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 duration. Treatment guidelines for HAE recommend that patients have access to medications for on-demand treatment of HAE attacks and that oral treatments be selected based on a change in the kallikrein-kinin system and with administration time required for medication preparation, injection site–associated pain and discomfort, time to on-demand treatment of HAE attacks, and patient preference. Sebetralstat (KVD900) is a novel investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks. Currently, all approved on-demand treatments require parenteral administration, which presents significant challenges with medication preparation, injection site–associated pain and discomfort, and patient preference for oral therapy.

Methods

Study Design and Patient Population

This phase 2 trial (KVD1001-001) recruited adults aged 18 years or older with HAE type I or II who had experienced at least 3 attacks in the past 6 months and were not on prophylaxis therapy.

Part 1 of the trial was an open-label phase to investigate the safety and pharmacokinetics (PK) and pharmacodynamics (PD) parameters of a single dose of sebetralstat (600 mg) in patients (N=12) (Figure 1). Part 2 of the trial was a double-blind, placebo-controlled phase evaluating efficacy and safety in patients randomized to either oral sebetralstat 600 mg or placebo (N=41) (Figure 1).

Figure 1. Study Design and Disposition

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.

In patients who were assessable in PK and PD parameters calculated, including maximum concentration (Cmax) and time to Cmax (Tmax). PK assessment was performed on plasma samples collected from 12 randomly selected patients that had the highest plasma kallikrein activity after dosing of sebetralstat. PK assessment was performed on plasma samples collected from 12 randomly selected patients that had the highest plasma kallikrein activity after dosing of sebetralstat.

Results

Proportion of Patients With Minimal to No Symptoms (PGI-C≤1)

Median for sebetralstat (6.0 h) vs placebo (9.0 h) (P=0.051) (Figure 6). Median time to symptom improvement on VAS was significantly shorter following treatment with sebetralstat compared with placebo (3.0 h [95% CI, 2.0 to 4.0 h]; P=0.006) (Figure 7).

Results

Proportion of Attacks Achieving Symptom Improvement

Median time to improvement in attack severity on PGI-C was significantly shorter following treatment with sebetralstat compared with placebo (9.0 h [95% CI, 6.0 to 12.0 h] vs 12.0 h [95% CI, 9.0 to 15.0 h]; P=0.006) (Figure 8).

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.

Disclosures

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

References