

Optimal design in the analysis of a clinical study in paediatric population



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Introduction

A safety dose ranging study that included a 3 days treatment period was conducted in paediatric patient population with drug S (marketed in adult). The drug S is rapidly absorbed, is mainly and rapidly metabolized by CYP1A2, has a large inter-individual variability and its PK in adult population is known to be gender-dependent and influenced by oestrogen intake and smoking habits.

Objectives

The objectives of this study were to build a population PK model in the paediatric population, to quantify and identify the variability in order to perform dose recommendation for the following phase III studies.

Methods

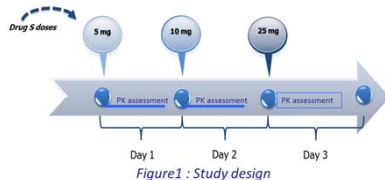
Patients & study design

51 participants :

- 24 children from 7-11 years old,
- 27 adolescents from 12-17 years old.

Demographic characteristics	%
Boys	51
Pre-pubertal girls	27
Post-pubertal girls	22
Smokers	4
Oestrogen	4

Given the PK characteristics of drug S, an interval of 24 hours was sufficient between the 3 periods.



Data

- 7 saliva PK samples were collected each day (0.5, 1, 2, 3, 4, 12 and 24 h after administration), for evaluating drug S PK, as it is a non-invasive procedure already used in adults during clinical trials.
- 1 PK blood sample was drawn, in order to assess the saliva/plasma (S/P) ratio of drug S.

Identifiability analysis

First, the study design was evaluated using the Fisher Information Matrix, as implemented in PFIM software [1] to anticipate the ability to estimate parameters of a two-compartment model with this study design, without the samples for which 90% of concentrations were expected to be BLQ. Expected standard errors associated with model parameters were predicted from the Fisher Information Matrix [2]. An estimate for a fixed effect associated with a RSE higher than 30% was considered as poorly estimated.

FIM-based evaluation of the power of detection of covariates

The ability of this study design to assess covariate effect was performed after the identifiability analysis, using a structural model that was expected to be fitted to the data. A gender effect and an effect of pubertal status were expected on bioavailability, as gender and oestrogen intake were found to influence the PK of the drug in adults. As the magnitude of these effects could be different in paediatric population from the one in adult population, the power of detection of these effects through a mixed effects approach was assessed using PFIM, for a range of plausible magnitudes (2-fold, 3-fold, 4-fold). The population was assumed to be evenly distributed between boys and girls, and it was assumed half of the girls would be post-pubertal.

Population PK analysis

Finally, to describe drug S saliva concentrations in children, a population PK model was developed and a S/P ratio was estimated. The effect of weight was tested early in the model building process using allometric scaling. Covariates (gender, pubertal status, smoking habits and oestrogen co-administration) were also investigated with a backward elimination method.

Model Assumptions

Parameter	Justification	Assumption
Bioavailability (F)	Cannot be estimated after oral administration	Fixed to 1
Absorption rate constant (Ka)	Design too sparse in absorption phase	Fixed to the adult value

Results

Identifiability analysis

PK samples 12h and 24h after administration were assumed to bring no information as most of concentrations were expected to be BLQ. Thus, a design with 6 sampling times (i.e. prior the administration and 0.5, 1, 2, 3 and 4 h after administration) was evaluated.

→ Because of the lack of information to estimate a 2nd compartment, the SE associated to Q and Vp were high.

Thus, a one compartment model will be further applied.

→ The design would not allow the estimation of Ka as RSE was high.

It confirms the need to fix Ka to the value found in the adult population for the children population PK analysis.

Parameter	RSE (%)
Fixed effect	
Ka (1/h)	173
Vc (L)	22
Q (L/h)	78
Vp (L)	480
CL (L/h)	30
IIV	
F	25
Ka	23
Vc	44
Vp	39760

Table 1 : RSE associated to model parameters predicted from the population FIM on the study design

FIM-based evaluation of the power of detection of a covariate

Consistently with the identifiability analysis results, the power of detection of covariates was assessed using a mono-compartmental model with a first order absorption and linear elimination. The absorption rate constant was considered as a fixed parameter, as it was shown to be non-identifiable, and assumed to be the same as in the adult population. For both gender effect and pubertal status, the power of detection of the covariate effect was found to be 65% for a 2-fold effect, 94% for a 3-fold effect, and 99% for a 4-fold effect.

Final children PK model

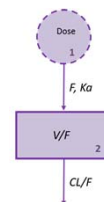


Figure 2: Final PK model

Ka : drug S first-order absorption rate constant,

F : drug S bioavailability,

V/F: drug S volume of distribution,

CL/F: drug S elimination clearance.

→ For children the S/P ratio was found to be very closed to the adult value meaning that the drug S repartition between plasma and saliva is similar between the two populations.

→ The data did not support any influential covariates, as opposed to the adult model (smoking habits and oestrogen co-administration not tested).

→ Inter-individual variability was high and inter-occasion variability was found on F and volume.

→ Individual PK parameters derived from the final PK model were calculated at each dose. A direct comparison was performed with adult values and showed no difference between the two populations.

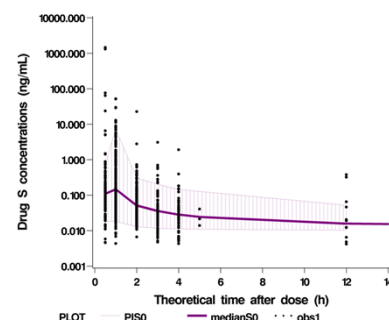


Figure 3 : Drug S dose normalized VPC

Conclusions

This model allowed to perform dosing recommendation for the next phase III study and will be further refined with the new data coming and potential addition of other studies performed in paediatric population, especially regarding covariate effect assessment.

References:

- www.pfim.biostat.fr, Bazzoli et al., 2010
- Retout S, Duffull S, Mentré F. Development and implementation of the population Fisher information matrix for the evaluation of population pharmacokinetic designs. Computer Methods and Programs in Biomedicine 2001; 65: 141-51.
- Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokin. 2009;24(1):25-36.