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Oral Sebetralstat (KVD900) Provides Rapid Inhibition of Plasma Kallikrein and Fast Improvement in Attack Symptoms in Patients With Hereditary Angioedema

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Introduction

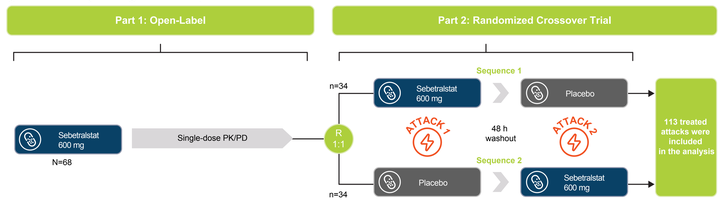
- Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease involving abnormal functioning of the kallikrein-kinin system, leading to increased vascular permeability and characterized by recurrent, often painful episodes of swelling of varying severity and location[1-4]
- Treatment guidelines for HAE recommend that patients have access to medications for on-demand treatment of HAE attacks and treat attacks as early as possible, aiming to decrease the intensity of symptoms, reduce attack duration, and achieve a more rapid resolution[5-7]
  - Currently, all approved on-demand treatments require parenteral administration, which presents significant challenges with administration, time needed for medication preparation, injection site–associated pain and discomfort[8-11]
  - There remains an unmet need for a safe and effective oral on-demand treatment option for HAE attacks
- Studies have demonstrated that uncontrolled plasma kallikrein activity is a key mechanism responsible for HAE attacks[3,4,12]
- Sebetralstat (KVD900) is a novel investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks
- In a phase 2 randomized clinical trial, the pharmacokinetics, pharmacodynamics, efficacy, and safety of a single oral dose of sebetralstat 600 mg were investigated in people living with HAE type I or II

Methods

Study Design and Patient Population

- This phase 2 trial (NCT04208412) included adults aged ≥18 years with HAE type I or II who had experienced at least 3 attacks in the past 93 days and were not on prophylactic therapy
- Part 1 of the trial was an open-label phase investigating the safety and pharmacokinetic (PK) and pharmacodynamic (PD) parameters of a single dose of sebetralstat 600 mg (**Figure 1**)
- Part 2 of the trial was a double-blind crossover phase evaluating efficacy and safety in patients randomized to treat 2 eligible attacks with sebetralstat 600 mg or placebo in 1 of 2 sequences (**Figure 1**)
  - Attacks were eligible for treatment if they were mild or moderate in severity and did not involve the face or larynx

Figure 1. Study Design and Disposition

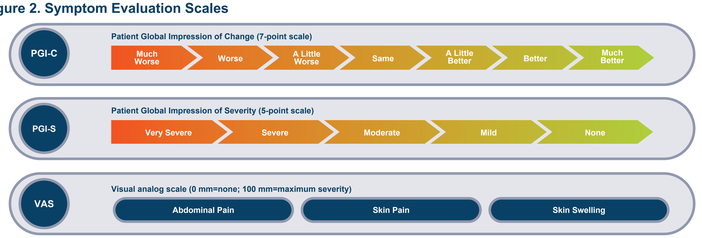


PD analysis set is a subset of patients included in the PK analysis.
h, hour; PD, pharmacodynamic; PK, pharmacokinetic; R, randomized.

PK and PD Assay Methods

- The PK and PD assessments were conducted on plasma samples taken predose and at repeated intervals beginning 15 minutes after dosing for up to 4 hours postdose
- Plasma concentrations were assessed in 42 patients and PK parameters calculated, including maximum concentration (C_{max}) and time to C_{max} (T_{max})
- PD assessment was performed in plasma from 12 randomly selected patients from the PK set to measure the inhibition of plasma kallikrein enzyme activity after dosing of sebetralstat
  - Stimulation of plasma samples with dextran sulfate was used to generate plasma kallikrein from prekallikrein
  - Plasma kallikrein enzyme activity was measured using a fluorescent substrate H-D-Pro-Phe-Arg-AFC and was based on the maximum rate of fluorescence increase

Figure 2. Symptom Evaluation Scales



PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; VAS, visual analog scale.

Symptom Assessment Scales and Efficacy Assessments

- Symptom relief was defined as a score of "A Little Better" or higher for 2 consecutive timepoints within 12 hours of study drug administration on the Patient Global Impression of Change (PGI-C) scale and was measured at 30-minute intervals from 0.5 to 4 hours, 1-hour intervals to 12 hours, and 3-hour intervals to 24 hours
- Improvement in attack severity on the Patient Global Impression of Severity (PGI-S) scale was defined as an increase by ≥1 level within 12 hours
- Symptom improvement on the composite visual analog scale (VAS) was defined as 50% reduction from baseline for 3 consecutive timepoints within 12 hours
- Results are presented using descriptive statistics; outcome measure scales are shown in **Figure 2**

Statistical Analyses

- *P* value for time to symptom relief and time to improvement was determined using Gehan's generalized Wilcoxon test with $P<0.05$ indicating statistical significance

Results

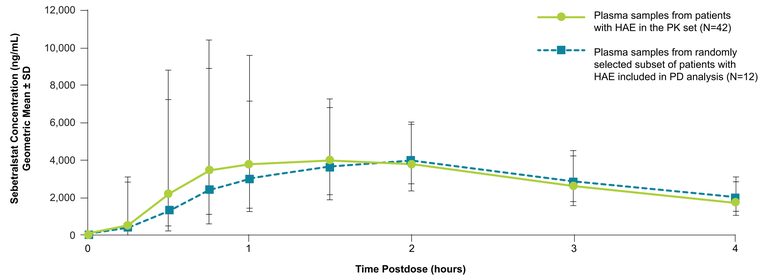
Patients

- Among the 68 dosed patients, 42 were included in the PK set (part 1)
- 60 patients completed treatment for at least 1 HAE attack (n=113 attacks) (**Figure 1**)

PK Analyses

- Following a single oral dose at 600 mg, sebetralstat was rapidly absorbed, with a geometric mean plasma concentration of 501 ng/mL at 15 minutes, the first timepoint 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 patients randomly selected for the PD analysis (N=12) were similar to those of the full PK set (N=42)

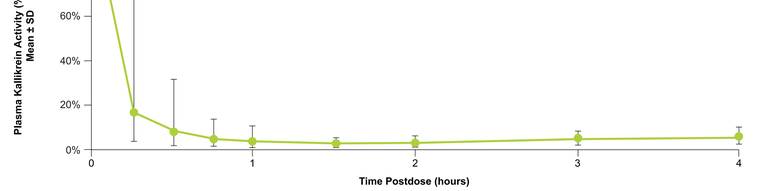
Figure 3. Plasma Sebetralstat Pharmacokinetics Following Oral Dosing[13]



HAE, hereditary angioedema; PD, pharmacodynamic; PK, pharmacokinetic.

- Following oral administration of sebetralstat, stimulated plasma kallikrein activity in plasma was inhibited >80% within 15 minutes (**Figure 4**)
  - Near-complete inhibition (≥95%) of plasma kallikrein activity was observed within 1 hour following oral administration of sebetralstat and maintained through 4 hours (the last timepoint measured)

Figure 4. Orally Administered Sebetralstat Rapidly Inhibits Plasma Kallikrein Activity in Patients With HAE[13]

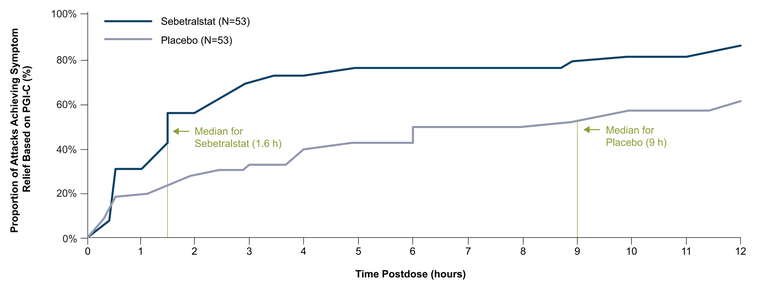


Plasma kallikrein activity is shown as a percentage of plasma kallikrein activity in the predose samples.
HAE, hereditary angioedema.

Symptom Improvement

- Median time to symptom relief on PGI-C* was significantly shorter following treatment with sebetralstat compared with placebo (1.6 [95% CI, 1.5:3.0] vs 9.0 [95% CI, 4.0 to ≥12.0] hours; $P<0.0001$) (**Figure 5**)

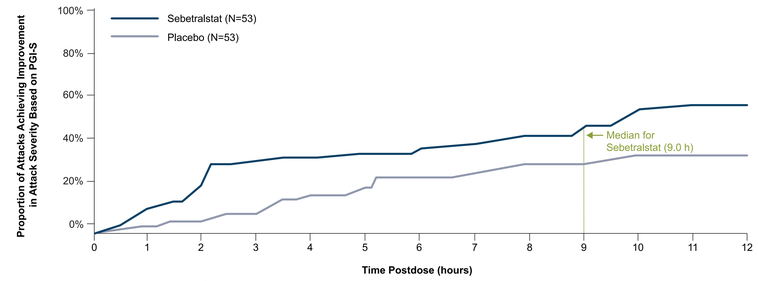
Figure 5. Time to Symptom Relief Based on PGI-C



*Symptom relief on PGI-C is defined as a rating of "A Little Better" or higher for 2 consecutive timepoints.
h, hours; PGI-C, Patient Global Impression of Change.

- Median time to improvement in attack severity on PGI-S* was significantly shorter following treatment with sebetralstat compared with placebo (9.0 [95% CI, 3.5 to ≥12.0] vs ≥12.0 [95% CI, 10.0 to ≥12.0] hours; $P=0.0002$) (**Figure 6**)

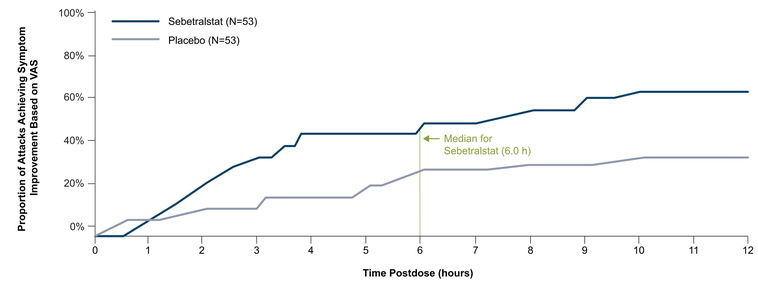
Figure 6. Time to Improvement in Attack Severity Based on PGI-S



*Improvement in attack severity on PGI-S is defined as increase by ≥1 level.
h, hours; PGI-S, Patient Global Impression of Severity.

- Median time to symptom improvement on VAS* was significantly shorter following treatment with sebetralstat compared with placebo (6.0 [95% CI, 3.0:9.0] vs ≥12.0 [95% CI, ≥12.0 to ≥12.0] hours; $P<0.0001$) (**Figure 7**)

Figure 7. Time to Symptom Improvement Based on Composite VAS



*Symptom improvement on VAS is defined as ≥50% reduction from baseline in composite VAS for 3 consecutive timepoints. Symptom improvement on VAS occured at 19.0 hours on placebo.
h, hours; VAS, visual analog scale.

Conclusions

- Oral administration of sebetralstat achieved rapid plasma exposure and near-complete inhibition of plasma kallikrein activity in people living with HAE
- Times to symptom relief on PGI-C, improvement in attack severity on PGI-S, and symptom improvement on VAS were significantly shorter for attacks treated with sebetralstat vs placebo
- Rapid plasma kallikrein inhibition following oral sebetralstat was associated with early symptom relief and improvement in people living with HAE

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Disclosures

All authors are employees of KalVista Pharmaceuticals, Salisbury, UK, and Cambridge, MA, USA

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