EudraCT No: 2012-000658-67	
Title: Multi-centre, oral single dose experimental and modelling study to evaluate the pharmacokinetics of deferiprone in patients aged from 1 month to less than 6 years of age affected by transfusion-dependent haemoglobinopathies.	
Rationale: deferiprone (DFP) was investigated as therapy for children from 1 month to less than 6 years of age affected by transfusion dependent haemoglobinopathies. A pharmacokinetic study allowed appropriate evaluation of systemic exposure of DFP in the target population. A model-based analysis of the data enabled pharmacokinetic bridging and dosing recommendation for the subsequent non-inferiority study, during which efficacy and safety will be assessed.	
Phase: II a	
Study Period: 31 January 2013 – 17 February 2014	
Study Design: multi-centre, randomised, single blind, and single dose PK study.	
Centres:	
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Site 7	Dr. Carlo Cosmi A.O. Universitaria Policlinico Di Sassari Viale San Pietro, 12 07100 Sassari
Treatment: patients were randomised according to a stratification scheme in which three different dose levels are used. Dose level 1: 8.3 mg/kg as a single dose Dose level 2: 16.7 mg/kg as a single dose	

Dose level 3: 33.3 mg/kg as a single dose

Objectives:

The primary objective of this study was to assess the pharmacokinetics of DFP in paediatric patients aged from 1 month to less than 6 years.

The secondary objectives of this study were:

1) To identify dose levels yielding deferiprone exposures comparable to adults and define the dose rationale in children aged from 1 month to less than 6 years.

2) To evaluate safety and tolerability of deferiprone after single dose administration in children aged from 1 month to less than 6 years.

3) To evaluate the effect of demographic covariates on DFP disposition and estimate the clearance distribution across the population.

It should be noted that in order to fully evaluate the effect of demographic covariates, further integration with prospective data on a larger population may be required.

Pharmacokinetic analysis:

Model building: the time course of deferiprone concentrations was analysed with Nonlinear mixed effects modelling in NONMEM, version 7.2.0. 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. 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). Comparison of hierarchical models was based on the likelihood ratio test. A superior model is also expected to reduce inter-subject variance terms and/or residual error terms. Standard error of the parameter estimates were approximated using the asymptotic covariance matrix.

Covariate 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 (i.e., body weight, age, height) were tested one by one into the population model (univariate analysis). After all significant covariates have 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 twice the log of the likelihood (ΔOBJF) 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 were considered significant (p<0.05). During the final steps of the model building, only the covariates which resulted in a difference of objective function ≥7.88 (p<0.005) were kept in the final model.*

Validation *of the final model was based on graphical and statistical methods. First, a bootstrap procedure was performed in PsN v3.5.3 (University of Uppsala, Sweden). Bootstrap was used to identify bias, stability and accuracy of the parameter estimates (standard errors and confidence intervals). PsN does so by generating a set of new datasets by sampling individuals with replacement from the original dataset, and fitting the model to each new dataset.*

Subsequently, parameter estimates were used to simulate plasma concentrations in paediatric patients with the similar demographic characteristics, dosing regimens and sampling scheme as in the original clinical studies. Furthermore, an internal validation of the final model, based on simulation techniques such as Visual Predictive Check (VPC) and Normalised Prediction Distribution Errors (NPDE), was performed to assess the predictive ability of the model.

Secondary PK parameters: In addition to the final model parameter estimates, secondary pharmacokinetic parameters were derived based on the individual predicted concentration vs. time profiles. Area under the concentration vs. time curve (AUC_∞), area under the concentration vs. time curve during the dosing interval ($AUC_{0\text{-}8h}$), time to peak concentration, concentration at steady-state

(Css) and trough concentration (i.e., at 8 hours post dose) (Cmin) were listed for each patient and summarised per dose level.

PK bridging and dosing recommendations: To optimise DFP dosing regimen in the target population, simulations were performed to obtain systemic exposure values similar to the adult reference population. Simulations were carried out to explore how differences in demographic covariates might affect steady-state exposure to DFP 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 range based on PK reference values in adults.

Safety analysis:

Descriptive statistics were used to summarise adverse events, vital signs and clinical lab data (haematology, biochemistry and virology). Findings arising from medical history, ECG monitoring, physical examination and concomitant medication were recorded for each patient and presented as listings or summary tables, where appropriate. As clinical chemistry (haematology and biochemistry) measurements were not performed by a central lab, a list of normal ranges from each participating centre was used for reference values. All other clinical measures and procedures, e.g. ECG measurements, were performed in each centre according to standard clinical practice.

All the medical occurrences that started prior to the drug administration were recorded as medical events. Assessment criteria for the classification of safety findings included causality, intensity, pattern, outcome, action taken with regard to IMP and other action taken.

Study Population: children from 1 month to less than 6 years of age affected by transfusion dependent haemoglobinopathies.

Number of subjects	
Planned, N	30
Enrolled, N	23
Dosed, N	18
Completed, N	18
Number of screening failures, N	2
Number of premature discontinuations, N	3
Demographics	
N (All subjects dosed – PK analysis population)	18
Males/Females	9/9
Age (Years) (mean and SD)	3.62 (1.33)
Weight (Kg) (mean and SD)	16.08 (3.18)
Height (Cm) (mean and SD)	98.95 (9.16)

Pharmacokinetics (PK) Endpoints: (All subjects dosed, i.e., PK analysis population)

Deferiprone PK parameter, median (5^{th} and 95^{th} quantiles)	**Dose 1 – 8.3 mg/kg**	**Dose 2 – 16.7 mg/kg**	**Dose 3 – 33.3 mg/kg**
N of subjects per dose group	6	6	6
AUC_{0-8} (µM/L*h)	116.7 (90.6-129.0)	210.0 (173.1-266.6)	428.8 (291.4-547.8)
Cmax (µM/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 (µM/L)	2.1 (1.6-2.3)	3.7 (3.1-4.9)	7.7 (5.1-10.0)

Cmin (µM/L)	1.5 (0.92-2.6)	1.9 (0.79-5.5)	6.8 (3.1-13.9)
Safety results (Safety population N=21): All adverse events (AEs) occurring before or after dosing were recorded			
Adverse Events:			
N	3		
No. subjects with AEs, N	3		
Serious Adverse Events (SAEs):			
No. subjects with any SAEs	0		

Conclusion:

DFP showed a very favourable safety profile in children younger than 6 years of age after administration of single oral doses of 8.3, 16.7 and 33.3 mg/kg. No serious adverse events were observed during the study. The pharmacokinetics of the new oral formulation of DFP was successfully characterised by a model-based approach. A one-compartment open model with first-order absorption and elimination processes accurately described the PK profile of the drug under investigation, allowing the estimation of the main PK parameters of interest. In addition, the inclusion of body weight on CL/F and V/F according to fixed allometric scaling showed that differences in size explain part of the variability in the data. As such, body weight was found to be a good predictor of inter-individual differences in the population under investigation.

Bridging concepts were applied to evaluate the exposure in the paediatric population with the objective of defining dosing recommendations that yield DFP levels comparable to those observed at efficacious doses in adults. Using the pharmacokinetic model developed for the paediatric population in this study in conjunction with a model previously developed for adult subjects, simulations were performed to evaluate drug exposure in children below 6 years of age and in adult patients. AUC and Css distributions were found to be comparable at 75 mg/kg/day and 100 mg/kg/day. Differences in Cmax were not considered clinically relevant. 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.