Efficacy and Safety of the Oral Plasma Kallikrein Inhibitor Sebetralstat (KVD900) in Adolescent and Adult Patients With Hereditary Angioedema: Phase 3 Trial Design

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Background

Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease, involving abnormal functioning of the kallikrein–kinin system (Figure 1), leading to increased vascular permeability and characterized by unpredictable, recurrent, and often painful episodes of swelling of varying severity and location.1-4

HAE treatment guidelines recommend that all patients have access to effective on-demand treatment and that all attacks are treated as early as possible.3-7

Currently, all approved on-demand treatments require parental administration, which presents significant challenges with preparation, venous access, and injection-site-associated pain and discomfort.8-10

There remains an unmet need for a safe and effective oral on-demand treatment option for HAE attacks.7

Sebetralstat (KVD900) is an investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks.

1. The phase 2 trial of sebetralstat previously reported a favorable pharmacokinetic and pharmacodynamic profile and positive efficacy and safety results.8-10

2. Here we present the design of the KONFIDENT phase 3 clinical trial evaluating the efficacy and safety of sebetralstat for the oral on-demand treatment of HAE attacks in a larger population of adult and adolescent patients with HAE (NCT02529957).11

Figure 1. Kallikrein-Kinin System

Trial Design

KONFIDENT is a phase 3, randomized, double-blind, placebo-controlled, crossover clinical trial enrolling patients aged 12 years with HAE type I or II, including patients on long-term prophylactic treatment.

Patients will be randomized to treat 3 eligible attacks with sebetralstat 300 mg, sebetralstat 600 mg, or placebo in a 3-way crossover design using 1 of 6 treatment sequences (Figure 2).

– Eligible attacks will be treated as soon as possible after the patient recognizes the start of the attack.
– Patients will treat each eligible attack with up to 2 doses of study drug, administered at least 3 hours apart.
– Laryngeal attacks considered severe are not eligible for treatment.
– All patients are required to have conventional attack treatment available during the trial.

Approximately 84 patients, including a minimum of 12 adolescents, are expected to complete treatment of 3 attacks

Figure 2. KONFIDENT Trial Design

Patient Population

Table 1. Key Inclusion Criteria

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<th>Key Inclusion Criteria</th>
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<tr>
<td>Male or female patients aged 12 years or older</td>
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<td>Confirmed diagnosis of HAE type I or II</td>
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<td>Access to and ability to use conventional on-demand treatment for HAE attacks</td>
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<td>Patients taking long-term prophylactic treatment (intravenous or subcutaneous plasma-derived C1 inhibitor [CI-INH] and/or lanadelumab) must be on a stable dose and regimen for at least 3 months prior to the trial and for the trial duration</td>
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<tr>
<td>Last dose of attenuated androgens ≤28 days prior to randomization</td>
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<td>At least 2 documented attacks within 3 months prior to randomization</td>
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Key Exclusion Criteria

– Diagnosis of other forms of chronic angioedema, including acquired C1-INH deficiency, HAE with normal CI-INH, idiopathic angioedema, or angioedema associated with urticaria
– Use of angiotensin-converting enzyme inhibitors after the screening visit or within 7 days prior to randomization
– Use of any estrogen-containing medications with systemic absorption within 7 days prior to the screening visit or during the trial
– Use of strong cytochrome P450 344 inhibitors and inducers during participation in the trial starting at the screening visit

Assessments

Primary Endpoint

– Time to first incidence of decrease from baseline in Patient Global Impression of Change (PGI-C) rating of at least “A Little Better” for 2 consecutive timepoints within 12 hours of study drug administration (Figure 3)

Secondary Endpoints

– Time to first incidence of decrease from baseline in Patient Global Impression of Severity (PGI-S) rating within 12 hours of study drug administration (Figure 3)
– Time to first incidence of decrease from baseline in PGI-S within 24 hours of study drug administration
– Time to HAE attack resolution, defined as a PGI-S score of “None” within 24 hours of study drug administration
– Proportion of attacks with beginning of symptom relief within 4 and 12 hours of study drug administration
– Time to PGI-C rating of at least “Better” within 12 hours of study drug administration
– Time to ≤50% decrease from baseline in composite visual analog scale (VAS) for 3 consecutive timepoints within 12 and 24 hours of study drug administration

Exploratory Endpoint

– Cumulative General Anxiety–Numeric Rating Scale expressed as area under the curve over 12 and 24 hours of study drug administration (Figure 3)

Disclosures

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References

11. KVD900 for on-demand treatment of angioedema attacks in adolescent and adult patients with HAE (NCT02529957).11

Trial Status

The KONFIDENT trial enrollment began in March 2022.

Enrollment will take place in North America, Europe, and Asia-Pacific countries

Figure 3. Efficacy Assessment Scales