Oral sebetralstat (KVD900) provides rapid inhibition of the kallikrein kinin system in patients with hereditary angioedema

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Background

- Hereditary angioedema (HAE) is a rare genetic disease characterized by recurrent, often painful episodes of swelling of the skin and mucosal membranes1,2.
- Previous studies have demonstrated that plasma kallikrein (PKa) activity is increased during attacks in patients with HAE and that uncontrolled PKa enzyme activity is a primary cause of HAE attacks 3-5.
- Sebetralstat is an investigational oral PKa inhibitor for the on-demand treatment of HAE.
- We evaluated pharmacokinetics (PK), pharmacodynamics (PD), and time to symptom relief in adult patients with HAE treated with sebetralstat in a phase 2 trial.

Methods

Study Population and Design

- The randomized, double-blind, placebo-controlled, phase 2 crossover trial (ClinicalTrials.gov identifier: NCT04208412) included adult patients aged ≥18 years with HAE type I or II who had experienced at least 3 attacks in the past 93 days and were not receiving prophylactic therapy.
- In part 1 of the trial, an open-label, single 600 mg dose of sebetralstat was administered to patients in the clinic for assessment of PK and PD parameters (Figure 1).
- In part 2 of the trial, patients were randomized to receive either 600 mg of sebetralstat for the first attack followed by placebo for the second attack, or placebo for the first attack followed by 600 mg of sebetralstat for the second attack.
  - Attacks were eligible for treatment if they were mild or moderate in severity and did not involve the face or larynx.
  - For eligible attacks, study treatment was to be taken within 1 hour of attack onset.

PK and PD Assay Methods

- In part 1 of the trial, plasma samples for PK and PD assessment were taken predose and at repeated intervals beginning 15 minutes after oral dosing and up to 4 hours postdose.
- PK parameters included plasma concentration over time, maximum observed concentration (Cmax), and time to Cmax (Tmax).
- For PD analyses, the contact system in plasma was stimulated by dextran sulfate (DXS), leading to PKa generation from the zymogen prekallikrein which resulted in high molecular weight kininogen (HK) cleavage (Figure 2).
  - PKa enzyme activity was measured using the fluorescent substrate H-D-Pro-Phe-Arg-AFC, activity was estimated based on the maximum rate of fluorescence increase.
  - Levels of kallikrein kinin system activation were monitored by capillary-based immunoassays detecting HK and prekallikrein.

Results

- In part 2 of the trial, symptom relief was assessed using the Patient Global Impression of Change (PGI-C) measure on a 7-point scale from “Much Worse” to “Much Better.”
  - The PGI-C was completed at 30-minute intervals from 0.5 to 4 hours, 1-hour intervals to 12 hours, and 3-hour intervals to 24 hours.
  - Time to symptom relief (PGI-C score of “A Little Better” or higher for 2 consecutive time points) was assessed within 12 hours of study drug administration.

Statistical Analyses

- Significant differences in levels of HK or prekallikrein were evaluated using one-way ANOVAs.
- P value for time to symptom relief data was determined using Gehan’s generalized Wilcoxon test.

Conclusions

- After oral administration to HAE patients, sebetralstat was rapidly absorbed to high concentrations in plasma.
- Sebetralstat provided near complete inhibition of HK and prekallikrein cleavage, this indicates that sebetralstat inhibits the contact activation system via interruption of the positive feedback loop mediated by PKa stimulated activation of FXII.

References


Conflict of interest disclosure

- All authors are employees of KalVista Pharmaceuticals.