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

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Background

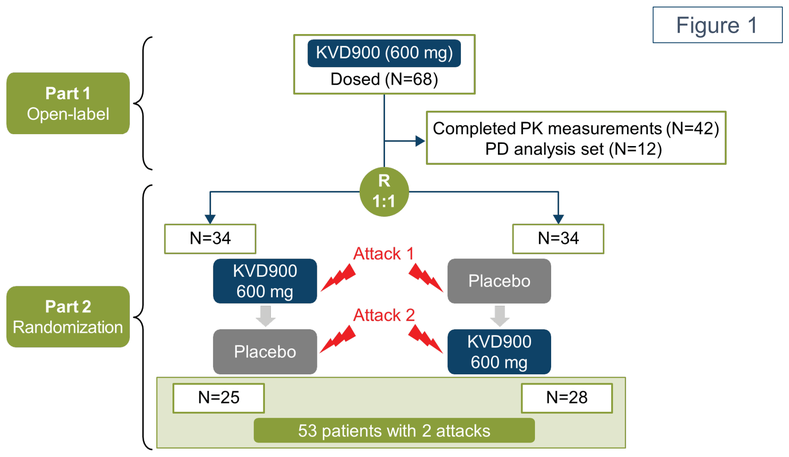
- Hereditary angioedema (HAE) is a rare genetic disease characterized by recurrent, often painful episodes of swelling of the skin and mucosal membranes[1,2]
- Previous studies have demonstrated that plasma kallikrein (PKa) activity is increased during attacks in patients with HAE and that uncontrolled 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

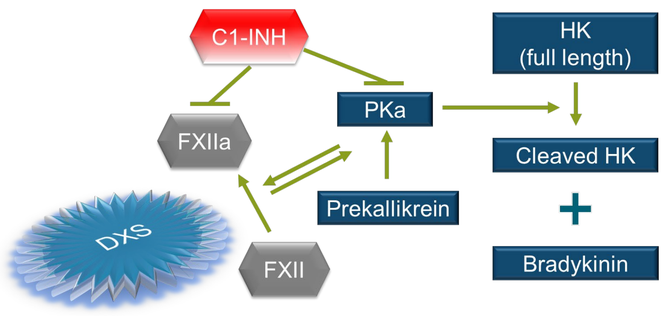
Figure 1



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 (C_{max}), and time to C_{max} (T_{max})
- 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

Figure 2



Methods

Outcome measures

- 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

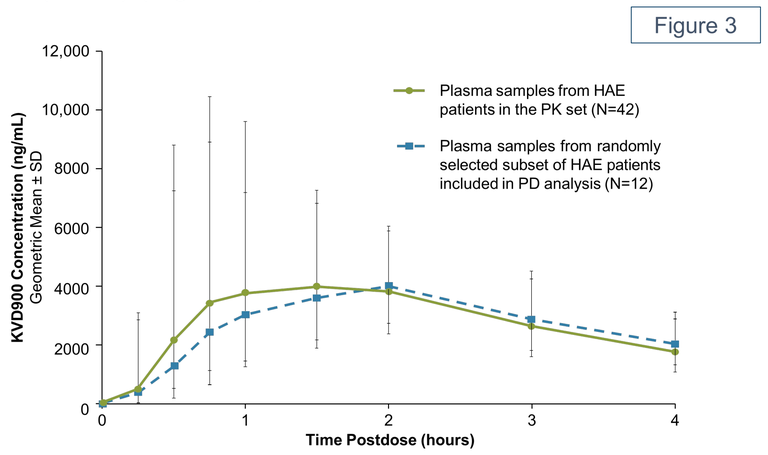
- Significant differences in levels of HK or prekallikrein were evaluated using one-way ANOVAs
- P value for time to symptom relief data was determined using Gehan’s generalized Wilcoxon test.

Results

PK Analysis

- Sebetralstat was rapidly absorbed following a single oral 600 mg dose, with a geometric mean plasma concentration of 501 ng/mL at 15 minutes, the first time point evaluated (Figure 3)
- Plasma levels of sebetralstat reached maximum values (geometric mean C_{max}: 6080 ng/mL) with an observed median T_{max} of 1.0 hour
- The mean PK profiles of selected samples from patients for the PD analysis (N=12) were similar to those of the full PK set (N=42) (Figure 3)

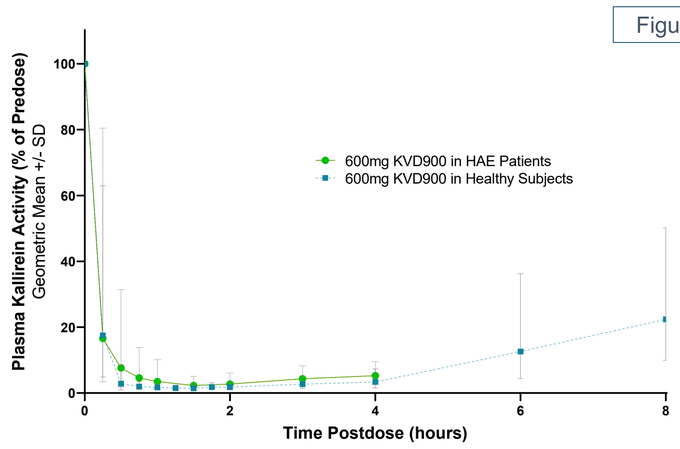
Figure 3



PD Analyses

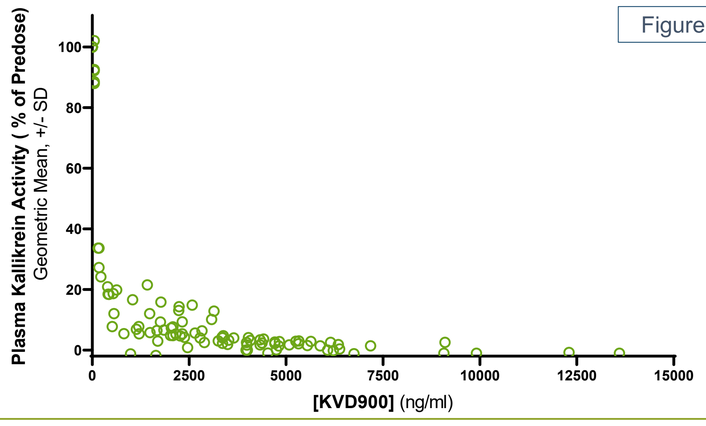
- Following oral administration of sebetralstat, stimulated PKa activity in plasma was inhibited >80% within 15 minutes (Figure 4)
- Near-complete inhibition (≥95%) of PKa activity was observed within 1 hour following oral administration of sebetralstat and maintained through 4 hours
- Inhibition profile in HAE patients matches well to profile seen in healthy subjects

Figure 4



- Inhibition of PKa activity in HAE plasma samples was sebetralstat concentration dependent (Figure 5)

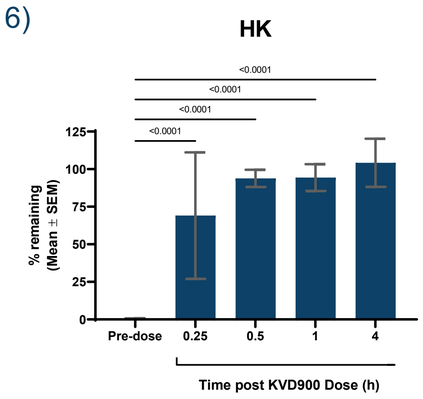
Figure 5

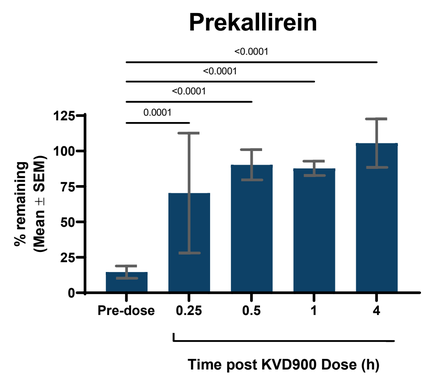


Results

- Sebetralstat provided near complete inhibition of HK and prekallikrein cleavage in HAE patient plasma with significant protection from 15 minutes to 4 hours post dose (Figure 6)

Figure 6



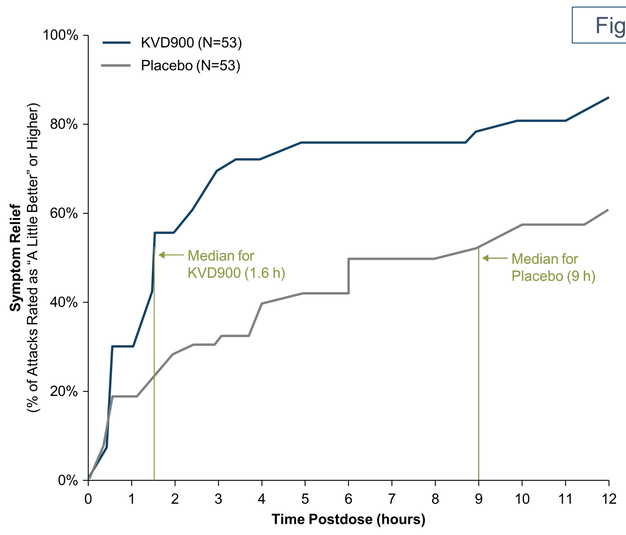


- Sebetralstat reduced both HK and prekallikrein cleavage, this indicates that sebetralstat inhibits the contact activation system via interruption of the positive feedback loop mediated by PKa stimulated activation of FXII [6]

Symptom Relief

- Median time to symptom relief was significantly shorter following treatment with sebetralstat compared with placebo (1.6 [95% confidence interval (CI), 1.5-3.0] vs 9.0 [95% CI,4.0-noncalculable] hours; P<0.0001) (Figure 7)

Figure 7



Conclusions

- After oral administration to HAE patients, sebetralstat was rapidly absorbed to high concentrations in plasma
- Sebetralstat provided rapid and near complete inhibition of PKa activity
- Sebetralstat inhibits the feedback loop of the kallikrein kinin system leading to a reduction in the generation of PKa
- The rapid inhibition of the kallikrein kinin system by sebetralstat was associated with fast symptom relief in HAE patients

References

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Conflict of interest disclosure

- All authors are employees of KalVista Pharmaceuticals.