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) of the complement-1 esterase inhibitor (C1-INH) protein and subsequent uncontrolled activation of the kallikrein kinin system (KKS).6,7
- People living with HAE experience painfull and debilitating attacks of tissue swelling in various locations of the body that can be life-threatening depending on the location affected.9
- All currently approved on-demand treatment options require either intravenous or subcutaneous administration.4
- Global HAE treatment guidelines recommend that people living with HAE carry a 30 mg of on-demand vial of natako for self-administered treatment at all times.12
- Sebetralstat is a non-selective KPK inhibitor that is rapidly absorbed and results in >80% PKP inhibition within 15 minutes after oral administration.9
- In a phase 1 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.12
- 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.3,4
- The phase 3 KONFIDENT trial is underway for sebetralstat, an investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema attacks.3

Trial Overview

- **KONFIDENT** is a phase 3, randomized, double-blind, placebo-controlled, event-driven crossover clinical trial enrolling patients aged ≥12 years with HAE types I or II, including patients on long-term prophylactic treatment.5
- Patients will be randomized to treat 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 64 patients, including a minimum of 12 adolescents, are expected to complete treatment of 3 attacks (252 attacks).

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.

Disclosures

- Unit has received grants from Calvita for research grants from BioCryst, Biontech, and Calvita (DB, Biotech, and BioCryst), and has received speaker’s honoraria from BioCryst and Biontech for research grants from BioCryst, Biontech, and Biotech.
- KVD900 has been extensively studied in patients with HAE types I and II, with a tissue-distributed pharmacokinetic profile.
- Sebetralstat is a non-selective KPK inhibitor that is rapidly absorbed and results in >80% PKP inhibition within 15 minutes after oral administration.
- 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.
- The phase 3 KONFIDENT trial is underway for sebetralstat, an investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema attacks.

Figure 1. KONFIDENT 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.
- 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 64 patients, including a minimum of 12 adolescents, are expected to complete treatment of 3 attacks (252 attacks).

Figure 2. Efficacy Assessment Scales

- **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**
  - 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.
- **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.

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 4 hours of 12 hours of study drug administration.
  - 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 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 24 hours of the first administration of study drug.

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.

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).

Table 1. Frequency of Patient Efficacy Assessments

<table>
<thead>
<tr>
<th>Time After First Dose of Study Drug</th>
<th>Frequency of Assessment</th>
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</thead>
<tbody>
<tr>
<td>0 to 4 hours</td>
<td>Every 0.5 ± 0.25 hour</td>
</tr>
<tr>
<td>5 to 12 hours</td>
<td>Every 1 ± 0.5 hour</td>
</tr>
<tr>
<td>14 to 24 hours</td>
<td>Every 2 ± 1 hour</td>
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<tr>
<td>25 to 48 hours</td>
<td>Every 12 ± 3 hours</td>
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</tbody>
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References