The handle http://hdl.handle.net/1887/35437 holds various files of this Leiden University dissertation

**Author:** Bellanti, Francesco  
**Title:** From data to models: reducing uncertainty in benefit-risk assessment: application to chronic iron overload in children  
**Issue Date:** 2015-09-24
CHAPTER 3

Population pharmacokinetics of deferiprone in healthy subjects

Francesco Bellanti, Meindert Danhof, and Oscar Della Pasqua

Br J Clin Pharmacol - 2014

Summary

Aims: To characterise the pharmacokinetics of deferiprone in healthy subjects using a model-based approach and assess the effect of demographic and physiological factors on drug exposure.

Methods: Data from 55 adult healthy subjects receiving deferiprone (solution 100 mg/ml) were used for model building purposes. A population pharmacokinetic analysis was performed using NONMEM VII. The contribution of gender, age, weight, and creatinine clearance (CLCR) on drug disposition was evaluated according to standard forward inclusion, backward deletion procedures. Model selection criteria were based on graphical and statistical summaries.

Results: A one-compartment model with first order oral absorption was found to best describe the pharmacokinetics of deferiprone. Simulated AUC and Cmax (respectively mean of 45.80 mg*h/L and 17.67 mg/L after 25 mg/kg single dose and 137.40 mg*h/L and 26.50 mg/L after 75 mg/kg b.i.d.) were comparable with literature references. Gender differences in the apparent volume of distribution (20%) have been identified, which may contribute to an increase in peak concentrations in females. Furthermore, simulation scenarios reveal that dose adjustment is required for patients with reduced CLCR. Doses of 60, 40 and 25 mg/kg for patients showing mild, moderate and severe renal impairment are proposed based on CLCR values of 60-89, 30-59 and 15-29 ml/min, respectively.

Conclusions: Our analysis has enabled the assessment of the impact of gender and CLCR on the pharmacokinetics of deferiprone. Moreover, it provides the basis for dosing recommendations in renal impairment. The implication of these covariates on systemic exposure is currently not available in the prescribing information of deferiprone.
CHAPTER 3

3.1 Introduction

Patients with β-thalassaemia and other transfusion-dependent diseases develop iron overload from chronic blood transfusions and require regular continuous iron chelation to prevent potentially fatal iron-related complications (1–5). Deferiprone (DFP) is the most extensively studied oral iron chelator to date. DFP is a hydroxypyridone derivative, 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.

Despite the wide clinical experience with DFP, its pharmacokinetics has not been fully characterised in patients. In addition, there are still limited experimental data available on DFP in children and no data in children under 6 years of age, where the drug is still used off-label. Thus far, it has been established that when administered orally, DFP is rapidly and completely 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 state, 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 (5,6,9–14). DFP forms a 3:1 complex with iron, which is removed mainly through the kidneys in a similar manner as for the free parent drug. The area under the curve (AUC) of free deferiprone in patients shows high inter-individual variability, which may be related to the variation in the therapeutic response (5,10–12).

The impact of demographic and other physiological factors on the exposure of DFP has not been assessed thus far. In addition, the consequences of such factors for the dosing regimen have not been described in the published literature or on the SmPC (Summary of Product Characteristics) of the drug. Moreover, no information on dose adjustment requirements is provided for patients with hepatic or renal impairment. Given the fast renal elimination of the glucuronide metabolite, renal function is expected to play a major role in affecting the overall exposure to the parent drug.

The aim of this analysis is to characterise the DFP pharmacokinetics in healthy subjects using a model-based approach and assess the effect of demographic and physiological factors on drug exposure. Furthermore, it is our endeavour to show the clinical relevance of simulation scenarios to evaluate the impact of renal impairment on drug disposition and consequently,
for the optimisation of the dosing regimen in special populations. Moreover, we anticipate that the availability of population pharmacokinetic model for deferiprone will facilitate the evaluation of extrapolation of pharmacokinetic data from adults to children. More specifically, it will provide the basis for pharmacokinetic bridging of the dosing regimen for the paediatric population.

3.2 Methods

Data

The pharmacokinetics of deferiprone was evaluated using data collected from two clinical studies: LA20-BA and LA21-BE (15,16), in which healthy subjects received a single dose of 1500 mg of DFP as a 100 mg/ml solution. The studies have been conducted in full conformance with the principles of the Declaration of Helsinki and with the local laws and regulations concerning clinical trials. The protocol and the informed consent documents for each study have been formally approved by the relevant research ethics committee of each clinical site. The data was supplied by ApoPharma Inc, Canada and shared within the DEEP consortium (www.deep.cvbf.net). The DEEP consortium addresses an EU call with the objective of increasing the knowledge of deferiprone chelation therapy in the paediatric population.

Both study protocols were approved by Ethics Committee and all experimental procedures performed according to good clinical practice guidelines. In brief, 55 adult healthy subjects (39 males and 16 females) who had received the active medication were included in the analysis. Blood samples for the evaluation of deferiprone concentrations were taken before and at the following sampling times after dosing: 0.167, 0.333, 0.5, 0.75, 1, 1.333, 1.5, 1.667, 2, 2.5, 3, 4, 5, 6, 8, 10, and 14 hours. On average, 15 samples were collected per subject. Median (range) age (years) and body weight (kg) of the adult population were 39 (19-55) and 72 (52-92) respectively.

Bioanalysis

Deferiprone plasma concentrations were analysed by a validated method previously developed by ApoPharma (Toronto, Canada) using 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 UV detector was set at 280 nm. In a recent review of the method, calibration, accuracy and precision estimates have been revisited by our group. 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 1 µM (equivalent to 0.14 µg/ml). Inter- and Intra-day accuracy and precision were found to be always below 10%, subsequently matching the GLP validation criteria (17).

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. 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:

$$\theta_i = \theta_{TV} \cdot e^{\eta_i}$$

in which $\theta_{TV}$ is the typical value of the parameter in the population and $\eta_i$ is assumed to be 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 jth observed concentration of the ith individual, the relation $Y_{ij}$:

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

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) (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.

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, age, gender, creatinine clearance) 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 $-2\log$ 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 (15). 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 (16). 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) (20), 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.

In addition to the graphical analysis, posterior predictive check was performed using AUC (area under the plasma concentration vs. time curve) and Cmax (peak plasma concentration) as a measure of model performance. AUC and Cmax values were calculated non-compartmentally by trapezoidal method from simulations of 1000 data sets with the same demographic characteristics, dosing regimens and sampling scheme as in the original clinical studies.

The distribution of model-predicted AUC and Cmax values were presented for geometric mean, lower and upper boundaries of the 95% confidence intervals and compared to the findings from non-compartmental analysis in the two clinical studies. Model performance was demonstrated by the location of the original estimates across the predicted distribution (histograms).
Simulation scenarios
Simulations were performed using the final model to assess whether predicted secondary PK parameters, such as AUC and CMAX would be in line with literature references (7,14,21). 30 simulated patients (15 males and 15 females) with a mean body weight of 55 kg (sd 8.4) received DFP under the following dosing recommendations: 25 and 75 mg/kg/day. Furthermore, additional simulation scenarios were evaluated to assess the implications of renal impairment for the pharmacokinetics of deferiprone in a group of patients with similar demographic characteristics, as described above. Taking into account the correlation between the reduction in creatinine clearance and the severity of renal impairment, three scenarios were considered, including 80, 50 and 25% of the normal clearance values. They were meant to reflect the changes in renal function in mild, moderate and severe impairment, respectively. Simulated patients received 75 mg/kg/day DFP and their exposure was compared to healthy subjects (reference population). Dosing regimens were adjusted to ensure that deferiprone exposure similar to the levels observed in the reference population is achieved and maintained irrespective of the degree of renal impairment.

3.3 Results
Population Pharmacokinetic Modelling
The pharmacokinetics of DFP was best described by a one-compartment model with first-order absorption, lag-time to central compartment, and first-order elimination. Inter-individual variability (IIV) could be estimated for apparent clearance (CL/F), apparent volume of distribution (V/F), and absorption rate constant (Ka). Residual variability was characterised by a proportional error model with a weighting factor. During covariate model selection, the effect of age, gender and body weight was tested on relevant pharmacokinetic parameters. Initially when tested separately, significant effects of gender on V/F and body weight on CL/F and V/F were identified and described according to a linear model. However, despite statistical significance and improvement in the goodness-of-fit, the inclusion of body weight on either CL/F or V/F also led to an important reduction in model stability during bootstrapping procedures, which is likely caused by the limited range of the covariate values in the study population. Therefore, only gender on V/F was retained in the final model. This resulted in a better description of the data, subsequently increasing the model performance. An overview of the parameter estimates is presented in Table 1.
Table 1. Population pharmacokinetic parameters of deferiprone and bootstrap results.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Final model</th>
<th>Bootstrap = 500 runs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Median</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>30.8</td>
<td>30.9</td>
</tr>
<tr>
<td>V/F males (L)</td>
<td>78.4</td>
<td>78.53</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>8.2</td>
<td>8.73</td>
</tr>
<tr>
<td>Lagtime (h⁻¹)</td>
<td>0.146</td>
<td>0.145</td>
</tr>
<tr>
<td>Error: weighting factor</td>
<td>2.4</td>
<td>2.41</td>
</tr>
<tr>
<td>V/F females (L)</td>
<td>65.3</td>
<td>65.3</td>
</tr>
<tr>
<td>Eta CL/F (%)</td>
<td>0.057 (23.87 %)</td>
<td>0.0557 (23.6 %)</td>
</tr>
<tr>
<td>Eta V/F (%)</td>
<td>0.0278 (16.67 %)</td>
<td>0.0267 (16.34 %)</td>
</tr>
<tr>
<td>Block CL-V</td>
<td>0.0345</td>
<td>0.0335</td>
</tr>
<tr>
<td>Eta Ka (%)</td>
<td>0.991 (99.54 %)</td>
<td>1.00 (100 %)</td>
</tr>
<tr>
<td>Sigma (%)</td>
<td>0.00566 (7.52 %)</td>
<td>0.00568 (7.53 %)</td>
</tr>
</tbody>
</table>

Internal model validation diagnostics were satisfactory. Individual predicted profiles and goodness-of-fit plots reveal that the model provides an adequate and non-biased description of the data, as shown in Figure 1 and 1S (see supplemental material in appendix). In addition, despite a small deviation at the tails of the distribution, NPDE summaries (Figure 2S, see supplemental material in appendix) show that the discrepancy between predicted and observed values can be assumed to be normally distributed.
Figure 1. Visual Predictive Check and a random selection of individual plots. VPC on the left panel: observed data are plotted using blue circles; the black solid line represents the median of the simulated data; the red solid lines represent the 5th and 95th percentiles of the simulated data. Individual plots of 4 randomly selected patients: 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).

The predictive performance of the model in subsequent simulations was deemed critical to achieve the objective of our analysis. To this purpose, mirror plots were therefore used to assess whether the variance and covariance structures have been well characterised. Lastly, the median parameter estimates from the bootstrap analysis were found to be in close agreement with the results observed during the original fitting. Results from the bootstrap analysis are presented in Table 1. Overall these diagnostic techniques confirm that the final model is suitable for the purposes of data simulation.

Simulation scenarios
First an attempt was made to perform external validation of the model by deriving secondary parameters (AUC and Cmax) and comparing model-predicted estimates literature references (7,14,21). As shown in Figure 2, reference values lie within the distribution of
simulated AUC and Cmax, for which the mean and 90% CI were 45.80 (44.42-47.17) mg*h/L and 17.67 (17.13-18.20) mg/L, respectively after administration of a single oral dose of 25 mg/kg deferiprone and 137.40 (133.27-141.52) mg*h/L and 26.50 (25.70-27.29) mg/L, respectively after administration of 75 mg/kg/day dose as a twice-daily regimen. Despite the gender differences in the volume of distribution, no significant differences observed when comparing Cmax values. This may be explained by the limited number of females in our analysis as well as by the differences in deferiprone formulation used in past protocols.

**Figure 2.** Comparison of secondary PK parameters (Cmax and AUC) with literature references. Predicted DFP exposure expressed as CMAX and AUC for adult patients receiving 25 mg/kg as a single dose and 75 mg/kg/day b.i.d. The dashed black lines depict the mean simulated values, whereas the solid coloured lines depict published results (7, 14, 17). Percent of total indicates the percentage of cases for each beam of 100 simulations with 55 patients in each simulated trial.

As the population available for the analysis was limited to healthy volunteers, the impact of another important covariate could not be estimated during the fitting procedures, namely, the role of glomerular filtration as determined by changes in creatinine clearance. Therefore
a simulation-based approach was used to quantify the implications of renal impairment for the disposition of deferiprone. Systemic exposure expressed as AUC was simulated for three scenarios representing mild, moderate and severe impairment and compared to the estimates obtained for healthy subjects. It is evident from Figure 3 that over-exposure occurs when comparing the three sub-populations receiving 75 mg/kg/day DFP with the reference data, particularly in the case of moderate and severe impairment. Given the magnitude of the increase in systemic exposure, dose adjustment should be recommended for patients with renal impairment.

Figure 3. AUC distributions: 80, 50 and 25% of total clearance (DFP 75 mg/kg/day). Predicted DFP exposure expressed as AUC for adult patients receiving 75 mg/kg/day and presenting 80%, 50% and 25% of the total clearance respectively. The black line represents the median of the reference population which presents normal renal function, whereas 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 100 simulations with 55 patients in each simulated trial.
As shown in Figure 4, dose adjustments can be considered that allow for deferiprone exposure to be maintained at the desired levels for all three scenarios. In addition, Figure 5 depicts the consequence of reduced clearance for the systemic exposure of deferiprone assuming first-order pharmacokinetics in this population. Doses of 60, 40 and 25 mg/kg for patients showing mild, moderate and severe renal impairment are proposed based on creatinine clearance values of 60-89, 30-59 and 15-29 ml/min, respectively. An overview of these recommendations is summarised in Table 2.

**Figure 4.** AUC distributions: 80, 50 and 25% of total clearance (new dosing recommendations). Predicted DFP exposure expressed as AUC for adult patients receiving the adjusted dosing recommendation based on the severity of renal impairment. The three populations present 80%, 50% and 25% of the total clearance respectively. The black line represents the median of the reference population which presents normal renal function, whereas 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 100 simulations with 55 patients in each simulated trial.
Figure 5. AUC – Dose relationship: 80, 50 and 25% of total clearance. AUC – Dose relationship in the presence of renal impairment. The open circles represent the reference population with normal renal function. The open triangles, filled circles and filled triangles represent mild (80%), moderate (50%) and severe (25%) renal impairment respectively.
Table 2. New dosing recommendations for renal impairment.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Degree of impairment</th>
<th>CrCL (ml/min)</th>
<th>Standard dosing recommendations</th>
<th>Proposed dosing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>80% of total Clearance</td>
<td>Mild</td>
<td>60-89</td>
<td>75 mg/kg/day</td>
<td>60 mg/kg/day</td>
</tr>
<tr>
<td>50% of total Clearance</td>
<td>Moderate</td>
<td>30-59</td>
<td>75 mg/kg/day</td>
<td>40 mg/kg/day</td>
</tr>
<tr>
<td>25% of total Clearance</td>
<td>Severe</td>
<td>15-29</td>
<td>75 mg/kg/day</td>
<td>25 mg/kg/day</td>
</tr>
</tbody>
</table>

3.4 Discussion and Conclusion

As generally known, inter-individual variability in PK can significantly affect the outcome of a given therapeutic intervention. Therefore, full optimisation of the therapeutic regimen cannot be achieved without taking variability into account. The use of model-based approaches for the evaluation of the dose rationale and personalisation of dosing regimens for subgroups of patients and special populations has become an invaluable tool as it allows characterisation and quantification of the contribution of different sources of variability to the overall pharmacokinetic properties. This has an even larger impact when considering special populations and rare diseases, as is the case of transfusion dependent diseases and other pathologies associated with renal and hepatic impairment. Despite the continuous emphasis on the need for evidence-based clinical and regulatory decisions, modelling and simulation is becoming an essential component of evidence synthesis, which ultimately underpins decisions and recommendations (22–24).

Deferiprone Pharmacokinetics

With this analysis we show how population pharmacokinetics can be used to explore the implications of different sources of variability on the exposure of the oral iron chelator deferiprone. The estimates of the main parameters of interest (table 1) were in line with previously published results (6,7,10–13,21,25–27). As shown in figure 2, similar agreement was also observed for the secondary PK parameters (AUC and Cmax). By contrast, no gender differences have been identified in previous studies. In this respect, our analysis illustrates the importance of parametric methods for accurate evaluation of covariate effects. We have quantified gender differences in the apparent volume of distribution, where V/F was estimated to be 78.4 and 65.3 L in males and females, respectively (i.e., a 20% difference between the two groups). Assuming that overall exposure (AUC) rather than Cmax is the primary determinant of response, these differences are likely to have minor clinical implications.
Dosing recommendations in patients with renal impairment
Considering the lack of details in the label of DFP regarding the dose rationale for special populations, it was our interest to provide insights on dosing recommendations for patients with renal impairment, which occurs as co-morbidity in thalassaemia. Given that, independently of the metabolic rate, 90% of the total drug (free, metabolised and iron-complex) is excreted in the urine within 5 to 6 hours of ingestion, we have assumed that renal impairment would be clinically more relevant, as compared to hepatic impairment. We have selected a discrete number of scenarios to describe different levels of impairment (mild, moderate and severe). As could be anticipated for any drug with primary renal elimination (28,29), use of the standard recommended dose of 75 mg/kg/day leads to overexposure to deferiprone; especially when clearance is reduced beyond 50% of the normal range. Taking into account the deferiprone levels associated with effective response, dosing regimens are proposed for the three sub-populations allowing exposure to remain comparable to values observed in patients with normal renal function.

A look into the future: rare diseases and special populations
As discussed above, model-based approaches can be critical for therapeutic decisions when limited evidence is available. This is certainly the case for transfusion dependent diseases, especially when considering young paediatric patients, for whom limited data or no data exist and the use of DFP is still off label.
Our analysis represents the first attempt to synthesise current knowledge on the pharmacokinetics of deferiprone and subsequently optimise the dosing regimen in special populations. In addition to renal impairment, we envisage the use of this model for the optimisation of clinical trial design in children. It is worth mentioning that optimisation of protocol design may enable the use of smaller cohorts as well as a considerable reduction in the burden associated with sampling procedures thanks to the use of sparse sampling techniques.

Limitations and Assumptions
Given that the model has been developed on data collected in healthy subjects, questions arise about the relevance of the parameter estimates for the target patient population. No differences have been found in previous analyses between healthy individuals and patients. In the work carried out by Stobie et al. (21), who compared the pharmacokinetics of DFP in healthy individuals with patients affected by β-thalassaemia, only a slight difference in the apparent volume of distribution was observed, but the results were found not to be statistically significant (6,21). Most importantly, the authors did not find any differences in the drug clearance between the two groups. Moreover, AUC and Cmax values simulated by our model (figure 2) were comparable with published data obtained in patients treated with
DFP. We have to acknowledge that a lower mean Cmax is observed when comparing simulated data and reference data at 75 mg/kg/day b.i.d. This could be the consequence of a difference in the Vd observed in patients and/or differences in the formulation. Having said that, we anticipate that such a change should have limited clinical implications for the following reasons: overall exposure is the determinant of the response and AUC values were comparable between the two groups; an increase in Cmax is not expected to have consequences from a safety perspective, as discussed also for gender differences; and additionally the recommended dosing regimen is given as a three times daily administration which further reduces the impact of Cmax changes. We believe therefore that eventual differences in haemodynamics in patient affected by transfusion dependent diseases will not be relevant for the overall disposition properties of deferiprone.

**Conclusion**

In conclusion, our analysis has allowed the identification of the effect of gender on the volume of distribution of DFP and enabled the evaluation of the dosing requirements for patients with renal impairment. The changes in dose regimen proposed for this special population should be considered when prescribing DFP to this population.
References


Appendix

Figure 1S: Goodness-of-fit Plots. Upper panels show the observed data (Obs) vs. population predictions (Pred) (left) and the observed data vs. individual predictions (IPred) (right). Lower panels show the conditional weighted residuals (CWRES) vs. population predictions (left) and the CWRES vs time (left).
Figure 2S: Model validation: normalised prediction distribution errors. Upper panels show the Q-Q-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).