

Use of PBPK Information to Select the Dose and Optimize the Number of Subjects for Early Dose Confirmation in a Pediatric POC study



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Objectives

To use PBPK model-based prior information to support pediatric dose selection and to determine the optimal number of subjects required to meet pre-defined criteria for early dose decision (either dose confirmation or dose adjustment) for the efficacy part of the POC study.

Background

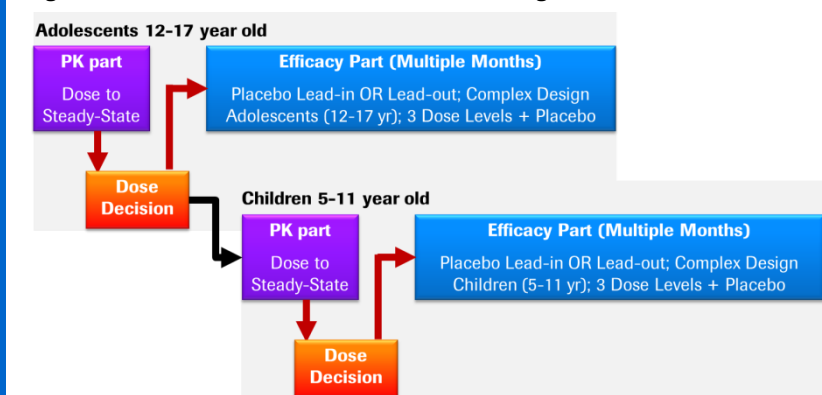
DrugA is a small molecule being developed for a neurologic disorder in a predominantly pediatric target population. While a proof of concept (POC) study in adults was ongoing, the pediatric POC study was planned with dose levels that should target adult-equivalent exposures.

Health authorities (HAs) generally encourage the use of *in silico* approaches, e.g. physiologically-based PK (PBPK) modeling, for pediatric dose prediction [1]. Furthermore, HAs increasingly request pre-defined criteria for early dose confirmation or adjustment (EDC), and sufficient confidence in the key PK parameter (CL, Vss) estimates in adolescents before dosing younger children. A 95% CI within 60 to 140% of the key PK parameter estimate has previously been proposed as acceptable pediatric PK parameter precision [2].

We propose a methodology that uses PBPK information together with bootstrap techniques to select the dose and determine the optimal sample size per pediatric age group that would meet the pre-defined criteria for dose decision and PK parameter precision.

Methods

Figure 1: Illustration of the Pediatric POC design



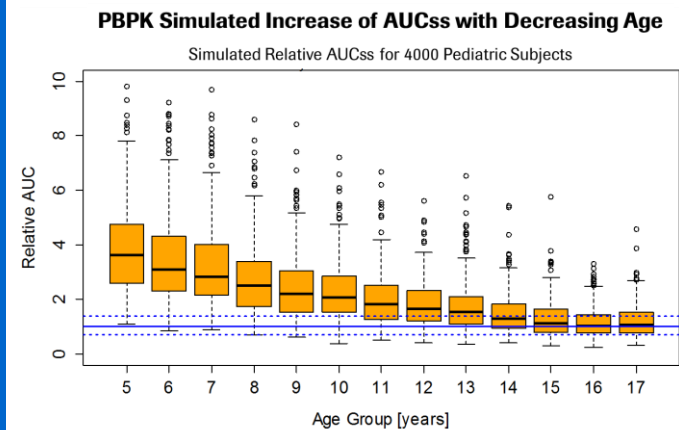
Dose Decision: Based on PK parameter estimates (CL/F)
→ Confirm OR Adjust Dose for Efficacy Part in Adolescents
→ Initiate PK part in Children
Q: What is the sample size for sufficient confidence in the dose decision?

Criteria for pediatric dose selection:

- Exposure: Median AUCss ~ 70 to 135 % of adult median exposure
 - This translates into CL/F within 74 and 142 % of the predicted value for each dose adjustment group (DAG)
- Safety: AUCss < 130 % of adult AUCss at the highest investigated dose
- Age-based DAG is preferred over weight-based by clinicians, if supported by the data
- Number of DAG limited to ≤ 4 over the range 5-17 years
- Limited available dose strengths (tablet combinations)

PBPK model based simulations of 4000 pediatric subjects

- A PBPK model for the adult population was built for DrugA based on SAD, MAD and DDI data. Hepatic Clearance is 85% due to CYP3A4, renal elimination is negligible.
- The pediatric module in SimCYP was used to scale PK from adult to children [3].
- PK profiles at steady-state were simulated for 4000 pediatric subjects aged 5 to 17 years, at the highest planned adult dose (i.e. without dose adjustment).
- Individual exposure (AUCss) and CL/F estimates were derived from the simulated PK profiles
- Pediatric relative CL (relCL) was defined as the ratio of pediatric CL/F estimate divided by the PBPK model predicted median CL/F in adults. Corresponding relative AUCss are displayed versus age in Figure 2.



Initial Dose Selection: Based on pediatric vs adult CL ratio (relCL)

As CL/F is independent of dose and inversely proportional to AUCss, initial selection of pediatric age-adjusted doses is guided by relCL, together with the previously defined criteria for dose selection.

Methods (cont'd)

Bootstrap to Assess the 90% CI for relCL Estimates for Early Dose Confirmation

The impact of sample size on the confidence for EDC was assessed by bootstrapping relCL from the pediatric simulated PBPK database. The age groups for PK assessments were defined according to the protocol design (adolescents and children, see Figure 1) and the DAG based on relCL.

For each age group, sample sizes of N=4...48 subjects were tested. For each sample size the PBPK database was resampled 1000 times. For each bootstrapped dataset the median relCL per age group was computed and from the 1000 medians a 90% confidence interval was established.

Results

Selection of Pediatric Age-Adjusted Doses

Median pediatric simulated CL/F approximated adult CL/F values at the age of 16, but was reduced to 27% of adult CL/F at the age of 5 years, as shown in Table 1.

As DrugA is mainly metabolized by CYP3A4, body size (correlated with liver size) was expected to be the main predictor for relCL. However, as age and weight are highly correlated in this pediatric population (5-17 yr), age-based pediatric dosing was also supported by the data

Age (years)	relCL	Dose (% of adult)	AUCss Ratio (Age)	AUCss Ratio (DAG)
5	0.275	30	1.09	0.96
6	0.322	30	0.93	
7	0.353	30	0.85	
8	0.395	45	1.14	1.02
9	0.448	45	1.00	
10	0.485	45	0.93	
11	0.546	65	1.19	1.03
12	0.603	65	1.08	
13	0.647	65	1.00	
14	0.770	65	0.84	1.02
15	0.884	95	1.07	
16	0.966	95	0.98	
17	0.945	95	1.01	

Table 1: PBPK predicted relCL in the pediatric population and proposed DAGs. Dose (% of adult): reduced dose corresponding to the average relCL within each DAG. AUCss Ratio: predicted ratio of AUCss for the reduced dose.

Based on the available dose strengths, the exact recommended dose may not be available for all dose levels. In this case, a dose as close as possible to the recommended % of adult dose should be selected.

For safety consideration, a conservative approach at the highest dose level (i.e. targeting slightly less than 100 % of adult exposure) may be followed.

Sample Size for Early Dose Confirmation

The pre-defined criteria for EDC was met with a sample size of N≥10 subjects per DAG. Figure 1 illustrates the corresponding 90% CI for relCL. The influence of sample size is presented in Table 2.

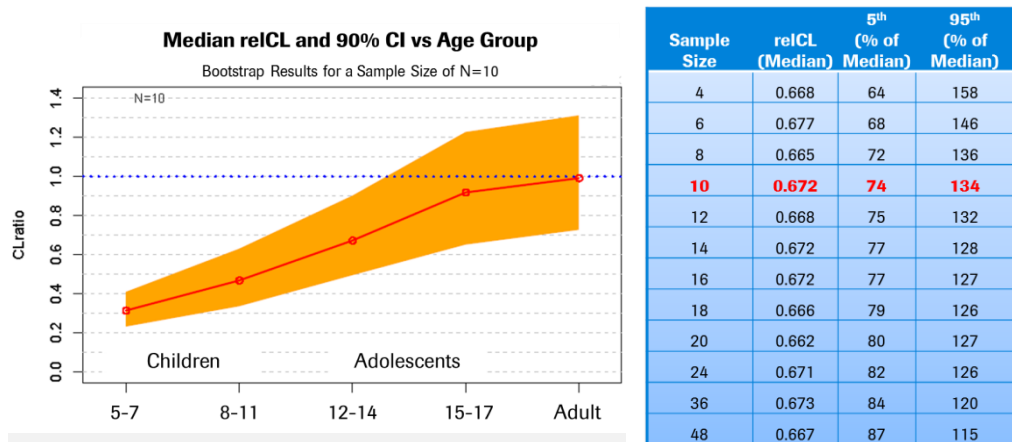


Figure 3: Bootstrap medians and 90% CI per age group. EDC criteria for the relCL estimates are met at N=10 subjects.

Sample Size	relCL (Median)	5 th (% of Median)	95 th (% of Median)
4	0.668	64	158
6	0.677	68	146
8	0.665	72	136
10	0.672	74	134
12	0.668	75	132
14	0.672	77	128
16	0.672	77	127
18	0.666	79	126
20	0.662	80	127
24	0.671	82	126
36	0.673	84	120
48	0.667	87	115

Table 2: Influence of sample size on 90% CI for CL estimate

Recommendation for Dose Decision

The initial dose in the pediatric DAG is confirmed if the median relCL is within the pre-selected criteria. Otherwise, dose adjustment according to the estimated relCL is recommended, subject to the available dose strengths and safety limits.

Conclusion

PBPK modeling information, including inter-individual variability, coupled with bootstrap techniques is a robust approach to optimize the sample size and assess the criteria for EDC in a pediatric POC study.

References:

- General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, FDA CDER Draft Guidance for the Industry, 2014
- Wang Y et al. J Clin Pharmacol. 52(10):1601-6, 2012
- Johnson, T. N. et al. (2006). Clin Pharmacokinet 45: 931-956.