Poster #29834

Extrapolation of the Efficacy of a Dextroamphetamine Transdermal System Investigated in Pediatric Populations to Adults Using Pharmacokinetic Modeling

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INTRODUCTION

- Similarities in pathophysiology, disease characteristics, and treatment outcomes between pediatric and adult patients with attention-deficit/hyperactivity disorder (ADHD) have been demonstrated[1] and are acknowledged by the US FDA in its guidance on developing ADHD treatments[2]
- Given that post-marketing experience and published evidence support a tight link between the pharmacodynamic effects of amphetamines and their pharmacokinetic (PK) profile in ADHD,[2] the approach of extrapolating efficacy data from children and adolescents to adults is warranted[1]
- The dextroamphetamine transdermal system (d-ATS) was developed as an alternative to the currently available oral amphetamine formulations for treatment of ADHD in children, adolescents, and adults
  - Although a transdermal formulation of methylphenidate is available in the US, there remains an unmet need for a transdermal amphetamine formulation[3]
- In a pivotal efficacy and safety study, d-ATS met its primary and secondary efficacy endpoints for treatment of ADHD in children and adolescents[4]
  - Among pediatric patients, the most common dose selected as optimal during the dose-optimization phase of the pivotal study was d-ATS 15 mg[4]
  - PK data were not collected in the pivotal study but were collected in previous studies

OBJECTIVE

- To construct and validate a population PK (PopPK) model to characterize transdermal amphetamine disposition across populations of patients with ADHD
- To extrapolate efficacy data in children (6 to <12 years) and adolescents (12 to <18 years) to an adult population (≥18 years) by simulating exposures at the doses evaluated in the pivotal pediatric study for the purpose of comparing and deriving an adult dose that yields exposures matching the efficacious pediatric doses

METHODS

- A PopPK dataset was developed from data pooled across six PK studies and used to develop a PopPK model in order to characterize amphetamine disposition following d-ATS administration across patient populations
- The PopPK analysis dataset included 156 subjects with a total of 6607 amphetamine plasma concentration data points. Concentrations that were below the limit of quantification (BLQ) in the elimination phase were not included in the parameter estimation.
  - The combined PK study population consisted of:
    - 122 (78%) adults (median age, 33 years; range, 18–62) with a median (range) body weight of 73.2 kg (43.8–101 kg)
    - 34 (22%) children (median age, 10 years; range, 6–12) with a median (range) body weight of 40.6 kg (23.1–63.5 kg)
- Nonlinear mixed-effects modeling was conducted using NONMEM software, Version 7.4.3 (ICON Development Solutions, Hanover, MD)
- Between-subject variability was modeled for apparent clearance (CL/F), apparent volume of distribution (V/F), first-order absorption rate constant (K_a), and duration of zero-order input (*D*1). Inter-occasion variability was estimated for *D*1 and bioavailability (F).
- A full covariate modeling approach was taken. Body weight was predefined as a covariate on CL/F, V/F, and K_a.
- The model was evaluated via 1) goodness-of-fit diagnostics and 2) simulation-based predictive checks, including visual predictive checks (VPCs) of amphetamine concentrations and quantile-quantile plots of exposure metrics
- Following model validation, simulations were performed to extrapolate (via exposure matching) amphetamine PK at the doses administered to children and adolescents in the pivotal study (5 mg, 10 mg, 15 mg and 20 mg)
  - Body weights for 1000 individuals per age group (adults, adolescents, children) were sampled from the National Health and Nutrition Examination Survey (NHANES) database to supply covariates for model-predicted d-ATS exposures
- The exposure metrics area under the concentration-time curve (AUC) and maximum concentration (C_{max}) were compared among children, adolescents, and adults across dose levels

RESULTS

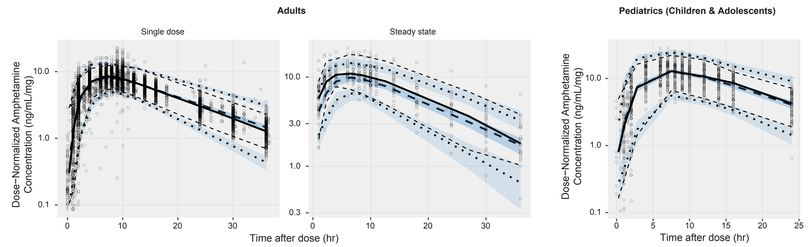
- A one-compartment model with sequential zero- and first-order absorption based on diagnostic plots and predictive checks adequately described the observed amphetamine PK data, with no apparent systematic bias. Model parameter estimates are shown in **Table 1**.
- Body weight was the only clinically meaningful covariate, with higher AUC and C_{max} values for lower body weights and lower values for higher body weights compared to the reference. Weight effects on the model parameter estimates are shown in **Table 1**.
- VPCs demonstrated that model-predicted amphetamine concentrations were in overall agreement with observed concentrations (**Figure 1**)
  - The median, 5th, and 95th percentiles of the observed data generally fell within the respective 95% confidence intervals (CIs) of the simulated data when stratified to different doses and age groups at both single doses and the steady state (**Figure 1**)

Table 1. Model parameter estimates

Parameter, units	Estimate	95% CI	Weight effect estimate	95% CI
CL/F, L/hr	18.4	17.6, 19.2	0.47	0.36, 0.58
Interindividual variance of CL/F, CV%	20.1	16.6, 23.1	–	–
V/F, L	51.9	48.1, 56.1	0.53	0.31, 0.75
Interindividual variance of V/F, CV%	37.4	30.3, 43.7	–	–
K_a, 1/hr	0.070	0.067, 0.073	-0.29	-0.43, -0.15
Interindividual variance of Ka, CV%	20.3	15.7, 24.1	–	–
*D*1, hr	1.9	1.8, 2.1	–	–
Interindividual variance of *D*1, CV%	48.6	40.6, 55.8	–	–

CI, confidence interval; CL/F, apparent clearance; *D*1, duration of zero order absorption time; hr, hour; K_a, first-order absorption rate constant; V/F, apparent volume of distribution.

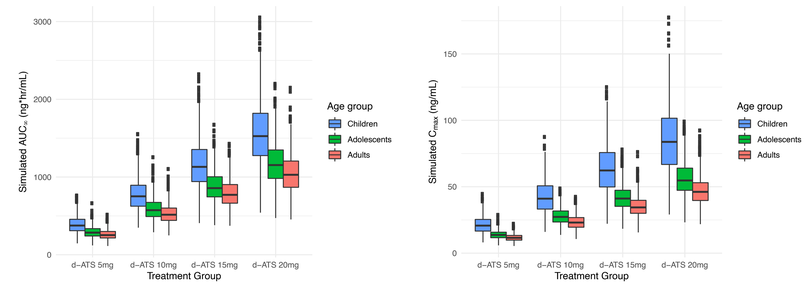
Figure 1. VPCs of dose-normalized amphetamine concentrations in adult and pediatric populations



In total, 500 Monte Carlo simulations were performed for each VPC. Open gray circles represent observed data. Black lines represent median (solid) and 5th and 95th percentiles (dashed) of observed data. Blue shaded regions represent the 95% prediction interval of the corresponding (ie, 5th, 50th, 95th) percentiles. Data are presented on a semi-log scale.
VPC, visual predictive check.

- Simulated exposure metrics for adults, children, and adolescents at 5 mg, 10 mg, 15 mg, and 20 mg are shown in **Figure 2**

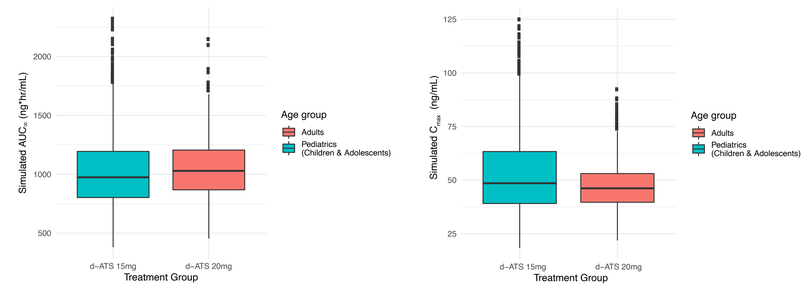
Figure 2. Simulated exposure metrics for the doses administered in the d-ATS pivotal study



Median values are designated by a line in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR and outliers are indicated outside of the whiskers by black circles.
Children, ages 6 to <12 years; Adolescents, 12 to <18 years; Adults, ≥18 years.
AUC, area under the concentration-time curve; C_{max}, maximum concentration; IQR, inter-quartile range.

- The simulated median (5th, 95th percentiles) AUC and C_{max} values for adults administered 20 mg d-ATS were comparable to simulated values for the pediatric group administered 15 mg d-ATS (**Figure 3**)

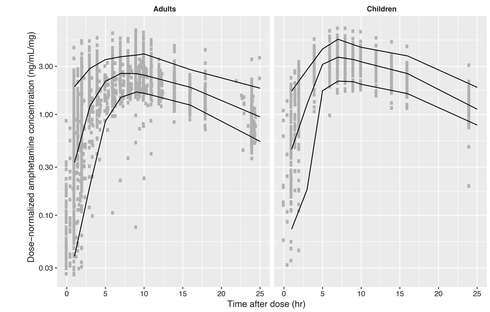
Figure 3. Simulated amphetamine exposures for pediatric patients at d-ATS 15 mg and adult patients at d-ATS 20 mg



Median values are designated by a line in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR, and outliers are indicated outside the whiskers by black circles.
AUC, area under the concentration-time curve; C_{max}, maximum concentration; IQR, inter-quartile range.

- Similarities in the PK profile shapes for pediatric and adult populations supported the efficacy extrapolation strategy
  - The observed d-ATS PK profiles were visually similar across age groups (**Figure 4**)
  - After accounting for body weight, one structural model described amphetamine disposition for both adults and pediatrics, indicating that the shapes of the PK profiles for the two age groups were similar

Figure 4. Dose-normalized amphetamine concentration over time for d-ATS in adults and children



Solid lines represent 5th percentile, median, and 95th percentile of the observed individual data (dots) for adults and children.

CONCLUSIONS

- A PopPK model was developed to characterize amphetamine disposition across adult and pediatric ADHD populations
  - The PopPK model provided an adequate description of the amphetamine concentrations, as evidenced by diagnostic plots and simulation-based predictive checks. Simulated observations were in overall agreement with observed data.
  - Exposure differences in the model predictions were primarily due to the difference in body weight among the age groups
  - Results demonstrated overall agreement between observed and simulated data when stratified to different doses and age groups at both single doses and the steady state
- Treatment with 20 mg d-ATS in adults produced exposures comparable to 15 mg in pediatric patients. The 15-mg dose was demonstrated as efficacious and deemed optimal in the pivotal study in pediatric patients.
- In addition, observed time-dose-normalized amphetamine concentration data from phase 1 studies were compared for adults and children, and the shape of PK profiles for d-ATS in adults was generally found to be similar to that in children
- The results of the PopPK modeling and simulation analyses demonstrate:
  - PK profiles were similar when comparing children, adolescents, and adults
  - Adults administered 20 mg d-ATS will achieve comparable exposures to the established efficacious dose (15 mg) for children and adolescents
  - These results support extrapolation of efficacy findings from children and adolescents to adults

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