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 pediactric patients with AUC0−24 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

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.

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 on the measures of the clinical response variable, as described in Table 1.

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 (cut-offs ≤ 5; > 5–20; > 20–35; and > 35 kg). Simulations were used to examine the expected distribution of exposure (AUC0−24 of Drug X) after administration of these regimens. A frequency distribution of the simulated Drug X exposure was estimated for the selected regimen and is provided in Figure 3.

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 the model. With an increasing 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 with 80% EU/20% US. The medium-dose regimen had the highest success rates within each trial design and was used in both 2 dosing regimens.

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 extra baseline (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.

REFERENCES
