Short-Term Prophylaxis With Sebetralstat, an Investigational Oral On-Demand Treatment for Hereditary Angioedema, in KONFIDENT-S

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Background

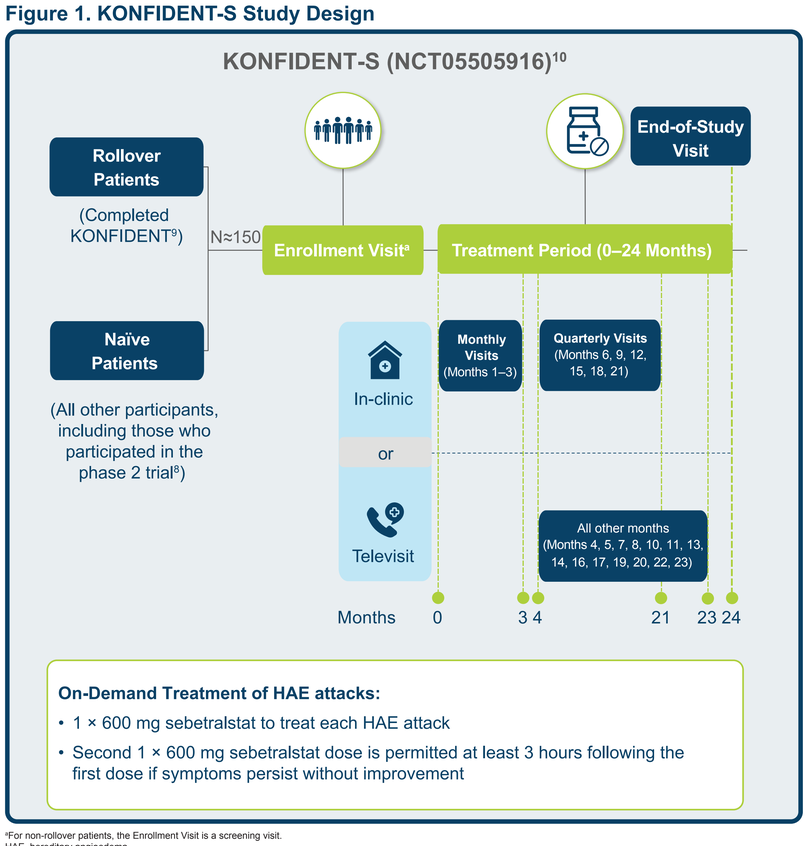
- The international guidelines for the management of hereditary angioedema (HAE) recommend short-term prophylaxis (STP) with an intravenous C1-inhibitor (C1-INH) before planned medical, surgical, or dental procedures in patients with HAE[1,2]
- Administration of STP with C1-INH concentrate or nanofiltered C1-INH in the periprocedural setting has been associated with significantly fewer HAE attacks[3–5]
- However, access to and administration of intravenous C1-INH may be challenging with regard to preparation, venous access, injection site–associated pain, and discomfort[6,7]
- 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 (NCT05259917), a phase 3, randomized, double-blind, placebo-controlled trial after recently meeting the primary endpoint in a phase 2 trial[8,9]
- An open-label extension study, KONFIDENT-S (NCT05505916), is evaluating the safety of sebetralstat for up to 2 years in patients aged ≥12 years with HAE type I or II[10]
- 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[9]
  - Naïve patients, ie, all other patients, including those who participated in the phase 2 trial[8]
- Full inclusion and exclusion criteria can be found at https://clinicaltrials.gov/ct2/show/NCT05505916

Figure 1. KONFIDENT-S Study Design

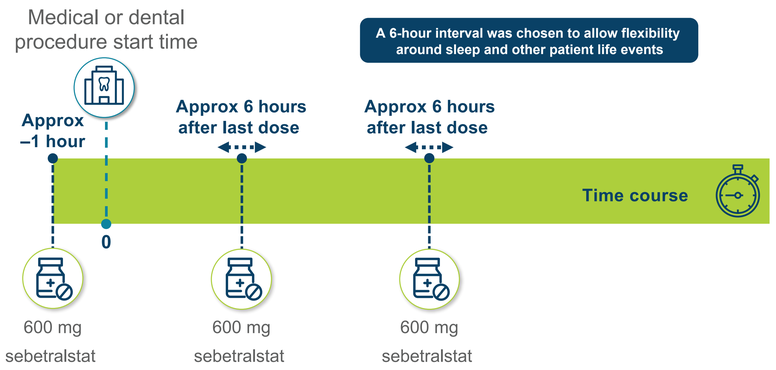


[a]For non-rollover patients, the Enrollment Visit is a screening visit.
HAE, hereditary angioedema.

STP Protocol in KONFIDENT-S

- The decision to use sebetralstat for STP therapy 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 three 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

Figure 2. Administration of Sebetralstat for STP in KONFIDENT-S Begins Approximately 1 Hour Prior to a Surgical, Medical, or Dental Procedure



STP, short-term prophylaxis.

- If an HAE attack occurs ≤24 hours before 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

STP Outcomes

- The proportion of procedures employing sebetralstat as STP treatment that did not result in an attack within 24 and 48 hours will be assessed
  - For any HAE attacks treated with conventional therapy (≤24 hours) or sebetralstat (>24 hours), patients will complete timed assessments over 48 hours from attack onset
- Safety and efficacy endpoints related to HAE attacks will be summarized

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[11,12]
- The full methods for this study were described previously[11,12] 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**)

Table. Maximum Plasma Concentrations After Dose 1 and Dose 3

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

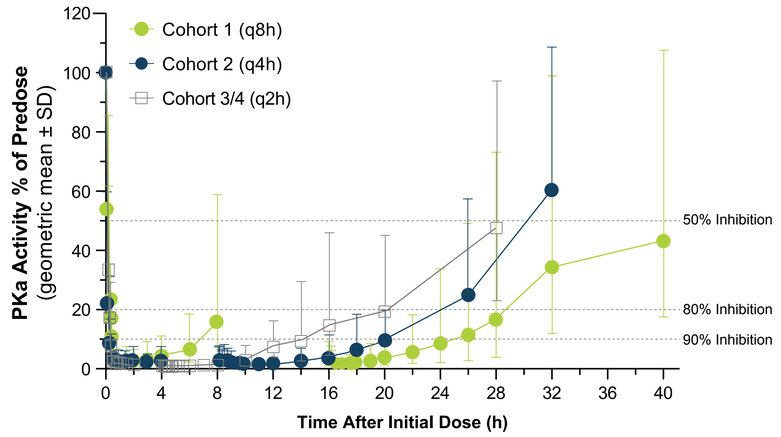
C_{max}, maximum plasma concentration; CV, coefficient of variation; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours.

- 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 the q4h and q2h dosing schedules, arithmetic mean plasma concentration of sebetralstat remained >1000 ng/mL between the first and third doses

Pharmacodynamic analysis

- A geometric mean PKa inhibition >90% was achieved within 30 minutes of dose 1 in all cohorts (**Figure 3**)

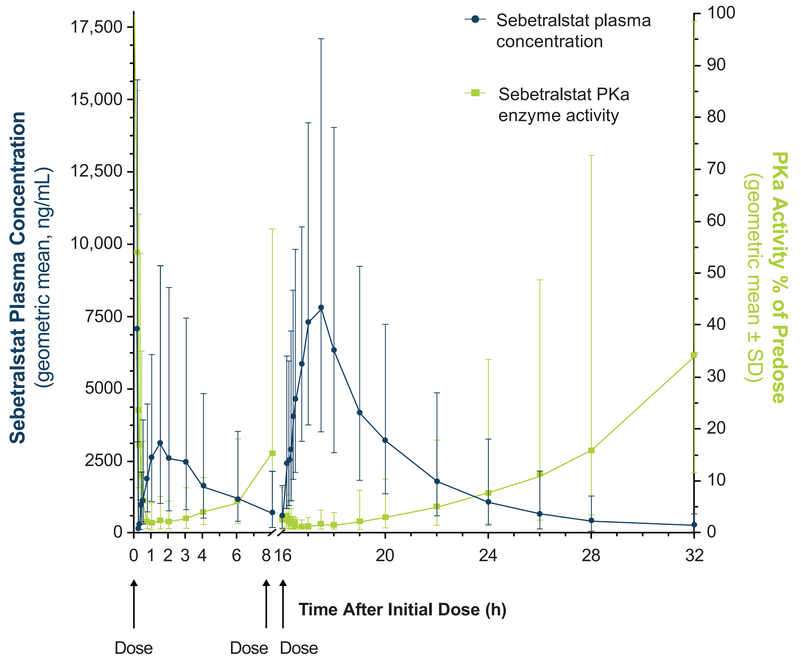
Figure 3. PKa Inhibition in the q8h Cohort (Cohort 1; n=6), q4h Cohort (Cohort 2; n=6) and q2h Cohort (Cohort 3/4; n=18) (Geometric Mean ± SD, Linear Scale)



PKa, plasma kallikrein activity; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours; SD, standard deviation.

- For cohorts 2 and 3/4, geometric mean PKa inhibition remained >90% through dose 1, while in cohort 1, the geometric mean of PKa inhibition rose to 84% at 8 hours after the first dose
- Geometric mean PKa inhibition >90% was maintained for at least 8 hours after dose 3 in all cohorts
  - For cohort 2, when sebetralstat was administered every 4 hours, the last measurement of a geometric mean PKa inhibition >90% was at 20 hours after initial dose
- For cohort 1 receiving 600 mg sebetralstat q8h, the geometric mean PKa inhibition was >90% for 6 hours, then 84% at 8 hours (before dose 2; **Figure 4**)

Figure 4. 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, n=6; Linear Scale)



PKa, plasma kallikrein activity; q8h, every 8 hours; SD, standard deviation.

- At 16 hours (before dose 3), the geometric mean PKa inhibition was >90%
- After dose 3, the geometric mean PKa inhibition was maintained at >90% through 24 hours, then at >80% through 28 hours

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[13]

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