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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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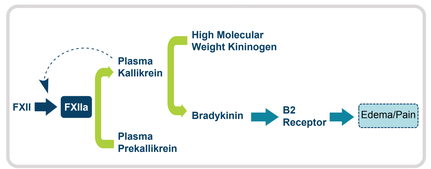
Background

- 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[5-7]
- Currently, all approved on-demand treatments require parenteral administration, which presents significant challenges with preparation, venous access, and 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
- Sebetralstat (KVD900) is an investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks
  - The phase 2 trial of sebetralstat previously reported a favorable pharmacokinetic and pharmacodynamic profile and positive efficacy and safety results[12-14]
- 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 (NCT05259917)[15]

Figure 1. Kallikrein-Kinin System



FXII, factor XII.

Trial Overview

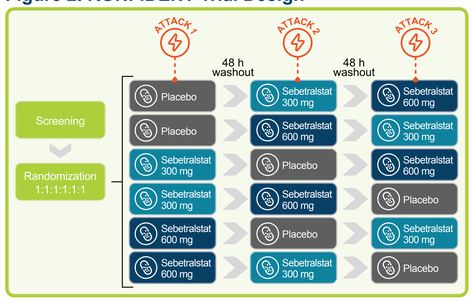
Trial Design

- 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

KONFIDENT
SEBETRALSTAT CLINICAL TRIAL

- 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



h, hour.

Patient Population

Key Inclusion Criteria

- Male or female patients aged 12 years or older
- Confirmed diagnosis of HAE type I or II
- Access to and ability to use conventional on-demand treatment for HAE attacks
- Patients taking long-term prophylactic treatment (intravenous or subcutaneous plasma-derived C1 inhibitor [C1-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
- Last dose of attenuated androgens at least 28 days prior to randomization
- At least 2 documented HAE attacks within 3 months prior to randomization

Key Exclusion Criteria

- Diagnosis of other forms of chronic angioedema, including acquired C1-INH deficiency, HAE with normal C1-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 3A4 inhibitors and inducers during participation in the trial starting at the screening visit

Assessments

Primary Endpoint

- Time to beginning of symptom relief, defined as a 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**)

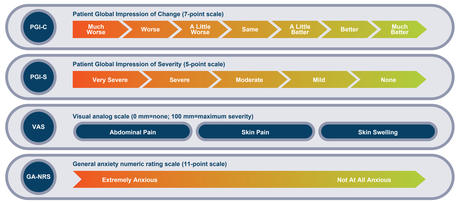
Secondary Endpoints

- 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**)

Figure 3. Efficacy Assessment Scales



GA-NRS, General Anxiety–Numeric Rating Scale; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; VAS, visual analog scale.

Frequency

- Efficacy assessments will be recorded by the patient in a diary at defined intervals (**Table 1**)

Table 1. Frequency of Patient Efficacy Assessments

Time After First Dose of Study Drug	Frequency of Assessment
0 to 4 hours	Every 0.5 ± 0.25 hour
5 to 12 hours	Every 1 ± 0.5 hour
14 to 24 hours	Every 2 ± 1 hours
25 to 48 hours	Every 12 ± 3 hours

Safety Assessments

- Physical examination
- Evaluation of vital signs
- Electrocardiogram
- Clinical safety laboratory assessments[a]
- Adverse events[b]

Safety assessments will be conducted at screening and at the final visit.
[a]Includes a hematology panel, clinical chemistry panel, electrolyte panel, C1-esterase inhibitor activity, C1-esterase inhibitor protein, complement C4, and pregnancy test.
[b]Will be recorded from the first dose of study drug through the final visit.

Trial Status

- The KONFIDENT trial enrollment began in March 2022
- Enrollment will take place in North America, Europe, and Asia-Pacific countries

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For more information about the KONFIDENT trial, please scan the QR code or visit www.konfidentstudy.com