Modeling and Simulation Approach to Pediatric Drug Development

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114

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ABSTRACT

Purpose. Describe a process for determining pediatric drug doses using pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation.

Methods. Using a PK model, 3 alternative dosage regimens were identified for Drug X. Drug exposures after administration of these regimens were simulated. Individual patient outcomes were then simulated using a PK/PD model.

Results. All of the 3 simulated regimens were found to provide pediatric patients with $AUC_{0\text{-}24}$ values comparable to those seen previously in adults. Clinical trial simulations showed that the trial success rate ranged from 34% to 88% using a breakpoint model. The trial success rate increased with increasing number of baseline clinical episodes per week.

Conclusions. Improvements in design of future pediatric clinical trials to support PK/PD modeling and simulation would facilitate selection of appropriate dosing regimens in children. Furthermore, the application of this approach may support the objectives of the European Union (EU) Pediatric Regulation.

INTRODUCTION

- Regulatory guidances allow extrapolating data from adults to create dosing guidelines for children when the mechanism of action of a drug and the disease process are similar between adults and children.[1]
- Drug X has been shown to be clinically effective and safe in adults at a recommended once-daily dose. Exposure-response relationships between drug dose and efficacy and safety endpoints have been established in adults.
- Given the limited ability to conduct trials in pediatric patients and a similarity in symptoms between pediatric and adult patients, body weight was used to set the pediatric dose of Drug X based on the adult dose. However, in Phase III pediatric clinical trials, superiority over placebo was not demonstrated with that dose.
- Modeling and simulation provided necessary information to determine pediatric dosing regimens that resulted in drug exposures similar to those achieved in adults and provided a strategy for salvaging the initial failed program.

OBJECTIVES

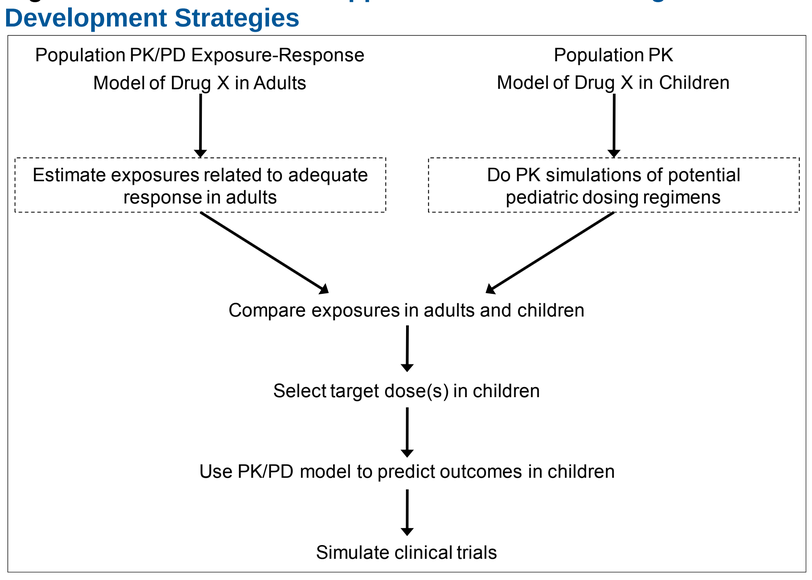
- Describe the process for determining pediatric drug doses using pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation.
- Demonstrate that this process was used to identify a safe and effective pediatric dose for Drug X.

METHODS

Pediatric Drug Development Strategy

A modeling and simulation approach to setting pediatric drug doses (**Figure 1**) can be used if a clear exposure-response relationship for safety and efficacy endpoints can be established in adults.

Figure 1. Pharmacometric Approach to Pediatric Drug Development Strategies



Comparison of Exposures in Adults and Children

Population PK/PD analyses of Drug X performed on data from adults identified the exposures that were related to adequate clinical response. A population PK model developed from pediatric data suggested that the initial dosing regimen calculated from the dose used in adults resulted in insufficient drug exposure for children. A scatterplot of $AUC_{0\text{-}24}$ versus patient weight is provided in **Figure 2**. In general, the administration of Drug X in pediatric patients resulted in steady-state $AUC_{0\text{-}24}$ values considerably lower than those seen in adults given the usual dose. Pharmacometric simulations were performed to support selection of an optimal pediatric dosing regimen expected to attain adequate exposure for drug effectiveness comparable to that observed in adults.

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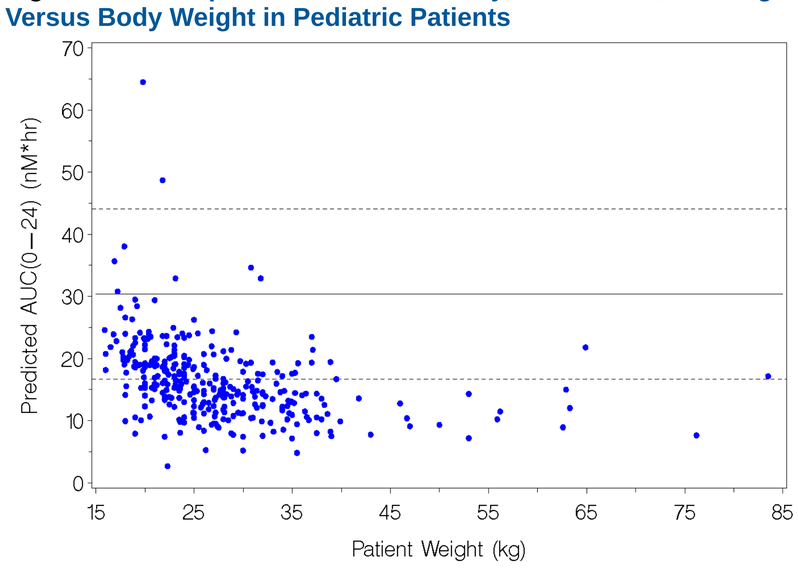
Figure 2. Scatterplot of Predicted Steady-State $AUC_{0\text{-}24}$ of Drug X Versus Body Weight in Pediatric Patients

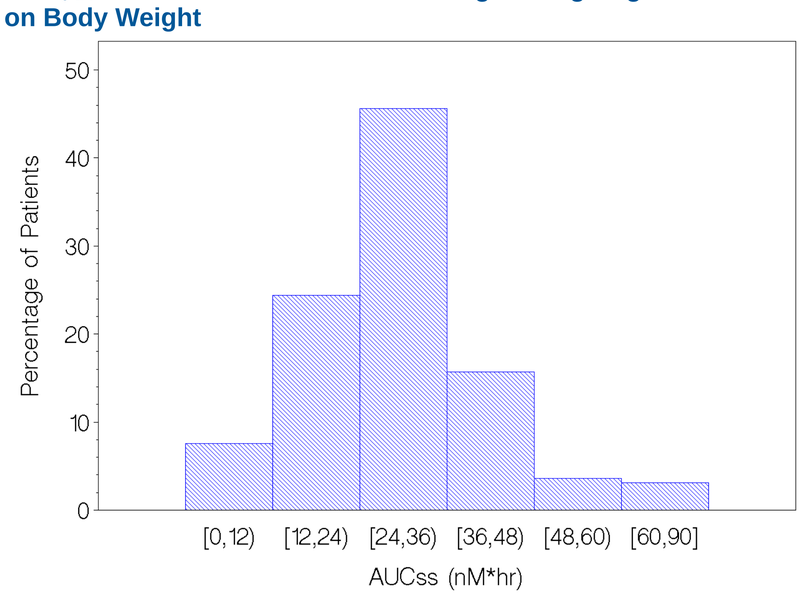


Note: Data from 2 pediatric studies. The horizontal lines represent the mean (solid line) and 1 standard deviation (dashed lines) of the $AUC_{0\text{-}24}$ in adults receiving the usual dose.

Selecting Target Doses in Children

Potential regimens were identified that would be expected to improve the efficacy profile of Drug X in children while maintaining its safety profile. These regimens included low-, medium-, and high-dose options based on patient body weight (cutoffs = ≤ 20; > 20-35; and > 35 kg). Simulations were used to examine the expected distribution of exposure ($AUC_{0\text{-}24}$ of Drug X) after administration of these regimens. A frequency distribution of the simulated Drug X exposure estimates for the selected regimen is provided in **Figure 3**.

Figure 3. Frequency Distribution of Predicted Steady-State $AUC_{0\text{-}24}$ for Pediatric Patients Receiving Dosing Regimens Based on Body Weight



Clinical Trial Simulations

Clinical simulations were conducted using data obtained from 2 pediatric Phase III studies. Nine study scenarios were designed based on 3 regional distributions of study sites in Europe (EU) and the United States (US) and 3 baseline measures of the clinical response variable, as described in **Table 1**.

Table 1. Description of Trial Scenarios

Trial Number	Patient Origin	Baseline Clinical Episodes
1	All EU	≥ 5
2	All EU	≥ 10
3	All EU	≥ 15
4	50%EU / 50%US	≥ 5
5	50%EU / 50%US	≥ 10
6	50%EU / 50%US	≥ 15
7	80%EU / 20%US	≥ 5
8	80%EU / 20%US	≥ 10
9	80%EU / 20%US	≥ 15

EU, European Union; US, United States

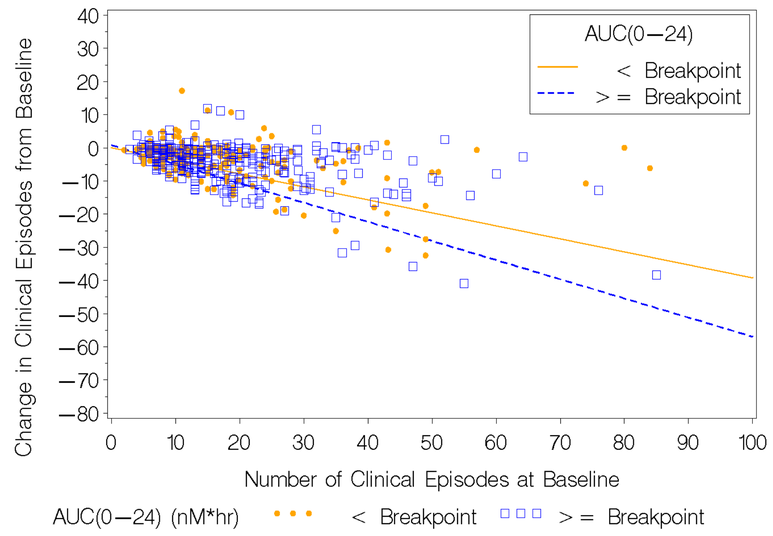
The first step in simulating individual patient outcomes was to randomly assign patients to treatment (active versus placebo) in a 2:1 ratio. All patients randomized to placebo treatment had their corresponding exposure estimates set to 0. An additional evaluation was done on a 1:1 randomization scheme.

Using an $AUC_{0\text{-}24}$ breakpoint model developed from 1 pediatric clinical study, individual predicted estimates of the change in clinical episodes from baseline were calculated for each dosing regimen. A random variability term was added to the model for the clinical trial simulations to take into account random variability expected in real world clinical trials.

A linear PD model was used to predict clinical response at end of treatment for each simulated patient based on their predicted exposure relative to the breakpoint value. A statistically significant difference ($\alpha = 0.05$) in the change in efficacy response from baseline between placebo and drug-treated patients was considered a successful trial.

Figure 4 provides the scatterplot of the change in number of clinical episodes from baseline versus baseline number of episodes with the final model fit overlaid, stratified by breakpoint.

Figure 4. Scatterplot of the Final Linear Regression Model for Drug X $AUC_{0\text{-}24}$ Breakpoint Overlaid on the Observed Data for Clinical Response



RESULTS

Clinical trial simulations showed that the trial success rate ranged from 34% to 88%. **Table 2** below provides a summary of percent trial success using this model. Within each region, the trial success rate increased with increasing number of baseline clinical episodes per week. Trials with the highest success rate had an inclusion criteria of at least 15 baseline episodes. In general, trials with 50% EU patients and 50% US patients had higher success rates at all baseline inclusion criteria as compared to all EU or 80% EU / 20% US. The medium-dose regimen had the highest success rates within each trial as compared with the other 2 dosing regimens.

Table 2. Percent Successful Trials (2:1 Randomization) Using the Breakpoint Model[a]

	All EU								
	≥ 5 (Trial = 1)			≥ 10 (Trial = 2)			≥ 15 (Trial = 3)		
Baseline Episodes / Regimen	Mean Delta	% Success	Missing*	Mean Delta	% Success	Missing*	Mean Delta	% Success	Missing*
Low dose	-1.6	35	4	-2.1	46	2	-3.3	79	2
Medium dose	-1.6	35	4	-2.2	54	2	-3.4	84	2
High dose	-1.5	34	4	-2.1	47	2	-3.2	78	2
	50%EU / 50%US								
	≥ 5 (Trial = 4)			≥ 10 (Trial = 5)			≥ 15 (Trial = 6)		
Baseline Episodes / Regimen	Mean Delta	% Success	Missing*	Mean Delta	% Success	Missing*	Mean Delta	% Success	Missing*
Low dose	-1.8	41	7	-2.2	59	7	-3.4	88	9
Medium dose	-1.8	41	7	-2.3	66	7	-3.6	88	9
High dose	-1.8	39	6	-2.2	59	7	-3.4	88	7
	80%EU / 20%US								
	≥ 5 (Trial = 7)			≥ 10 (Trial = 8)			≥ 15 (Trial = 9)		
Baseline Episodes / Regimen	Mean Delta	% Success	Missing*	Mean Delta	% Success	Missing*	Mean Delta	% Success	Missing*
Low dose	-1.6	40	3	-2.2	59	3	-3.0	83	14
Medium dose	-1.6	43	4	-2.3	63	3	-3.1	85	16
High dose	-1.6	39	8	-2.1	59	3	-3.0	81	15

* A value for success or failure of a trial was missing if the statistical procedure failed due to errors.

[a] Number of studies for each scenario is 100 replications.

The evaluation of the interaction between country and treatment indicated that between approximately 7% and 22% of the time, the interaction term was statistically significant at 0.10. This necessitated the retention of both the main effects of country and treatment to preserve hierarchy in the model. In all clinical trials, the baseline number of clinical episodes was highly statistically significant all of the time. The country effect was statistically significant between 9% and 19% of the time. The treatment effect was statistically significant 46% to 89% of the time and increased with increasing number of baseline clinical episodes.

CONCLUSIONS

- These results suggest that the use of PK/PD modeling and simulation with adult data can be used to select appropriate dosing regimens in children.
- When comparing the trial success rates using the 3 simulated dosing regimens, minimal differences are observed. This is likely due to the very similar exposure estimates for the 3 regimens. These results suggest that the most convenient regimen, from a commercialization standpoint, can be used without adversely affecting future clinical trial success.
- As expected, increasing the entrance criteria (baseline clinical episodes) results in an increase in the clinical trial success rate. This finding was consistent regardless of the dosing regimen or study site distribution used.
- These simulations provide predictions of clinical trial success rates using an array of trial designs which can be used to improve the chances for a successful future trial.
- The application of this approach may support the objectives of the EU Pediatric Regulation.[2]

REFERENCES

1. Food and Drug Administration. *Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population*. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); December 2000.
2. Committee for Medicinal Products for Human Use (CHMP). *Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Pediatric Population.* London: European Medicines Agency; 2008.