Predicting Paediatric PK In Order To Investigate It

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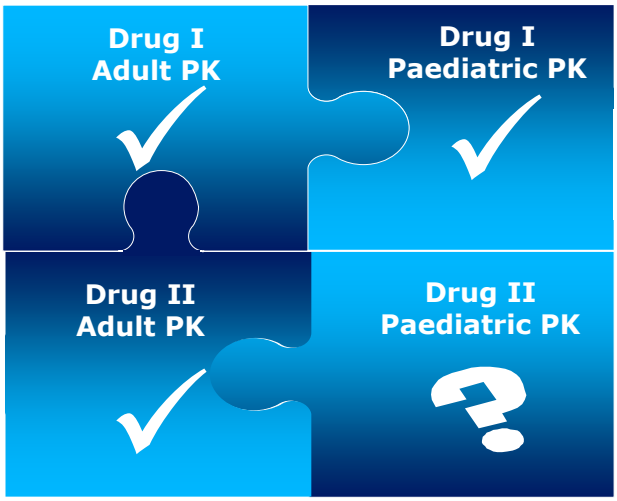
Background

- Regulatory expectations to paediatric drug development is increasing to ensure adequate information is obtained to support paediatric dose selection and labelling.
- Subjecting children to intensive sampling is ethically challenging.

⇒ Appropriate bridging of prior data is called for to optimise paediatric trials.

- We attempt to design a paediatric trial for a new 2nd generation drug using adult data combined with adult & paediatric data from the 1st generation drug.



Method – drug II paediatric sample size

- To ensure precise PK parameter estimates (95% CI within 60-140% of the geometric mean for primary PK parameter estimates), the sample size requirements for each age group were calculated using the equation

$$\frac{CI_{95\%,U}}{CI_{95\%,L}} = \frac{1+t_{0.05,N-1}CV}{1-t_{0.05,N-1}CV} < \frac{140\%}{71\%} \quad (=1.96)$$

- Estimated sample size requirements with different PK sampling designs are shown in Table 1.

Method – drug II paediatric dosing based on drug I allometry

- The aim for the paediatric dose-setting was to ensure an exposure in children (<12 y) comparable to that obtained in adults (>=18 y).
- Rather than attempting to estimate allometric exponents from the narrow BW range in the Drug II FHD trial, we estimated exponents from adult & paediatric data with Drug I for CL and V, respectively.

$$CL_{DrugII,BW=X} = TVCL_{DrugII,BW=70kg}\left(\frac{BW}{70kg}\right)^{Exp,DrugI} e^{\eta}$$

- Relative exposure measures (AUC and C_{Max}) across the wider scale of BWs relevant for children predicted using Drug I allometric exponents are shown in Figure 1.

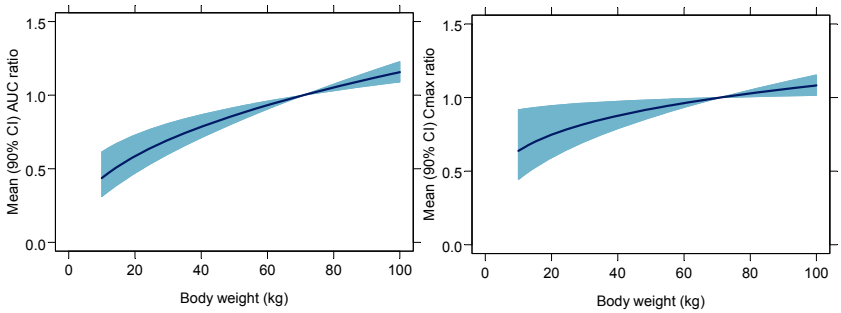


Figure 1 Predicted paediatric exposure (AUC and C_{Max}) relative to adults

Results

- The predicted paediatric exposure from dosing in proportion to body weight is reasonably within adult exposure (Figure 1).
- The estimated sample size per age group is 3 children assuming rich PK sampling (7 time points per child) (Table 1).
- A sparser sampling schedule with 4 **homogeneously timed** samples per child was predicted to increase the required recruitment to10 children per age group.
- In contrast, a sparse sampling schedule **distributing 7 different time points between 2 groups** of children with 4 samples each preserved the required sample size of full sampling (3 children) (Table 1).

Table 1 Predicted sample sizes to achieve adequate paediatric PK parameter estimates

	Adult results (*N*=23): $CI_{95\%,U} / CI_{95\%,L}$		Paediatric predictions: *N* required to give $CI_{95\%,U} / CI_{95\%,L}$ <1.96	
	CL	V	CL	V
"Full sampling": 7 time points per subject	1.16	1.15	3	3
Sparse homogenous sampling: 4 time points per subject	1.84	1.20	10	3
Sparse heterogeneous sampling: 7 time points in total, 4 per subject	1.18	1.22	3	3

Conclusions

- **Using prior adult and paediatric PK data, a paediatric PK study of a 2nd generation drug was designed to get adequate PK information with feasible sample size and sampling.**
- **The proposed method of designing paediatric PK studies ensures informative paediatric data is acquired to inform dose selection and labelling.**

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