Background

- The international guidelines for the management of hereditary angioedema (HAE) recommend short-term prophylaxis (STP) with an intravenous C1-inhibitor (C1-INH) before planned medical, surgical, or dental procedures in patients with HAE.1,2
- Administration of STP with C1-INH concentrate or nanofiltered C1-INH in the periprocedural setting has been associated with significantly fewer HAE attacks1,3
- However, access to and administration of intravenous C1-INH may be challenging with regard to geographical availability and access to and administration of intravenous C1-INH.4
- The efficacy and safety of the oral plasma kallikrein inhibitor sebetralstat for the on-demand treatment of HAE attacks is currently being evaluated in KONFIDENT (NCT05255917), a phase 3, randomized, double-blind, placebo-controlled trial after recently meeting the primary endpoint in a phase 2 trial.4
- An open-label extension study, KONFIDENT-S (NCT05505915), is evaluating the safety of sebetralstat for up to 2 years in patients aged 12 years with HAE type I or II.5
- As part of KONFIDENT-S, the safety and efficacy of sebetralstat as a potential STP treatment will be evaluated.

Trial Overview

Patients

- Approximately 150 eligible patients aged ≥12 years (including a minimum of 12 adolescents) with HAE will be enrolled in KONFIDENT-S (Figure 1).
- The patient population will include:
  - Rollover patients, who participated in the KONFIDENT trial
  - Naïve patients, including those who participated in the phase 2 trial
- Full inclusion and exclusion criteria can be found at https://clinicaltrials.gov/ct2/show/NCT05505916

Figure 1. KONFIDENT-S Study Design

Rationale for the STP Regimen in KONFIDENT-S

- The dosing regimen for STP treatment in KONFIDENT-S was informed by a phase 1, double-blind, placebo-controlled, multiple-dose, multiple-cohort study that evaluated the safety, tolerability, and pharmacokinetics of multiple doses of 600 mg sebetralstat in healthy adults.1,2
- The full methods for this study were described previously1,3,4 and are summarized here.
- Briefly, healthy volunteers were assigned to three cohorts with every-8 hour (q8h) (cohort 1), every-4 hour (q4h) (cohort 2), or every-2-hour (q2h) (cohort 3/4) dosing schedules and then randomized to receive 3 × 600 mg sebetralstat or placebo while fasting.
- Venous blood was collected for pharmacokinetic and pharmacodynamic measurements at prespecified intervals following the first and third doses up to 40 hours postdose.
- An exploratory pharmacodynamic assessment was performed to measure the effect of sebetralstat on plasma kallikrein (PKa) enzyme activity.
- Results are presented using descriptive statistics.

Pharmacokinetic analysis

- Maximum plasma concentrations of sebetralstat were similar after dose 1 (Table 1).

Table 1. Maximum Plasma Concentrations After Dose 1 and Dose 3

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cohort 1 (q8h)</th>
<th>Cohort 2 (q4h)</th>
<th>Cohort 3 (q2h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>3916 ng/mL (104.7%)</td>
<td>4412 ng/mL (54.3%)</td>
<td>5035 ng/mL (54.2%)</td>
</tr>
<tr>
<td>AUC0-∞</td>
<td>8838 ng·h/mL (92.8%)</td>
<td>7136 ng·h/mL (32.8%)</td>
<td>15,627 ng·h/mL (32.2%)</td>
</tr>
</tbody>
</table>

For non-rollover patients, the Enrollment Visit is a screening visit.

STP Protocol in KONFIDENT-S

- The decision to use sebetralstat for STP treatment in KONFIDENT-S will be made on a case-by-case basis, after consultation with the investigator and the patient, and based on whether treatment with sebetralstat for STP therapy is medically appropriate for the patient.
- To assess the safety and efficacy of these doses of 600 mg sebetralstat as an STP treatment, patients will administer the first of the three-dose course of 600 mg sebetralstat approximately 1 hour prior to a surgical, medical, or dental procedure, and then administer the other two doses approximately 6 hours apart (Figure 2).
- All uses of sebetralstat as STP treatment will be recorded in each patient’s diary, which records the type of procedure as well as any attack characteristics if an attack occurs.

STP Outcomes

- If an HAE attack occurs ≤24 hours after the start of the procedure, sebetralstat as STP therapy must be stopped.
  - The patient should be treated with conventional on-demand treatment.
- If an HAE attack occurs >24 hours after the start of the procedure, then sebetralstat may be used as on-demand treatment.

Conclusions

- The KONFIDENT-S trial will provide long-term safety and efficacy data for on-demand treatment with sebetralstat while also evaluating its use as an STP therapy to prevent HAE attacks potentially triggered by medical, surgical, or dental procedures.
- KONFIDENT-S is the first prospective trial that will evaluate an oral therapy for STP

References