Acknowledging Parameter Uncertainty in the Simulation-Based Design of an Actinomycin-D Pharmacokinetic Study in Pediatric Patients with Wilms' Tumor or Rhabdomyosarcoma	
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Background: Actinomycin-D (AMD) has been used for the treatment of Rhabdomyosarcoma and Wilms' tumor for over 40 years. Despite its longstanding and widespread use in pediatric oncology, there is virtually no pharmacokinetic (PK) information from which safe and appropriate age-based pediatric dosing can be derived. Infants under the age of 12 months are known to exhibit higher toxicity rates than older children administered equivalent body-weight adjusted doses of actinomycin. It is not currently known if this higher toxicity rate is due to dispositional differences in developing infants. Elucidating these potential differences in actinomycin pharmacokinetics will be a key aspect in providing dosing guidance in this population.

Objective: The objectives of this study were to: (1) Construct a population PK model to describe AMD disposition in children and young adults. (2) Perform clinical trial simulations incorporating parameter uncertainty for the design and evaluation of a prospective large-scale actinomycin trial in pediatric cancer patients, and subsequent sensitivity analysis. (3) Perform simulations to calculate the number of subjects under the age of one year old required to reliably estimate a clinically meaningful change in clearance.

Methods: A population PK model was constructed from data collected from 33 patients age 1.58 to 20.3 years receiving AMD as part of their standard chemotherapy. The population PK data were analyzed using nonlinear mixed-effects modeling with the NONMEM software system. Age, gender, and body size were screened as potential covariates to explain inter-subject variability in AMD parameters. The final population PK model was used to simulate new studies. Simulations incorporated uncertainty in the parameter estimates via probability density functions for all model parameters. Uncertainty distributions for fixed effect parameters were provided as multivariate normal distributions using the estimates and covariance matrix of estimates from the final NONMEM run in the model development stage. Uncertainty distributions for the variance-covariance matrix of the random effects parameters and for the residual error were provided as inverse Wishart distributions. From these distributions, 500 sets of population PK parameters were simulated. These 500 parameter sets and the final population PK model were used to simulate 500 replicate data sets for a preliminary clinical trial construct. The original PK model was then fit to each replicate data set and the bias and precision in parameter estimation was evaluated for a given trial design. A global sensitivity analysis was performed by examining plots of bias and precision estimates versus the uncertainty in each of the model parameters. Plots were examined for the magnitude of estimation bias and any trends in estimates over the range of plausible values. Deficiencies in the trial designed were then identified and iteratively refined until a construct was identified that produced minimal bias for all PK parameters, particularly total drug clearance and the volume of distribution in the central compartment. Once the study design was defined, a hypothetical age effect was incorporated using a power model to describe the possible maturational changes in clearance for children less than one year old. The assumed age effect ranged from no effect to a four-fold decrease in clearance for a 3 month old infant. The results from a simulation study that included 20 subjects below the age of one were used to construct sample size curves over the range of possible clearance values.

Results: AMD pharmacokinetics were well described by a three-compartment model with all parameters allometrically scaled by total body weight, normalized to a weight of 70 kg. Population mean (%CV) parameter estimates for V1, V2, V3, CL, Q2, and Q3 were 3.88 (54.4%) L, 443 L, 23.7 L, 8.27 (57.2%) L/h, 252 L/h, and 12.7 L/h. The simulation study yielded a final design consisting of 200 patients, which will be randomized to one of two sampling schemes:

(1) 5 minutes, 10 minutes, 2 - 3 hours, 24 – 28 hours and 48 – 96 hours

(2) 5 minutes, 0.75 – 1.5 hours, 5 - 6 hours, 24 – 28 hours and 48 - 96 hours

For this design, bias estimates were within $\pm$ 20% for V1 and $\pm$ 10% for CL. No trends in estimation bias were evident across the ranges of parameter uncertainty. From the sample size analysis, it was concluded that 50 subjects under the age of one would be required to detect a 30% change in clearance in children under the age of one. Simulations performed to confirm this sample size showed that CL could be accurately estimated in children under one year old.

Conclusion: A feasible and informative trial design was identified for an actinomycin clinical trial in pediatric patients. This design was modified to be robust across the uncertainty in parameters, and is appropriately powered to capture potential clearance differences in children less than one year of age. The simulation with uncertainty and global sensitivity approach for designing clinical trials allows for a quantitative description of outcome dependencies on model assumptions. The results of this effort have been incorporated into a prospective trial design to be conducted through the Children's Oncology Group Phase I Consortium. PK, Safety, and clinical response data will be evaluated with the existing mixed-effects model and the final population PK analysis derived from this study will be used to revise AMD labeling.