Poster ID: 001360

Population Pharmacokinetic Analysis of Sebetralstat (KVD900) in Healthy Adult Volunteers and Patients With Hereditary Angioedema Predicts Similar Exposure in Adolescent Patients

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Background

- Hereditary angioedema (HAE) is a rare genetic disease characterized by C1 inhibitor deficiency, which causes abnormal functioning of the kallikrein-kinin system, leading to unpredictable, recurrent, and often painful episodes of swelling of the skin and mucosal membranes[1-4]
- The clinical manifestation of HAE in patients with C1 inhibitor deficiency most often occurs during adolescence or early adulthood
- Treatment guidelines recommend that people living with HAE always have access to medications for on-demand treatment of attacks, and treat attacks as early as possible[5-7]
- All currently approved on-demand therapies require parenteral administration, which presents a significant treatment burden.[8-11] Therefore, a safe and effective oral on-demand treatment option could be beneficial for all ages, including adolescents with HAE
- Sebetralstat (KVD900) is a novel oral plasma kallikrein inhibitor in development for the on-demand treatment of HAE attacks
- A single oral dose of sebetralstat demonstrated fast symptom relief and was generally safe and well tolerated in a phase 2 clinical trial in adults with HAE[12-14]
- The purpose of this analysis was to characterize the population pharmacokinetics (PK) of sebetralstat in healthy adults and adult patients with HAE, and subsequently predict exposure in adolescent patients to be included in the phase 3 clinical trials of sebetralstat

Methods

Study Population and Design

- The analysis included sebetralstat plasma concentration data from the following 3 clinical trials of sebetralstat:
  - A phase 1 trial in 68 healthy adult male volunteers (88 total doses) to evaluate the safety, tolerability, PK, and food effects of single ascending doses of sebetralstat (NCT04349800)[15]
  - A phase 1 trial in 30 healthy adult volunteers (90 total doses) to evaluate the safety, tolerability, and PK of multiple doses of sebetralstat
  - A phase 2, randomized, double-blind, placebo-controlled, crossover trial in 68 adult patients with HAE to evaluate the safety and efficacy of sebetralstat, as well as PK and pharmacodynamics of a single 600-mg dose of sebetralstat in plasma samples from 42 patients (NCT04208412)[16]
- Each study included repeated sampling for PK analysis

Model Development

- The population PK model was developed via nonlinear mixed effects modeling using NONMEM 7.4.3 (ICON plc)
- The model was originally developed using data from the phase 1 single ascending dose trial to describe the time course of sebetralstat concentrations in healthy adults
- The base model was expanded using data from the phase 1 multiple ascending dose and phase 2 trials and finalized by assessing and incorporating the influence of covariates
  - Tested covariates included the continuous covariates of age, body weight, body mass index, and liver enzyme values, and the categorical covariates of drug formulation (tablet or capsule), food status (fasting, normal meal, or high-fat meal), sex, and single versus multiple dosing
  - All covariate-parameter relationships of interest were entered into the model simultaneously
- The final population PK model was used to perform simulations of an adolescent population (aged 12 to <18 years) created from sex-specific, age-matched body weights based on Centers for Disease Control and Prevention growth chart data from 2000[17]
  - A 2:1 female-to-male ratio in the adolescent population reflected the greater prevalence of HAE attacks in females
  - Simulations were performed in the virtual adolescent population using a single-tablet dose of sebetralstat under fasting conditions
  - The simulated exposure in adolescents was compared with that of adults

Results

Characteristics of Analysis Populations

- 2381 quantifiable sebetralstat concentrations from 140 adults (42 patients with HAE and 98 healthy volunteers) were included in the analysis (**Table 1**)
  - Demographics of the patients included in the analysis data set and the simulated adolescent population are summarized in **Table 1**

Table 1. Demographics of Analyzed and Simulated Populations

Parameter	Adults (N=140[a])	Adolescents (N=600[b])
Age (years), mean (min-max)	37.5 (19-68)	15.1 (12-17.9)
Female sex,[c] n (%)	34 (24.3)	400 (66.7)
Weight (kg), mean (min-max)	80.3 (56.7-122)	54.6 (31.0-93.3)

[a]Includes 98 healthy volunteers and 42 patients with hereditary angioedema (HAE).
[b]Simulation population.
[c]Of the 42 patients included with HAE, 19 were male (45.2%) and 23 were female (54.8%).
Min-max, minimum-maximum.

Final Population PK Model

- The population PK was best described by a two-compartment model with mixed zero- and first-order absorption, a lag time associated with the zero-order absorption process, and first-order elimination
- The model included effects of formulation, repeat administration, and consumption of food
  - Body weight was not a statistically significant covariate but was retained in the model to facilitate simulations for an adolescent population
  - No other covariate was found to be statistically significant
- Parameter estimates for the final population PK model in healthy adults and adult patients with HAE are presented in **Table 2**

Table 2. Parameter Estimates for Final Population PK Model

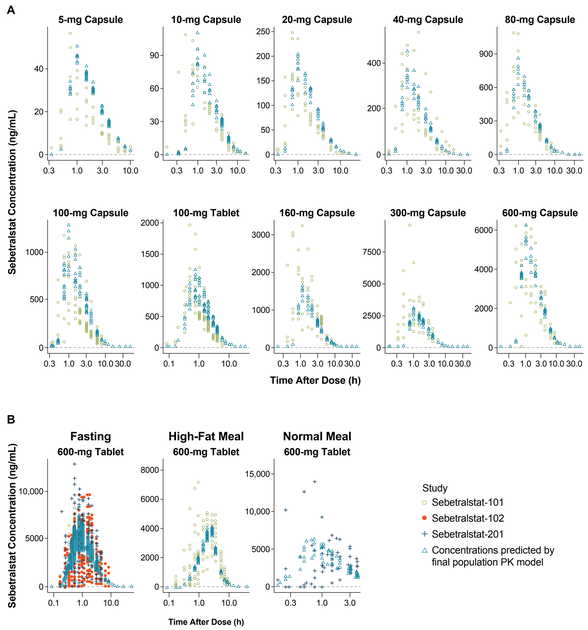
Parameter (unit)	Estimate[a]	%RSE[b]	95% CI[a]	IIV[c]
CL/F (L/h)	31.6	3.65	29.4-33.9	41.6
V_c/F (h)	74.6	3.54	69.6-80.0	35.1
Q/F (L/h)	1.49	7.83	1.27-1.73	64.0
V_p/F (h)	17.9	14.1	13.6-23.6	154
D (h)	0.432	7.11	0.376-0.496	64.4
ALAG (h)	0.168	7.04	0.147-0.193	84.1
Ka (h^{-1})	0.174	11.5	0.139-0.218	85.2
LF	0.164	16	0.120-0.225	284
F zero	0.859	—	—	—
F first	0.141	—	—	—
MD~F	1.63	5.09	1.47-1.79	1.63
Tablet high-fat food SD~D	5.94	7.74	5.03-6.84	5.94
Tablet normal diet MD~D	9.22	11.4	7.16-11.3	9.22
Formulation~ALAG	2.87	1.47	2.79-2.95	2.87
Tablet high-fat food SD~ALAG	1.49	3.27	1.40-1.59	1.49
Tablet normal diet MD~ALAG	3.74	13.2	2.77-4.71	3.74
Tablet high-fat SD and normal diet MD~LF	0.114	20.8	0.068-0.161	0.114
Time ≤1 h~σ^2 add	2.54	4.75	2.30-2.77	2.54
Weight~CL/F and Q/F	0.750	—	—	—
Weight~V_c/F and V_p/F	1.00	—	—	—
σ^2 add	0.025	5.26	0.023-0.0281	—

[a]Back-transformed from natural log scale (except for σ^2).
[b]RSE = SE·100 (except for σ^2). RSE for σ^2 = SE(σ^2)/σ^2·100.
[c]CV% for IIV. Only the diagonal elements of the full covariance matrix are presented.
ALAG, absorption lag time; CI, confidence interval; CL/F, apparent clearance; CV%, coefficient of variation; D, duration of the zero-order absorption process; F first, fraction of absorption via first-order processes; F zero, fraction of absorption via zero-order process; IIV, interindividual variability; Ka, absorption rate constant; LF, linearity factor; MD, repeat dosing; PK, pharmacokinetic; Q/F, apparent intercompartmental clearance; RSE, relative standard error; SD, single dose; V_c/F, apparent volume of the central compartment; V_p/F, apparent volume of the peripheral compartment; σ^2 add, additive component of the residual error model.

Fit of Final Model and Observed Data

- The final population PK model described the observed data with no systematic bias in model predictions
- The observed and predicted sebetralstat plasma concentrations increased with increasing dose across the dose range of 5 to 600 mg (**Figure 1A**)
- The consumption of a normal meal prior to a single dose of sebetralstat did not alter the sebetralstat PK compared with taking the dose after fasting (**Figure 1B**)
  - However, absorption lag time was significantly longer after consumption of a high-fat meal before a single dose or after consumption of a normal meal during repeat dosing
- For a dose of 600 mg (one of the doses of clinical interest) under fasted conditions, 13.1% of the predicted concentrations were outside the 90% prediction interval (PI) in the final model, indicating the model provided a good description for the observed data

Figure 1. Predicted and Observed Sebetralstat Concentration vs Time Plots in Healthy Adult Volunteers and Patients With HAE by (A) Dose and (B) Food Status – Final Population PK Model



A. Sebetralstat concentration after fasting and administration of dose 1, by dose and formulation. B. Sebetralstat concentration after administration of 600-mg tablet, by food status and dose number.
Linear-log scale.
HAE, hereditary angioedema; PK, pharmacokinetic.

Predicted Exposure in Adolescents and Adults

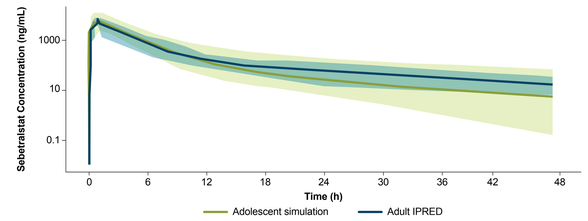
- Median sebetralstat exposure in the virtual adolescent population was predicted to be higher than predicted exposure in adults after administration of a single 600-mg dose of sebetralstat, reflecting the expected lower body weights of adolescents
- The range of the predicted overall exposure (area under the curve from 0 to 24 h [$AUC_{0\text{-}24}$]) and peak exposure (maximum serum concentration [C_{max}]) in the adolescent population were comparable to adult exposures using the individual prediction (IPRED) concentrations for each adult receiving 600 mg of sebetralstat in the data set (**Table 3** and **Figure 2**)
  - The 90% PI for $AUC_{0\text{-}24}$ in adults was wholly contained within the PI for simulated adolescents, and the 90% PIs for C_{max} in adults and adolescents largely overlapped (**Table 3**)

Table 3. Predicted Plasma Sebetralstat Exposure in Adolescents (Single 600-mg Dose)

Parameter	Adolescents (N=600)	Adults: IPRED (N=77[a])	Adults: Observed (N=77[a])
C_{max} (ng/mL)			
Median (90% PI)	7375 (4050-12,658)	5613 (2274-8142)	6340 (3128-9374)
Mean (SD)	7974 (3611)	5396 (2185)	6159 (2470)
$AUC_{0\text{-}24}$ (ng•h/mL)			
Median (90% PI)	21,914 (12,331-38,494)	18,363 (13,573-23,121)	17,744 (14,414-24,059)
Mean (SD)	24,050 (11,126)	18,691 (3872)	19,070 (4283)

[a]N=12 for $AUC_{0\text{-}24}$, because observed data were available only to 24 h for Study 101.
IPRED: estimated using individual predicted concentrations from the final population PK model. Observed: estimated using observed concentration data.
$AUC_{0\text{-}24}$, area under the curve from 0 to 24 h; C_{max}, maximum serum concentration; IPRED, individual prediction; PI, prediction interval; SD, standard deviation.

Figure 2. Predicted Plasma Sebetralstat Exposure at a 600-mg Sebetralstat Dose After Fasting in Adolescents and Adults



Shaded regions are 90% prediction intervals. IPRED: estimated using individual predicted concentrations from the population PK model.
IPRED, individual prediction; PK, pharmacokinetic.

Conclusions

- The PK of sebetralstat in healthy adult volunteers and patients with HAE was well described by a two-compartment population PK model with mixed zero- and first-order absorption and a lag time associated with the zero-order absorption process and first-order elimination
- Single-dose PK of sebetralstat was linear across the evaluated dose range
- Consuming a normal meal prior to a single dose of sebetralstat did not appear to alter the sebetralstat PK compared with taking the dose after fasting
- This population PK model predicted that overall sebetralstat exposure in an adolescent population would be similar to that in adults for a single 600-mg dose
- This model supports the use of the same doses of sebetralstat for adults and adolescents in phase 3 clinical trials

Acknowledgments

This study was supported by KalVista Pharmaceuticals Ltd. Medical writing assistance was provided under the direction of the authors by Courtney Niland, PhD, Lisa Baker, PhD, Brittany Eldridge, PhD, and Michael Howell, PhD, of Cadent, a Syneos Health group company, and was supported by KalVista Pharmaceuticals, Inc.

Presented during the EAACI Hybrid Congress, July 1-3, 2022, Prague, Czech Republic.

Disclosures

MDS, JS, and PM are employees of KalVista Pharmaceuticals. TR and CF are employees of ICON plc who received professional fees to conduct this analysis. RT has received speaking and consulting fees from Takeda, CSL Behring, Pharming, and BioCryst, and research fees from Takeda, BioCryst, Ionis, KalVista, and Pharvaris. SS has received speaking and consulting fees from Takeda, CSL Behring, and BioCryst, and a research grant from CSL Behring.

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