Pharmacokinetic, Pharmacodynamic, and Safety Profile of Sebetralstat in Healthy Japanese and White Adults: Results From a Phase 1, Randomized, Double-Blind, Placebo-Controlled Trial

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Background

- Hereditary angioedema (HAE) is a genetic disorder that manifests as unpredictable attacks of tissue swelling caused by uncontrolled activation of the kallikrein-kinin system[1]
- Globally, the prevalence of HAE type 1 or type 2 is estimated to be 1/50,000 to 1/100,000.[2,3] It is assumed that there are 2000 to 3000 people with HAE type 1 or type 2 in Japan; however, unofficial data collected from case reports and pharmaceutical company databases suggest only 450 patients have been diagnosed in Japan[4]
- Sebetralstat, a novel oral plasma kallikrein (PKa) inhibitor that has shown promising clinical activity in a randomized phase 2 trial, is being investigated in a phase 3 trial as an on-demand treatment for patients who experience HAE attacks[5,6]
- Most participants in sebetralstat trials have been White.[6] This trial was designed to evaluate whether the pharmacokinetic (PK), pharmacodynamic (PD), and safety profiles in individuals of Japanese descent were similar to those in White individuals

Objective

- This phase 1 trial was designed to determine whether the PK, PD, and safety profiles of sebetralstat were similar in healthy Japanese adults and healthy White adults (as defined according to the study definition of Japanese and White)

Methods

Study Design

- In this single-center, randomized, double-blind, placebo-controlled, phase 1 trial, healthy Japanese and White adults were enrolled
  - Definition of Japanese: a participant for whom both parents and all grandparents were Japanese and who had not lived outside of Japan for >10 years
  - Definition of White: participants who confirmed that all grandparents were White (verbally self-reported)
- Participants received a single dose of oral sebetralstat 300 mg, 600 mg, 1200 mg, or placebo after fasting

Key Eligibility Criteria

- Eligible participants were healthy male or female nonsmokers aged 18-55 years with a body mass index (BMI) between 18.5 and 32.0 kg/m^2
- No over-the-counter or prescription medications were allowed within 14 days, no pharmaceutical agents affecting drug metabolism were allowed within 30 days, and no angiotensin-converting enzyme inhibitors were allowed within 93 days of study drug administration

Endpoints

- Plasma concentrations of sebetralstat were determined using a validated liquid chromatography-mass spectrometry method
- Concentration-time curves were assessed for the following parameters:
  - Area under the concentration-time curve from time 0 to the last observed nonzero concentration ($AUC_{0\text{-}t}$) or extrapolated to infinity ($AUC_{0\text{-}inf}$)
  - Maximum observed plasma concentration (C_{max})
  - Time to maximum observed plasma concentration (t_{max})
- PD was assessed ex vivo; plasma was exogenously stimulated with dextran sulfate and PKa activity was measured using a fluorogenic substrate
- Safety was evaluated through collection of treatment-emergent adverse events (TEAEs)

Analysis Populations

- The safety analysis population (N=50) consisted of all randomly assigned participants who received at least 1 dose of study drug (sebetralstat or placebo)
- The PK analysis population (n=36) consisted of all participants in the safety analysis population with at least 1 quantifiable sebetralstat plasma concentration and no major protocol deviations that affect PK
- The PD analysis population (n=49) consisted of all participants in the safety analysis set with at least 1 measured PD assessment in the predose sample

Results

Participants

- The mean (SD) age of participants was 39.3 (9.29) years; 26 participants (52%) were male and 24 participants (48%) were female
  - Baseline characteristics were balanced across the 2 populations in each cohort (**Table 1**)

Table 1. Baseline Characteristics

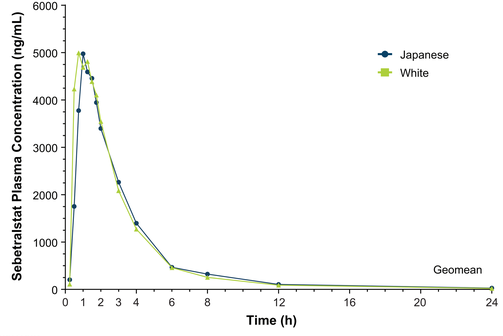
	Sebetralstat 300 mg		Sebetralstat 600 mg		Sebetralstat 1200 mg		Placebo	
	Japanese n=7	White n=7	Japanese n=6	White n=6	Japanese n=6	White n=6	Japanese n=6	White n=6
Age, mean (SD)	42.6 (11.9)	43.4 (10.4)	37.0 (11.3)	37.7 (9.8)	40.8 (6.5)	33.8 (7.5)	40.2 (9.8)	37.7 (12.2)
Female, n (%)	4 (57.1)	2 (28.6)	4 (66.7)	4 (66.7)	1 (16.7)	2 (33.3)	4 (66.7)	3 (50.0)
Height, mean (SD), cm	164.7 (10.3)	167.9 (10.1)	163.8 (10.7)	165.0 (7.0)	169.2 (4.6)	173.7 (13.5)	162.7 (6.9)	174.2 (7.9)
Weight, mean (SD), kg	62.23 (8.50)	76.54 (16.77)	62.00 (14.98)	71.80 (12.35)	71.23 (8.32)	75.65 (14.80)	60.02 (11.12)	78.47 (12.09)
BMI, mean (SD), kg/m^2	23.14 (4.41)	26.89 (4.01)	22.83 (3.51)	26.27 (3.10)	24.87 (2.59)	25.08 (4.08)	22.60 (3.57)	25.85 (3.59)

BMI, body mass index.

Pharmacokinetics

- Geometric mean (SD) plasma concentrations for sebetralstat 600 mg in Japanese and White participants are shown in **Figure 1** and **Table 2**
- PK parameters were consistent between healthy Japanese and White adults after administration of a single dose of sebetralstat 300 mg, 600 mg, or 1200 mg (**Table 2**)

Figure 1. Mean Plasma Concentration of Sebetralstat 600 mg



Geomean, geometric mean.

Table 2. Summary of Plasma PK Parameters of Sebetralstat After a Single Oral Dose

	Sebetralstat 300 mg		Sebetralstat 600 mg		Sebetralstat 1200 mg	
	Japanese n=6	White n=6	Japanese n=6	White n=6	Japanese n=6	White n=6
$AUC_{0\text{-}t}$, geometric mean (CV%), ng·h/mL	7458 (51.2)	8162 (22.3)	16,410 (66.8)	16,200 (28.2)	23,490 (62.8)	23,690 (35.2)
$AUC_{0\text{-}inf}$, geometric mean (CV%), ng·h/mL	7495 (50.4)	8190 (22.2)	16,600 (64.8)	16,400[a] (31.8)	21,800[b] (39.0)	24,450 (35.5)
C_{max}, geometric mean (CV%), ng·h/mL	2832 (90.4)	2243 (53.7)	6178 (51.8)	5961 (41.4)	7736 (111.8)	5746 (31.6)
t_{max}, median (range), h	1.3 (0.55–1.8)	1.3 (0.95–1.6)	0.99 (0.50–1.5)	1.0 (0.50–1.2)	0.75 (0.50–4.0)	1.0 (1.0–1.5)

$AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last observed nonzero concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; PK, pharmacokinetics; t_{max}, time to maximum observed plasma concentration.

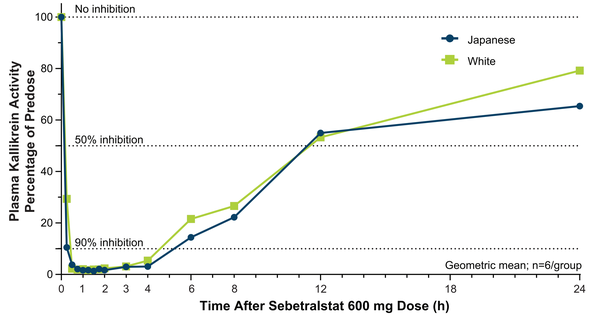
[a]n=5.

[b]n=4.

Pharmacodynamics

- ≥95% geometric mean inhibition of PKa enzyme activity was observed within 30 minutes and was maintained out to 4 hours in both participant groups after receiving sebetralstat 600 mg (**Figure 2**)
- PD parameters were also consistent between healthy Japanese and White adults after administration of a single dose of sebetralstat 300 mg or 1200 mg

Figure 2. Plasma Kallikrein Activity in Healthy Japanese and White Adults Who Received Sebetralstat 600 mg



Safety

- Sebetralstat was well tolerated in both study populations (**Table 3**)
  - In the Japanese population, 3 TEAEs (abdominal pain upper, headache, and epistaxis) were reported in 2 participants who received sebetralstat and 1 TEAE (dysmenorrhea) was reported in 1 participant who received placebo
  - In the White population, 2 TEAEs (headache) were reported in 2 participants who received sebetralstat and 1 TEAE (dysmenorrhea) was reported in 1 participant who received placebo
- No deaths, serious AEs, or discontinuation due to AEs occurred during the trial

Table 3. Safety

	Sebetralstat 300 mg		Sebetralstat 600 mg		Sebetralstat 1200 mg		Placebo	
	Japanese n=7	White n=7	Japanese n=6	White n=6	Japanese n=6	White n=6	Japanese n=6	White n=6
Any TEAE, n (%)	1 (14.3)	0	0	2 (33.3)	1 (16.7)	0	1 (16.7)	1 (16.7)
Headache	0	0	0	2 (33.3)	1 (16.7)	0	0	0
Abdominal pain upper	1 (14.3)	0	0	0	0	0	0	0
Dysmenorrhea	0	0	0	0	0	0	1 (16.7)	1 (16.7)
Epistaxis	0	0	0	0	1 (16.7)	0	0	0

TEAE, treatment-emergent adverse event.

Safety analysis set.

Participants with multiple events in the same category are counted only once in that category.

Only on-treatment period TEAEs were considered. AEs were coded to system organ class and preferred term using MedDRA coding dictionary version 25.0.

Conclusions

- **Sebetralstat had comparable PK, PD, and safety profiles in healthy Japanese and White adults**
- **These findings support the inclusion of Japanese patients with HAE in the KONFIDENT phase 3 trial (NCT05259917) to assess sebetralstat as on-demand treatment for HAE attacks**

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