Deferiprone sampling optimisation in a pharmacokinetic bridging study including children with β-thalassaemia

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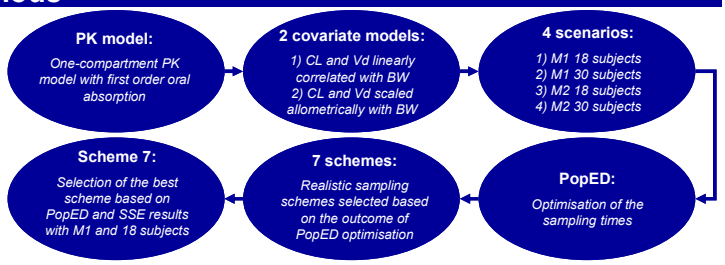
Introduction and objectives

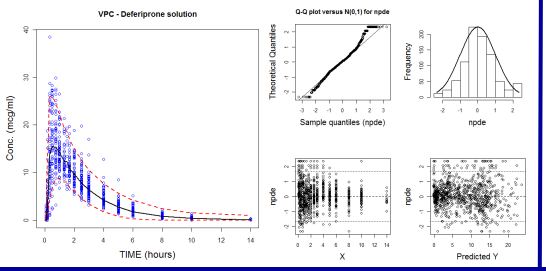
Practical and ethical constraints impose careful planning and design of clinical trials in children. The use of population pharmacokinetics to analyse sparse data allows reducing the burden in such a vulnerable population [1]; yet often little attention is paid to the quality of the information gathered. The aim of this analysis is to optimise sampling times for the characterisation of the pharmacokinetics of deferiprone in children to subsequently optimise the dosing regimen in this paediatric population.

Methods

A one-compartment PK model with first order elimination and first order oral absorption has been developed on adult data using a non-linear mixed effects approach, as implemented in NONMEM VII. Two covariate models have been used to optimise sampling times in children, namely M1 (body weight linearly correlated with CL/F and Vd/F), and M2 (fixed allometric scaling). Uncertainty (20%) in CL/F and Vd/F estimates has been accounted for in the optimisation procedures. The study consisted of a parallel design with three dose levels randomised across 18 children (aged between 2 and 10 years).



PK model validation

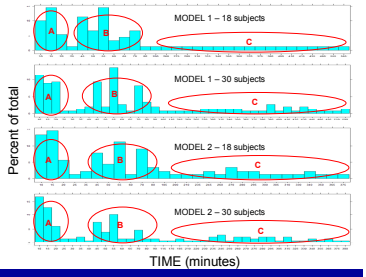


PopED optimisation

The outcome of four scenarios in PopED (v.2.12), suggests that, independently of model and number of subjects, sampling times should be gathered in three main time windows. Specifically:

- Group A, about 30% in the range 10 to 20 minutes;
- Group B, about 40% between 40 and 75 minutes;
- Group C, about 30% after 200 minutes;

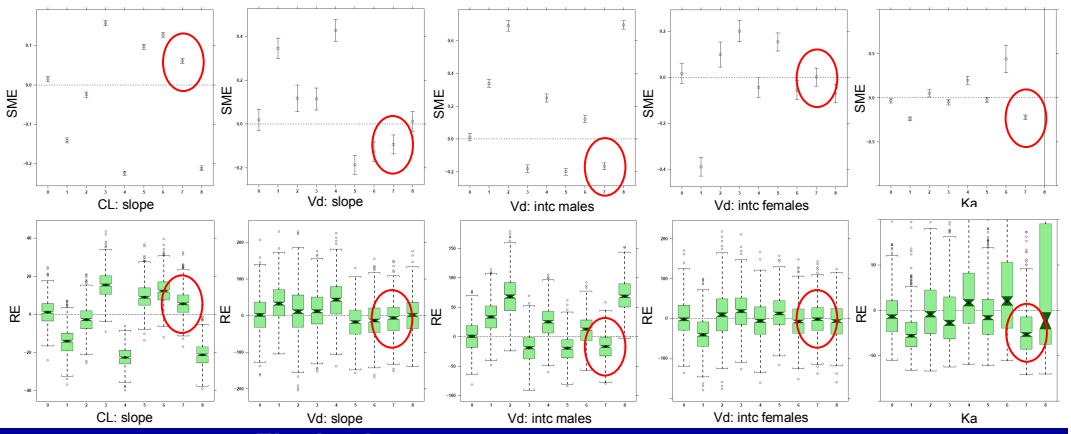
Seven sampling schemes have been created and evaluated as a result of a compromise between full optimisation and feasibility in a real clinical trial.



7 realistic sampling schemes

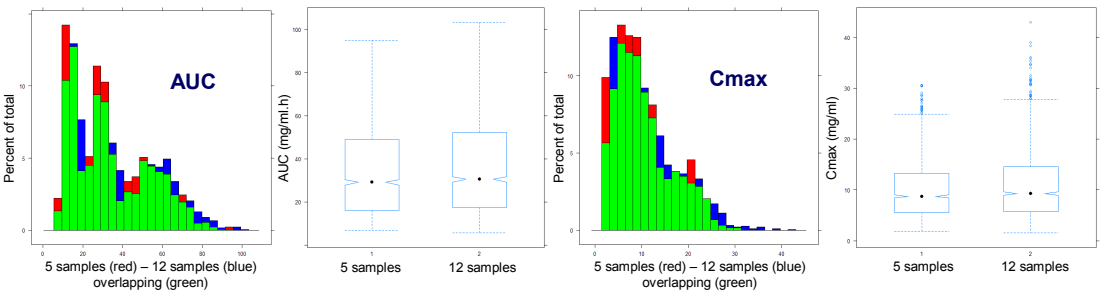
Stocastic Simulations and Estimations (SSE) have been used to compare the seven realistic schemes with the fully optimised scheme (0) and an empirical (non optimised) PK scheme (8). Accuracy (RE: relative error) and bias (SME: standard mean error) in parameters estimates and model robustness have been evaluated.

Scheme number 7 provided the best results in terms of precision of parameter estimates as of model robustness with only 1 failed minimisation and 435 successful covariate steps out of 500 runs.



Final scheme

The accuracy and precision of parameters estimates were estimated for primary and secondary (i.e., AUC and Cmax) PK parameters. The closer the value to zero, the higher accuracy and precision. Predicted AUC and Cmax estimates were compared with simulated data using frequent sampling (n=12) according to the trapezoidal rule.



The accuracy of primary PK parameters estimates was below 10% except for KA (-11%); whereas precision, as expected, was slightly lower given the small sample size (> 30% for Vd/F and KA). AUC values (mean and standard deviation) were found to be 33.37 (19.24) and 35.61 (20.22) µg/ml.h and Cmax values 10.17 (6.05) and 10.94 (6.68) µg/ml in sparse and frequent sampling respectively.

Conclusions

Our analysis illustrate that despite feasibility issues, ED-optimality concepts can be used to optimise study design. Predefined sampling schemes and sample sizes do not warrant accurate model structure and parameter identifiability. Of particular importance is the accurate estimation of the magnitude of the covariate effects, as they may determine the final dose recommendation for the population of interest.

[1] Anderson BJ, Allegaert K, Holford NH, (2006) Population clinical pharmacology of children: general principles. Eur J Pediatr, 2006 165:741–746.

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DEFERIPRONE EVALUATION IN PAEDIATRICS

SEVENTH FRAMEWORK PROGRAMME

Universiteit Leiden