population pharmacokinetic parameters of deferiprone in children below 6 years of age and bootstrap results.

Model predicted primary PK parameters				
	Estimate	**SE**	**Bootstrap[a] (mean)**	**CV (%)**
CL/F (L/h)	8.3	0.569	8.30	8.07
V/F (L)	18.7	1.16	18.74	7.95
Ka (h-1)	9.13	1.41	8.91	10.54
WT on V/F Fix allom.	1 FIX	/	1 FIX	/
WT on CL/F Fix allom.	0.75 FIX	/	0.75 FIX	/
Error (prop)	0.0953	0.0182	0.0916	39.3
IIV CL/F[b]	0.0644	0.0115	0.0642	11.37
IIV V/F[b]	0.0392	0.0077	0.0393	13.23
Block CL-V	0.031	0.0058	0.0313	12.14
Model predicted secondary PK parameters stratified per dose level				
	Median (5th and 95th quantiles)			
	8.3 mg/kg	**16.7 mg/kg**	**33.3 mg/kg**	
AUC_{0-8} (µmol/L*h)	116.7 (90.6-129.0)	210.0 (173.1-266.6)	428.8 (291.4-547.8)	
Cmax (µmol/L)	61.7 (45.1-80.7)	119.8 (106.0-154.0)	229.5 (179.7-278.1)	
Tmax (h)	0.33 (0.19-0.92)	0.33 (0.21-0.63)	0.37 (0.27-0.42)	
Css (µmol/L)	2.1 (1.6-2.3)	3.7 (3.1-4.9)	7.7 (5.1-10.0)	
Cmin (µmol/L)	1.5 (0.92-2.6)	1.9 (0.79-5.5)	6.8 (3.1-13.9)	

[a] 0 minimisation terminated out of 500

[b] Eta shrinkage was -11% and 0% for CL/F and V/F respectively

Table 3: Summary statistics of the simulation scenarios for the PK bridging study.

	75 mg/kg/day						100 mg/kg/day					
	Adults			Children			Adults			Children		
	AUC	Cmax	Css	AUC	Cmax	Css	AUC	Cmax	Css	AUC	Cmax	Css
Median	318.5	132.2	5.5	340.6	170.7	5.9	424.2	176.0	7.4	453.7	227.4	7.9
1st quartile	263.9	109.2	4.6	286.6	145.0	5.0	351.5	145.4	6.1	381.8	193.2	6.6
3rd quartile	383.0	159.0	6.7	404.7	200.5	7.0	510.0	211.9	8.8	539.0	267.1	9.4
5th quantile	200.4	81.6	3.5	223.2	114.9	3.9	266.9	108.7	4.6	297.3	153.1	5.2
95th quantile	499.0	205.6	8.7	520.0	253.0	9.0	664.0	273.9	11.5	693.0	337.0	12.0

AUC: µmol/L*h; Cmax: µM/L; Css: µM/L

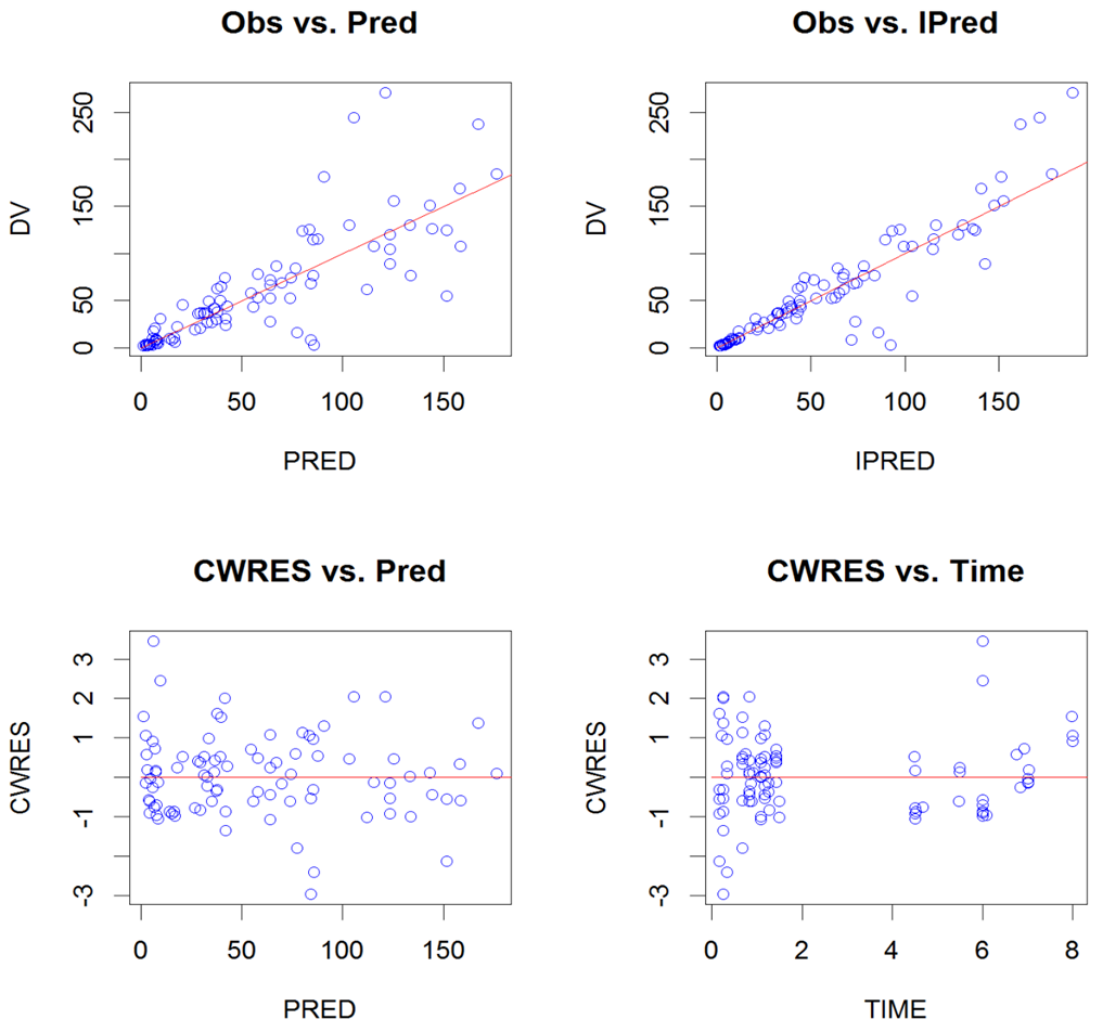

Figure 1: Goodness-of-fit plots. Upper panels show the observed data (Obs) vs. individual predictions (IPred) (left) and the observed data vs. population predictions (Pred) (right). Lower panels show the conditional weighted residuals (CWRES) vs. population predictions (left) and the CWRES vs. time (left).

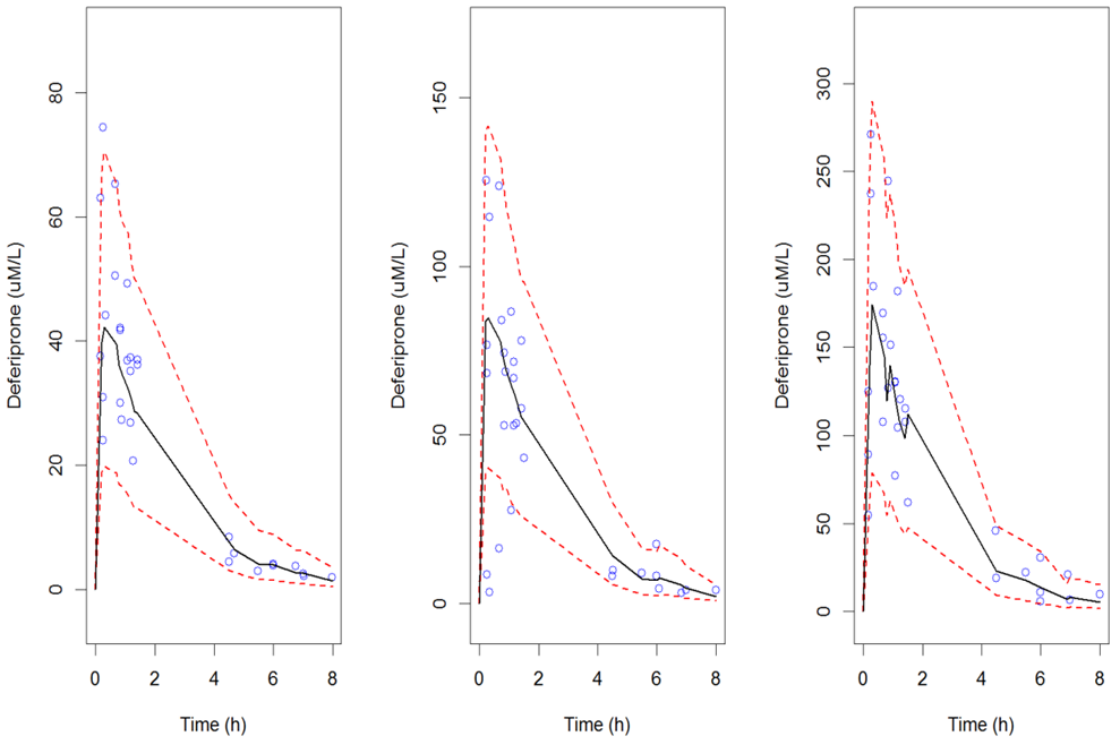

Figure 2: Visual Predictive Check (VPC): observed data are plotted using blue circles; the black solid line represents the median of the simulated data; the red dashed lines represent the 5th and 95th percentiles of the simulated data. The left, mid and right panels show respectively dose group 1 (8.3 mg/kg), 2 (16.7 mg/kg) and 3 (33.3 mg/kg).

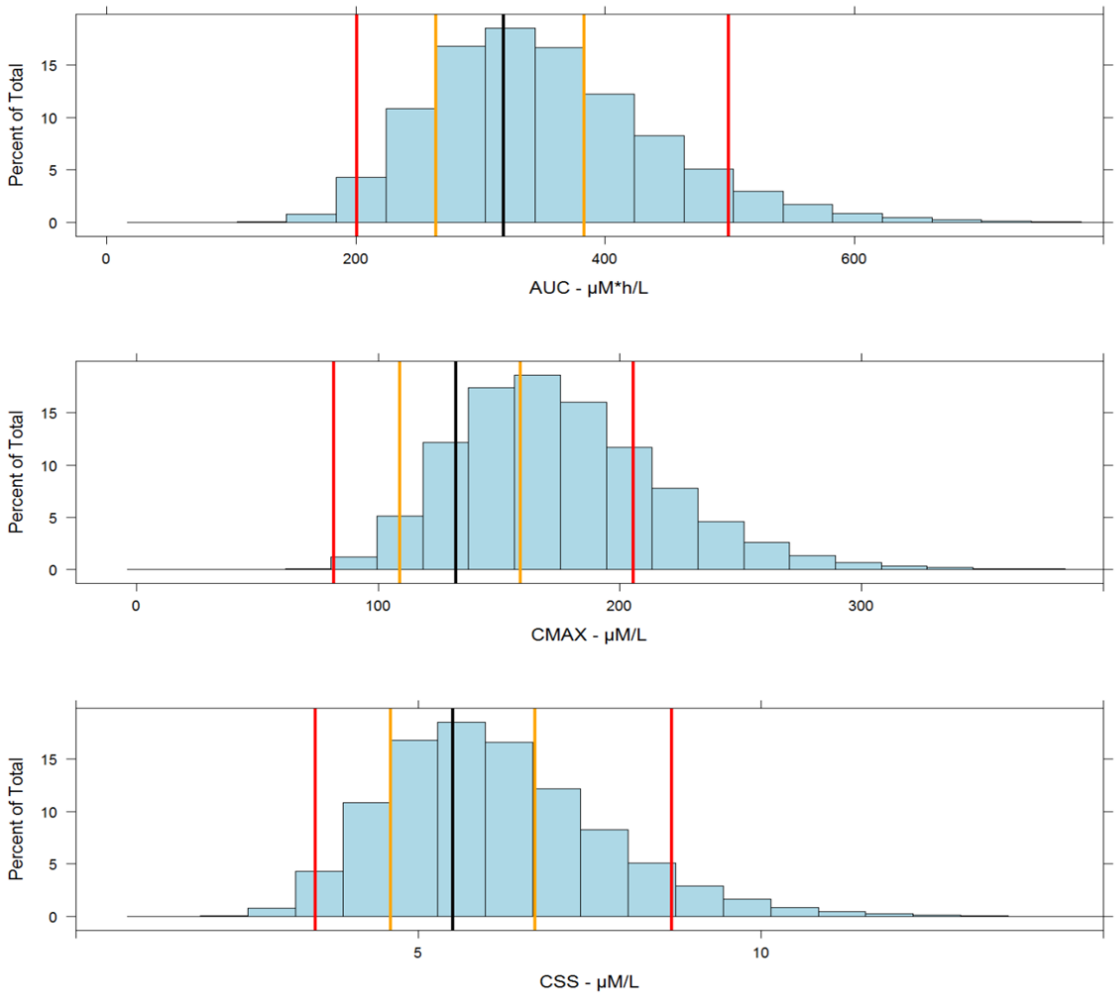

Figure 3: Predicted deferiprone exposure expressed as AUC 0-8 (upper panel), Cmax (mid panel) and Css (lower panel) for children below 6 years of age receiving 75 mg/kg/day. The black line represents the median of the reference population (adults' thalassaemic population), whereas the orange lines represent 1st and 3rd quartiles and the red lines represent 5th and 95th percentiles of the same reference population. Percent of total indicates the percentage of cases for each beam of 1000 simulations with 100 patients in each simulated trial.

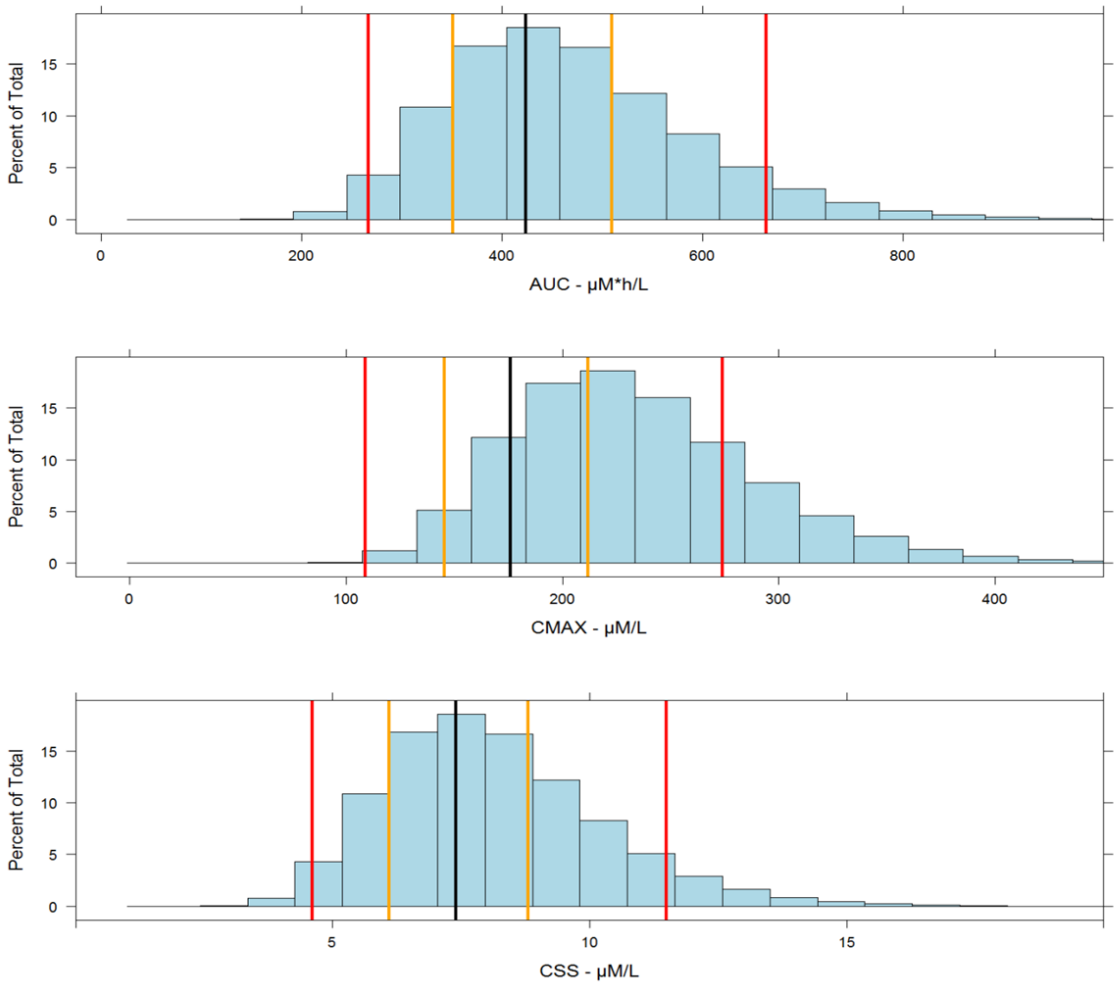

Figure 4: Predicted deferiprone exposure expressed as AUC 0-8 (upper panel), Cmax (mid panel) and Css (lower panel) for children below 6 years of age receiving 100 mg/kg/day. The black line represents the median of the reference population (adult thalassaemic population), whereas the orange lines represent 1st and 3rd quartiles and the red lines represent 5th and 95th percentiles of the same reference population. Percent of total indicates the percentage of cases for each beam of 1000 simulations with 100 patients in each simulated trial.