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KONFIDENT Phase 3 Trial Design for Sebetralstat (KVD900), a Novel Investigational Oral Plasma Kallikrein Inhibitor for the On-Demand Treatment of Hereditary Angioedema Attacks

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Introduction

- Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease characterized by recurrent episodes of swelling; attacks can have a significant negative impact on patients' quality of life[1-4]
- Treatment guidelines for HAE recommend that patients have access to medications for on-demand treatment of attacks and treat attacks as early as possible[5-7]
  - All approved on-demand treatments require parenteral administration, which presents significant challenges with preparation, venous access, 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 that allows fast administration and reduces treatment burden
- HAE is driven by abnormal functioning of the kallikrein-kinin system, and studies have demonstrated that uncontrolled plasma kallikrein activity is a key mechanism responsible for HAE attacks[3,4,12]
- Sebetralstat (KVD900) is an investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks that showed a favorable pharmacokinetic and pharmacodynamic profile and positive efficacy and safety results in a previous phase 2 trial[13-15]
- Here we present the design of KONFIDENT, a randomized, double-blind, placebo-controlled, crossover 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). KONFIDENT is currently enrolling patients in North America, Europe, and Asia-Pacific countries (**Figure 1**)

Figure 1. KONFIDENT Trial

KONFIDENT
SEBETRALSTAT CLINICAL TRIAL

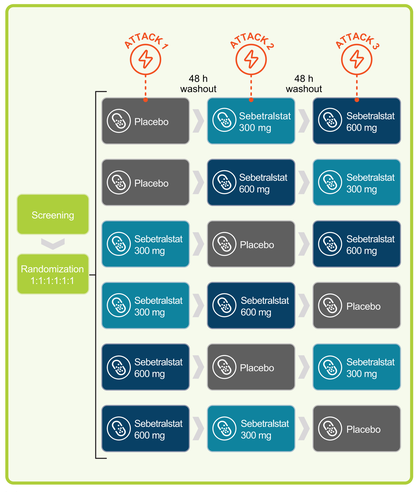
A current list of trial sites is available at www.konfidentstudy.com.

Trial Overview

Trial Design

- 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**)
  - Consistent with HAE guidelines, patients are instructed to treat eligible attacks as soon as possible after recognition of start of attack[5-7]
  - Patients may 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 around 12 adolescents, are expected to complete treatment of 3 attacks

Figure 2. KONFIDENT Trial Design



h, hour.

Patient Population

Key Inclusion Criteria	Key Exclusion Criteria
▪ Male or female patients aged ≥12 years ▪ Confirmed diagnosis of HAE type I or II ▪ At least 2 documented HAE attacks within 3 months prior to randomization ▪ 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 immediately prior to the trial and for the trial duration ▪ Last dose of attenuated androgens at least 28 days prior to randomization	▪ 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

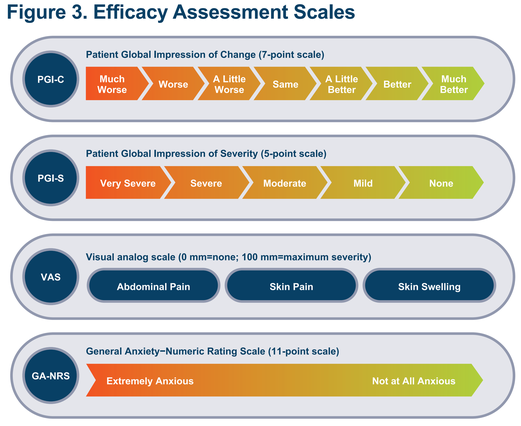
Primary Endpoint

- 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

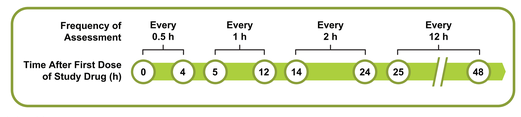
Figure 3. Efficacy Assessment Scales



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.

- Efficacy assessments will be recorded by the patient in a diary at defined intervals (**Figure 4**)

Figure 4. Frequency of Patient Efficacy Assessments



h, hour(s).

Exploratory Endpoint

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

Safety Assessments

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

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.

Conclusion

- The KONFIDENT phase 3 trial will evaluate sebetralstat as an oral therapy for on-demand treatment of HAE attacks in a large population of adult and adolescent patients with HAE to provide data on efficacy and safety

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

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