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# Sebetralstat, Investigational Oral On-Demand Treatment for HAE: KONFIDENT Trial Design

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## Background

- Hereditary angioedema (HAE) is a genetic disease resulting in deficiency (type I) or dysfunction (type II) in the complement-1 esterase inhibitor (C1-INH) protein and subsequent uncontrolled activation of the kallikrein kinin system (KKS)[1,2]
- People living with HAE experience painful and debilitating attacks of tissue swelling in various locations of the body that can be life-threatening depending on the location affected[3]
- All currently approved on-demand treatment options require either intravenous or subcutaneous administration[1]
- Global HAE treatment guidelines recommend that people living with HAE carry on-demand treatment with them at all times and should treat all attacks as early as possible to optimize clinical outcomes[4]
- Sebetralstat is an investigational, orally administered, small molecule plasma kallikrein (PKa) inhibitor that protects high molecular-weight kinonogen (HK) against PKa-mediated cleavage and suppresses PKa-mediated amplification of the KKS[5-7]
- Sebetralstat is a highly selective PKa inhibitor that is rapidly absorbed and results in >80% PKa inhibition within 15 minutes after oral administration[5]
- In a phase 2 trial, beginning of symptom relief, reduction of attack severity, and attack resolution were faster with sebetralstat than placebo in patients with HAE who self-administered treatment[7]
- In phase 1 and 2 trials, sebetralstat was generally safe and well tolerated, and had a safety profile comparable with placebo, including for gastrointestinal-related adverse events[5,7]
- The phase 3 KONFIDENT trial is underway for sebetralstat, an investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema attacks[8]

## Trial Overview

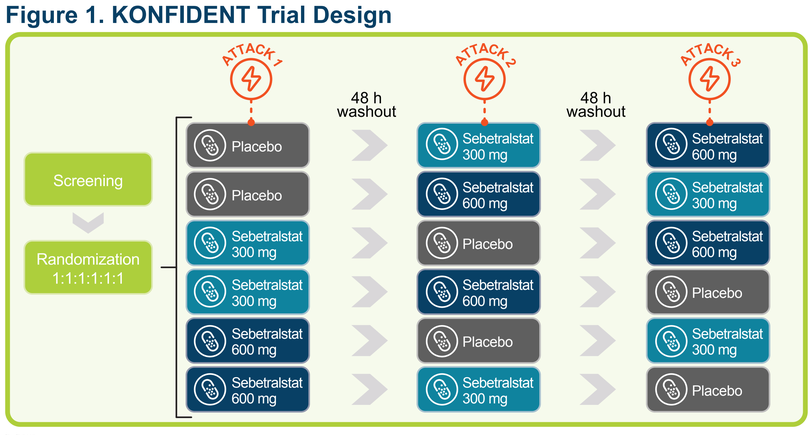
### Trial Design

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

KONFIDENT™
KVD-900 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 1**)
  - 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 (252 attacks)

### Figure 1. 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
- 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-INH, lanadelumab, berotralstat, or low-dose danazol) must be on a stable dose and regimen for at least 3 months (except for danazol, which requires a stable dose and regimen for 6 months) prior to the trial and for the trial duration
- For participants not receiving androgens for long-term prophylaxis, last dose of attenuated androgens at least 28 days 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 time points in a row within 12 hours of study drug administration (**Figure 2**)

#### Secondary Endpoints

##### Key secondary endpoints

- Time to first incidence of decrease from baseline in Patient Global Impression of Severity (PGI-S) for 2 time points in a row within 12 hours of the first dose of study drug (**Figure 2**)
- Time to HAE attack resolution defined as PGI-S score of "none" within 24 hours of the first dose of study drug

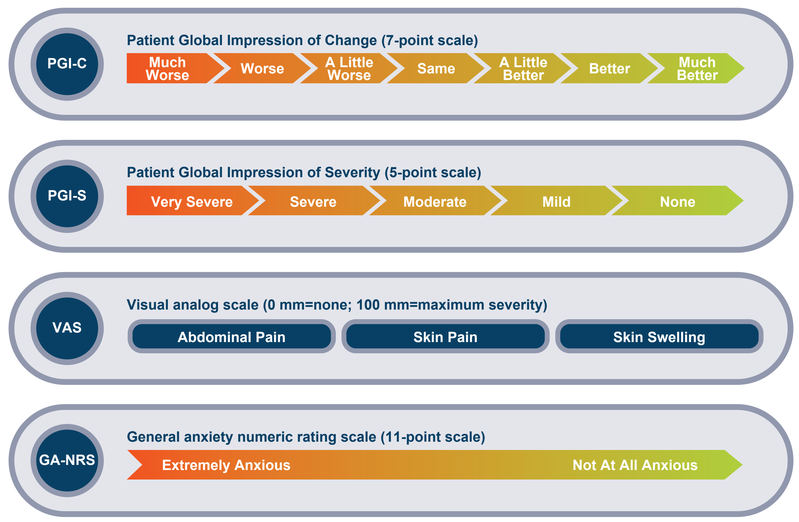
##### Secondary endpoints

- Proportion of attacks with beginning of symptom relief defined as a PGI-C rating of at least "a little better" for 2 time points in a row within 4 hours and within 12 hours of the first dose of study drug
- Time to a PGI-C rating of at least "better" for 2 time points in a row within 12 hours of the first administration of study drug
- Time to first incidence of decrease from baseline in PGI-S score for 2 time points in a row within 24 hours of the first administration of study drug
- Time to at least a 50% decrease from baseline in composite visual analog scale (VAS) for 3 time points in a row within 12 hours and within 24 hours of the first administration of study drug

#### Exploratory Endpoint

- Cumulative General Anxiety−Numeric Rating Scale expressed as area under the curve over 12 and 24 hours of study drug administration (**Figure 2**)

### Figure 2. 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.

### Assessment 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

- Safety assessments will include physical examinations, evaluations of vital signs, electrocardiograms, clinical safety laboratory assessments, and adverse events
- Safety assessments will be conducted at screening and at the final visit
- Adverse events will be recorded from the first dose of the study drug through the final visit

## Conclusions

- KONFIDENT phase 3 trial will provide data on the efficacy and safety of sebetralstat in adult and adolescent patients with HAE
- Sebetralstat has the potential to be the first oral therapy for on-demand treatment of HAE attacks
- Data readout is expected in Q4 of 2023[8]

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