Rationale for the Short-term Prophylaxis Regimen With Sebetralstat in KONFIDENT-S

Matthew Iverson, Edward Duckworth, Erik Hansen, Sally L. Hampton, Michael D. Smith, Paul K. Audhya, Christopher M. Yea

KalVista Pharmaceuticals, Salisbury, UK, and Cambridge, MA, US
Disclosures and Acknowledgments

• Disclosures: All authors are employees of KalVista Pharmaceuticals

• This study was performed by KalVista Pharmaceuticals Ltd. Medical writing assistance was provided under the direction of the authors by Katherine Stevens-Favorite, PhD, of Cadent, a Syneos Health Group company, and was supported by KalVista Pharmaceuticals, Inc
Background

• 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

  – For many patients with HAE, guidelines recommend the use of STP prior to medical or dental procedures to reduce the risk of HAE attacks

• All recommended STP treatments require parenteral administration, which presents significant challenges with preparation, venous access, injection-site–associated pain, and discomfort

  – Additionally, STP treatments may not be the typical therapies used by patients for long-term prophylaxis or on-demand treatment, so there may be an additional administrative burden for the patient to obtain a prescription for recommended STP therapies

• There remains an unmet need for a simple, safe, and effective oral STP option for HAE

HAE, hereditary angioedema; STP, short-term prophylaxis.
KONFIDENT Trials

- Sebetralstat is a novel investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks that showed a favorable PK and PD profile and positive efficacy and safety results in a recent phase 2 trial\(^1,^2\).

- The phase 3, randomized, double-blind, placebo-controlled trial KONFIDENT (NCT05259917) is underway to evaluate the efficacy and safety of sebetralstat in patients aged 12 years or older with HAE type I or II for the on-demand treatment of HAE attacks\(^3\).

- An open-label extension trial, KONFIDENT-S (NCT05505916), is evaluating the safety of sebetralstat for up to 2 years\(^4\).

---

HAE, hereditary angioedema; PD, pharmacodynamic; PK, pharmacokinetic.

KONFIDENT-S Includes Rollover Patients From KONFIDENT and Naïve Patients

KONFIDENT-S (NCT05505916)\(^1\)

Rollover Patients
(Completed KONFIDENT\(^2\))

Naïve Patients
(All other participants including those who participated in phase 2\(^3\))

Enrollment Visit\(^a\)

Treatment Period (0-24 Months)

End-of-Trial Visit

Monthly Visits
(In-clinic
(Months 1-3))

Quarterly Visits
(Months 6, 9, 12, 15, 18, 21)

All Other Months
(Months 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23)

For naïve patients, the Enrollment Visit is a screening visit.

HAE, hereditary angioedema.


On-Demand Treatment of HAE attacks:
- 1 × 600 mg sebetralstat to treat each HAE attack
- Second 1 × 600 mg sebetralstat dose is permitted at least 3 hours following the first dose if symptoms persist without improvement
Evaluation of Short-term Prophylaxis in KONFIDENT-S Trial

• During KONFIDENT-S, participants may use sebetralstat for on-demand treatment or, on a case-by-case basis, after consultation with the investigator and the patient, as STP therapy for a surgical, medical, or dental procedure.

• To support the rationale for the STP regimen in KONFIDENT-S, we report PK, PD, and safety data from a phase 1 trial that evaluated three doses of sebetralstat q8h compared with dosing q2h or q4h.

STP, short-term prophylaxis; PD, pharmacodynamic; PK, pharmacokinetic; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hour.
Methods

- This phase 1, double-blind, placebo-controlled, multiple-dose, multiple-cohort study evaluated the safety, tolerability, and PK of multiple doses of 600 mg sebetralstat in healthy adults under fasted conditions.

Participants were assigned to three cohorts with different dosing schedules:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>Randomized to receive 600 mg sebetralstat or placebo q8h at 0, 8, and 16 hours</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>Randomized to receive 600 mg sebetralstat or placebo q4h at 0, 4, and 8 hours</td>
</tr>
<tr>
<td>Cohorts 3/4</td>
<td>Randomized to receive 600 mg sebetralstat or placebo q2h at 0, 2, and 4 hours</td>
</tr>
</tbody>
</table>

- Venous blood was collected for PK and PD measurements at prespecified intervals following the first and third doses, up to 40 hours postdose.

- An exploratory PD assessment was performed to measure the effect of sebetralstat on PKa enzyme activity.

- All participants receiving sebetralstat and having any measurable plasma concentrations were included in the PK analysis; all participants receiving at least one dose of sebetralstat or matching placebo were included in the PD and safety evaluations.

- Safety was measured by the assessment of vital signs and the collection of adverse events.

- Results are presented using descriptive statistics.

PD, pharmacodynamic; PK, pharmacokinetic; PKa, plasma kallikrein; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours.

Maximum Plasma Concentrations of Sebetralstat Were Similar After Dose 1

### Maximum Plasma Concentrations After Dose 1 and Dose 3

<table>
<thead>
<tr>
<th>Cohort</th>
<th>C_{max}</th>
<th>Geometric mean (CV%)</th>
<th>Dose 1</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1; q8h (n=6)</td>
<td>C_{max}</td>
<td>Geometric mean (CV%)</td>
<td>3916 ng/mL (104.7%)</td>
<td>8838 ng/mL (92.8%)</td>
</tr>
<tr>
<td>Cohort 2; q4h (n=6)</td>
<td>C_{max}</td>
<td>Geometric mean (CV%)</td>
<td>4412 ng/mL (54.3%)</td>
<td>7136 ng/mL (32.8%)</td>
</tr>
<tr>
<td>Cohorts 3/4; q2h (n=18)</td>
<td>C_{max}</td>
<td>Geometric mean (CV%)</td>
<td>5035 ng/mL (54.2%)</td>
<td>15,627 ng/mL (32.2%)</td>
</tr>
</tbody>
</table>

- The lowest arithmetic mean plasma concentrations in the q8h cohort were 758.5 ng/mL at 8 hours prior to the second dose and 749.8 ng/mL at 28 hours and thereafter
- For q4h and q2h dosing schedules, arithmetic mean plasma sebetralstat remained >1000 ng/mL between the first and third doses

C_{max}, maximum plasma concentration; CV, coefficient of variation; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours.
A Geometric Mean PKa Inhibition of >90% Was Achieved Within 30 Minutes of Dose 1 in All Cohorts

PKa inhibition in the q8h cohort (cohort 1; n=6), q4h cohort (cohort 2; n=6) and q2h cohort (cohort 3/4; n=18) (geometric mean ± SD, linear scale)

PKa, plasma kallikrein activity; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours.
Geometric Mean PKa Inhibition Was at >90% Through 24 Hours and Then
>80% Through 28 Hours After 3 Doses of Sebetralstat in Cohort 1 (q8h)

Sebetralstat plasma concentration (blue, geometric mean ± SD) and inhibition of PKa activity as a percentage of the activity in predose samples (green, geometric mean ± SD) in the q8h cohort (cohort 1, linear scale)

PKa, plasma kallikrein activity; q8h, every 8 hours.
Sebetalstat Was Well Tolerated in All Cohorts

• Adverse events were mild and comparable between treatment groups receiving sebetalstat and placebo
  – No participants discontinued the trial because of an adverse event
• No serious adverse events occurred during the trial, and all adverse events were resolved by trial exit
Administration of Sebetralstat for Short-term Prophylaxis in KONFIDENT-S Begins 1 Hour Prior to a Surgical, Medical, or Dental Procedure

A 6-hour interval was chosen to allow flexibility around sleep or other patient life events.
Conclusions

- Three doses of sebetralstat within 24 hours were well tolerated and led to drug accumulation
- Geometric mean PKa inhibition of >80% was maintained for 28 hours when dosing sebetralstat q8h
- Based on these data, KONFIDENT-S will prospectively evaluate the effectiveness and safety of three doses of 600 mg sebetralstat administered before and approximately 6 hours after each previous dose in the periprocedural STP setting

PKa, plasma kallikrein activity; q8h, every 8 hours; STP, short-term prophylaxis.
Thank You