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**Title:** From data to models: reducing uncertainty in benefit-risk assessment: application to chronic iron overload in children  
**Issue Date:** 2015-09-24
CHAPTER 5

Model-based dosing recommendations for the use of deferiprone in children affected by transfusional iron overload younger than 6 years of age


Submitted for publication

Summary
Despite long clinical experience with deferiprone, there is still limited information on its pharmacokinetics in children and essentially none in children below 6 years of age. The objective of this analysis is to characterise the pharmacokinetics of deferiprone in the target population using a model-based approach and to assess the effect of demographic and physiological factors on drug exposure. Furthermore, it is our aim to ascertain whether equivalent doses on a mg/kg basis produce PK in children consistent with that in adults. Data from 18 paediatric patients receiving deferiprone orally (solution 80 mg/ml) were used for model building purposes. A one-compartment model with first order oral absorption was found to best describe the pharmacokinetics of deferiprone. Goodness-of-fit plots, visual predictive check (VPC) and NPDE summaries indicated that the model provides an unbiased description of the data. Simulation scenarios revealed that similar mg/kg dose levels yield comparable exposure in children and adults, with median AUC values respectively of 340.6 and 318.5 \(\mu\)mol/L*h at 75 mg/kg/day and 453.7 and 424.2 at 100 mg/kg/day t.i.d. doses evenly spaced. Based on these 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.
5.1 Introduction

Patients with hemoglobinopathies and certain other conditions 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 1–5. Deferiprone (DFP) is a hydroxypyridinone, which was authorised in Europe in 1999 for the treatment of iron overload in patients with β-thalassaemia major when deferoxamine (DFO) is contraindicated or inadequate. When administered orally, DFP is rapidly and well absorbed. Plasma levels show peak concentrations (Cmax) within 1 hour of administration. Food reduces its absorption rate without affecting the overall exposure to the drug. In patients with β-thalassaemia, the administration of deferiprone at doses of 75 mg/kg/day as a twice-daily regimen 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. DFP is for the most part inactivated by glucuronidation (>85%) and more than 90% of the drug is removed 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. DFP forms a 3:1 complex with iron, which is removed mainly through the kidneys, as is the free parent drug. Despite the extensive clinical experience with DFP, there are few PK data in children, and effectively none 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 of DFP 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 DFP exposures comparable to those in adults.

5.2 Methods

Clinical Study

This experimental and modelling study is a multi-centre, randomised, single blind, single dose PK study to evaluate the pharmacokinetics of DFP in children aged from one month to less than 6 years affected by transfusion-dependent haemoglobinopathies. The pharmacokinetics of deferiprone was evaluated using data collected from the clinical study: DEEP-1 PK Study (EudraCT, 2012-000658-67), in which paediatric patients affected by transfusion-dependent haemoglobinopathies received a single oral dose of DFP as an 80 mg/ml solution. 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 above 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 not considered eligible for inclusion in the study. Patients were randomised to three dose levels: 8.3, 16.7 and 33.3 mg/kg. The study was performed within the DEEP Consortium (www.deep.cvbf.net) according to an approved PIP (EMEA-001126-PIP01-10). The study protocol was approved by concerned Ethics Committees and all experimental procedures performed according to good clinical practice guidelines. In brief, 18 children aged from 1 month to 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 for the evaluation of deferiprone concentrations were taken before (one pre-dose sample) and at 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 sampling schemes selected based on 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. Mean (sd) age (years), body weight (kg) and height (cm) of the patient population were 3.62 (1.33), 16.08 (3.18) and 98.95 (9.16) respectively.

**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). 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 ºC. 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). The analytical range was between 3.13 and 800 µM (equivalent to 0.43 to 111 µg/ml); and an R² value greater than 0.98 was required to accept the standard 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 \( \theta_{TV} \) is the typical value of the parameter in the population and \( \eta_i \) is assumed to be a random variable with zero mean and variance \( \omega^2 \). 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 \( \varepsilon_{ij} \) the random variable with mean zero and variance \( \sigma^2 \). \( W \) is a proportional weighing factor for \( \varepsilon \).

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) \(^{17,18}\). 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 \(^ {19} \) 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 \(^ {20} \) were used as prior information for the pharmacokinetic analysis of DFP 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 \(-2\text{Log likelihood (DOBJF)}\) between the base and the full model is approximately \(\chi^2\) 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 \(^{17}\). 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 \(^{18}\). 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) \(^{21}\), 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 \(^{20}\). 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 duration of one week 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 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.

5.3 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. Mean (and sd) body weight, height and age of the children were respectively 16.08 (3.18) Kg, 98.95 (9.16) cm and 3.62 (1.33) years.

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 include (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 \(^20\). The following values were used for the different parameters: 8.2 h\(^{-1}\) for Ka with an uncertainty of 4.02; 0.057 (23.87\%) variation on CL/F and 0.0278 (16.67\%) 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 \(^22\) 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. An overview of the final parameter estimates is provided in Table 1.

Table 1. Population pharmacokinetic parameters of deferiprone in children below 6 years of age and bootstrap results

<table>
<thead>
<tr>
<th>Model predicted primary PK parameters</th>
<th>Estimate</th>
<th>SE</th>
<th>Bootstrap(^a) (mean)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>8.3</td>
<td>0.569</td>
<td>8.30</td>
<td>8.07</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>18.7</td>
<td>1.16</td>
<td>18.74</td>
<td>7.95</td>
</tr>
<tr>
<td>Ka (h(^{-1}))</td>
<td>9.13</td>
<td>1.41</td>
<td>8.91</td>
<td>10.54</td>
</tr>
<tr>
<td>WT on V/F Fix allom.</td>
<td>1 FIX</td>
<td>/</td>
<td>1 FIX</td>
<td>/</td>
</tr>
<tr>
<td>WT on CL/F Fix allom.</td>
<td>0.75 FIX</td>
<td>/</td>
<td>0.75 FIX</td>
<td>/</td>
</tr>
<tr>
<td>Error (prop)</td>
<td>0.0953</td>
<td>0.0182</td>
<td>0.0916</td>
<td>39.3</td>
</tr>
<tr>
<td>IIV CL/F(^b)</td>
<td>0.0644</td>
<td>0.0115</td>
<td>0.0642</td>
<td>11.37</td>
</tr>
<tr>
<td>IIV V/F(^b)</td>
<td>0.0392</td>
<td>0.0077</td>
<td>0.0393</td>
<td>13.23</td>
</tr>
<tr>
<td>Block CL-V</td>
<td>0.031</td>
<td>0.0058</td>
<td>0.0313</td>
<td>12.14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model predicted secondary PK parameters stratified per dose level</th>
<th>Median (5(^{th}) and 95(^{th}) quantiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1(^c)</td>
</tr>
<tr>
<td>AUC(_{0-8}) ((\mu)mol/L*h)</td>
<td>116.7 (90.6-129.0)</td>
</tr>
<tr>
<td>Cmax ((\mu)mol/L)</td>
<td>61.7 (45.1-80.7)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.33 (0.19-0.92)</td>
</tr>
<tr>
<td>Css ((\mu)mol/L)</td>
<td>2.1 (1.6-2.3)</td>
</tr>
<tr>
<td>Cmin ((\mu)mol/L)</td>
<td>1.5 (0.92-2.6)</td>
</tr>
</tbody>
</table>

\(^a\) 0 minimisation terminated out of 500; \(^b\) Eta shrinkage was -11\% and 0\% for CL/F and V/F respectively; \(^c\) 8.3 mg/kg; \(^d\) 16.7 mg/kg; \(^e\) 33.3 mg/kg
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 be found in Table 1.

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 2.

![Figure 1](image)

**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. Individual plots: observed data are plotted using blue circles; the black solid line represents the population prediction (Pred) and the red solid line represents the individual predictions (IPred). Panel A shows patients in dose group 1 (8.3 mg/kg); panel B shows patients in dose group 2 (16.7 mg/kg); and panel C shows patients in dose group 3 (33.3 mg/kg).

In addition, NPDE summaries (Figure 3) 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 4). Overall these diagnostic techniques confirm that the final model is suitable for the purposes of data simulation.
Figure 3. Normalised prediction distribution errors: upper panels show the QQ-plot of the distribution of the NPDEs for a theoretical N(0, 1) distribution (left) and the histogram of the distribution of the NPDE together with the density of the standard normal distribution (right). Lower panels show the NPDEs vs. time (left) and NPDEs vs. individual predictions (right).
CHAPTER 5

Figure 4. Visual Predictive Check (VPC): observed data are plotted using open circles; the black solid line represents the median of the simulated data; the dashed lines represent the 5th and 95th quantiles 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).

PK bridging and dosing recommendations
The results of the simulations are shown in Figures 6 and 7 and Table 2. A similar exposure is achieved in adults and children in terms of AUC and Css when receiving the current recommended dosing regimen both at 75 and 100 mg/kg/day. 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.
Figure 5. 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 (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.
**Figure 6.** 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.
Table 2. Summary statistics of the simulation scenarios for the PK bridging study.

<table>
<thead>
<tr>
<th></th>
<th>75 mg/kg/day</th>
<th></th>
<th>100 mg/kg/day</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td></td>
<td>AUC  Cmax</td>
<td>Css</td>
<td>AUC  Cmax</td>
<td>Css</td>
</tr>
<tr>
<td>Median</td>
<td>318.5</td>
<td>132.2</td>
<td>5.5</td>
<td>340.6</td>
</tr>
<tr>
<td>1st quartile</td>
<td>263.9</td>
<td>109.2</td>
<td>4.6</td>
<td>286.6</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>383.0</td>
<td>159.0</td>
<td>6.7</td>
<td>404.7</td>
</tr>
<tr>
<td>5th quantile</td>
<td>200.4</td>
<td>81.6</td>
<td>3.5</td>
<td>223.2</td>
</tr>
<tr>
<td>95th quantile</td>
<td>499.0</td>
<td>205.6</td>
<td>8.7</td>
<td>520.0</td>
</tr>
</tbody>
</table>

AUC: μmol/L*h; Cmax: μmol/L; Css: μmol/L

5.4 Discussion and Conclusion

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 wisely imposed by regulatory authorities, make paediatric clinical investigation a true challenge. The lack of exhaustive experimental data available on the use of deferiprone in children including deferiprone pharmacokinetic data in children below 6 years of age hampered the ability to assess whether doses, used in adults, adjusted for weight, would produce comparable exposure in young children. The need for a better understanding of DFP behaviour 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 better understanding DFP behaviour and allowing adequate dosage in the <6 years of age group, reducing at the same time the sampling burden on such a vulnerable population (i.e., by the use of optimal design techniques to increase the quality of the information gathered and by the use of population PK analysis in the presence of sparse sampling). Modelling and Simulations (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. Furthermore, continuous emphasis has been placed on the need for evidence-based clinical and regulatory decisions, where modelling and simulation is becoming more and more an essential component.

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 1). 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 can overcome the limited evidence generated in the clinical study.

**Dosing recommendations**

Bridging concepts are applied in this context to evaluate the exposure in the paediatric population as compared to efficacious exposure in adults. Using the model developed for this population, and a previously developed model in the adult population, simulations were performed to compare PK exposure between children below 6 years of age and a standard thalassaemic adult population. As shown in Figures 6 and 7, 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.

In conclusion, based on these findings, a dosing regimen of 25 mg/kg t.i.d. (75 mg/kg/day) is recommended for children aged from 1 month to < 6 years, with the possibility of titration up to 33.3 mg/kg t.i.d. (100 mg/kg/day), if necessary. Noticeable, this dosage will be used to conduct further efficacy-safety comparative phase III study and will be also adopted in any SmPC possible modifications.
References


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