Dose Optimization of Berotralstat in Pediatric Patients with Hereditary Angioedema via Population Pharmacokinetic Modeling and Simulation

PII-057

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INTRODUCTION

- Hereditary angioedema (HAE) is a rare genetic disorder characterized by unpredictable swelling attacks, often beginning in childhood.[1,2]
- Berotralstat, a plasma kallikrein inhibitor, is the only approved oral targeted long-term prophylaxis (LTP).[1,3]
- Berotralstat was recently approved in the United States for use in pediatrics aged 2 to <12 years, addressing a key unmet need in this population.[3]
- Berotralstat pharmacokinetics (PK) in pediatric participants with HAE was characterized in the ongoing open-label study, APeX-P (NCT05453968), which utilized weight-based dosing.[2]
- PK data from APeX-P were used to refine modeling and simulation (M&S) analyses and confirm pediatric doses, which were designed to match exposures of adults receiving the labelled dose of 150 mg once daily (QD).

METHODS

APeX-P Data Collection

- APeX-P enrolled 29 pediatric participants with HAE aged 3 to 11 years, utilizing weight-based dosing determined via preliminary M&S analyses, as shown in **Table 1**.
- PK samples were collected serially at Week 2 with sparse (single) collections at Weeks 12, 24, 36, and 48. Berotralstat plasma concentrations were determined using a validated assay.

Table 1. APeX-P Dosing and Enrollment

Cohort[a]	Weight band	Berotralstat starting dose (QD)	Enrolled participants
1	≥40 kg	150 mg[b]	7
2	32 to <40 kg	108 mg[c]	9
3	24 to <32 kg	96 mg[c]	9
4	12 to <24 kg	78 mg[c]	4

QD, once daily. [a]Cohorts 1 and 2 were enrolled in parallel. Cohorts 3 and 4 were opened sequentially following review of preliminary data, including safety, PK, and modeling and simulation analyses, from prior cohorts. [b]Oral capsule formulation. [c]Oral pellets formulation.

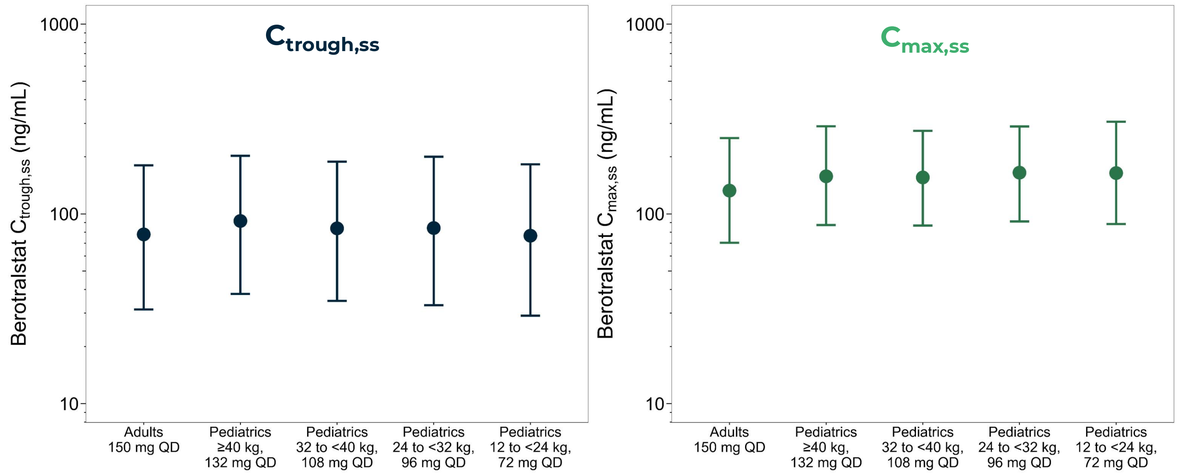
M&S Analyses to Support Dose Selection

- PK data from APeX-P were incorporated into the adult and adolescent registrational population PK (PPK) model dataset (N = 786 individuals and N = 12394 evaluable PK samples in registrational dataset).
- The structural model from the adult registration was re-evaluated, beginning with all serially collected PK data.
- Covariates were assessed via stepwise forward addition and backward elimination.
- The dataset was then augmented with sparsely collected data. The full dataset was then used to fit PPK parameters and explore covariate effects.
- Validation and predictiveness checks of the final model were performed to confirm that the model was fit-for-purpose.
- The final PPK model was used to conduct Monte Carlo simulations of berotralstat steady-state exposures of various dosing scenarios in the pediatric population.
- Key exposure parameters were steady-state trough concentration ($C_{trough,ss}$) for efficacy and steady-state maximum concentration ($C_{max,ss}$) for safety (QT prolongation).
- The simulated pediatric exposures were compared to simulated adult exposures at the labelled dose (150 mg capsules QD) to support the registered pediatric posology.

RESULTS

- The final PPK model was a 2-compartment model with dual (fast and slow) lagged parallel first-order absorption and linear elimination. Body weight was identified as the only intrinsic covariate affecting berotralstat exposure.
- The final model reasonably described the observed adult and pediatric data, as shown in **Figures 2** and **3.**
- Monte-Carlo simulations identified pediatric dosing regimens that produced similar $C_{trough,ss}$ and $C_{max,ss}$ relative to the adult population, as shown in **Figure 1** and **Table 2.**

Figure 1. Simulated Berotralstat $C_{trough,ss}$ (Left) and $C_{max,ss}$ (Right) for Adults and Pediatric Individuals in the Labeled Dosing Regimens



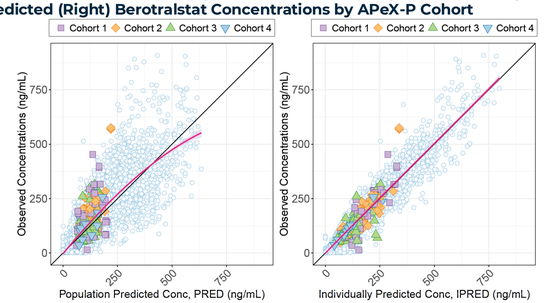
$C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; QD, once daily.
Figure displays median values with 5th and 95th percentiles.

Table 2. Comparison of Simulated Pediatric Versus Adult Berotralstat $C_{trough,ss}$ and $C_{max,ss}$ in the Labeled Dosing Regimens

Weight band	Berotralstat dose (QD)[a]	$C_{trough,ss}$		$C_{max,ss}$	
		Pediatric vs adult ratio of medians	*% of pediatrics below adult 5th percentile*	*Pediatric vs. adult ratio of medians*	*% of pediatrics above adult 95th percentile*
≥40 kg	132 mg	1.18	2.8%	1.19	10.6%
32 to <40 kg	108 mg	1.08	3.7%	1.17	8.9%
24 to <32 kg	96 mg	1.08	3.8%	1.24	10.4%
12 to <24 kg	72 mg	0.99	6.1%	1.23	13.3%

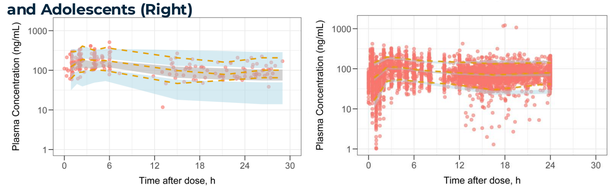
$C_{max,ss}$, maximum concentration at steady state; $C_{trough,ss}$, trough concentration at steady state; QD, once daily. [a]All labeled doses use the oral pellets formulation.

Figure 2. Observed Versus Population-Predicted (Left) and Individually Predicted (Right) Berotralstat Concentrations by APeX-P Cohort



Blue circles represent reference adult and adolescent data. Pink lines represent a smoothing function.

Figure 3. Prediction-Corrected Visual Predictive Check for Berotralstat Concentration Relative to Time After Last Dose, Pediatrics (Left) and Adults and Adolescents (Right)



Points plotted are observed plasma concentrations. Time is time since the prior dose in hours. Gold dashed lines are the 50th, 5th, and 95th percentiles of the observed concentrations. Blue-shaded areas are 95% confidence intervals for the 50th, 5th, and 95th percentiles of 1000 replicates of simulated data, using the final PPK model.

CONCLUSIONS

1. M&S analyses were developed to describe berotralstat pediatric PK data collected in APeX-P.
2. The final PPK model adequately described the observed data and supported pediatric dose selection to match adult exposures for key PK parameters informing efficacy and safety.
3. These dosing regimens were approved in the US for LTP in patients with HAE aged 2 to <12 years.

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