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

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.
- Sebetralstat, a novel oral plasma kallikrein (PKa) inhibitor, has shown promising clinical activity in a randomized phase 2 trial, being investigated in a phase 1 trial as an on-demand treatment for patients who experience HAE attacks.

Methods

Objectives

- This phase 1 trial was designed to determine whether the pharmacokinetic (PK), pharmacodynamic (PD), and safety profiles in individuals of Japanese descent differ from those in White individuals.

Study Design

- In this single-center, randomized, double-blind, placebo-controlled, phase 1 trial, healthy Japanese and White adults were enrolled.

Specifics

- In total, 50 participants were enrolled: 25 participants were randomized to receive sebetralstat 300 mg, 600 mg, or 1200 mg, and 25 participants were randomized to receive placebo.

Key Eligibility Criteria

- Eligible participants were healthy male or female nonsmokers aged 18-55 years with a body mass index (BMI) of 18-30 kg/m² and a body weight greater than 50 kg.

Endpoints

- Pharmacokinetics: Concentrations of sebetralstat were determined using a validated liquid chromatography–mass spectrometry method.
- Pharmacodynamics: The percent inhibition of PKa enzyme activity was measured using the fluorogenic substrate assay.
- Safety: Any treatment-emergent adverse event (TEAE) was recorded.

Pharmacokinetics

- Geometric mean concentration of sebetralstat in plasma was determined using a fluorogenic substrate assay.

Pharmacodynamics

- Geometric mean inhibition of PKa enzyme activity was observed within 30 minutes and was maintained for up to 12 hours after a single dose of sebetralstat 300 mg, 600 mg, or 1200 mg.

Safety

- Sebetralstat had comparable PK, PD, and safety profiles in healthy Japanese and White adults.

Results

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Age, mean (SD), years</th>
<th>42.6 (8.5)</th>
<th>43.4 (6.7)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>23.1 (4.4)</td>
<td>26.9 (5.0)</td>
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Table 2. Summary of Plasma PK Parameters of Sebetralstat After a Single Oral Dose

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<thead>
<tr>
<th>Parameter</th>
<th>Japanese</th>
<th>White</th>
</tr>
</thead>
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<tr>
<td>Cmax, ng/mL</td>
<td>76.54 (14.98)</td>
<td>78.9 (12.35)</td>
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<tr>
<td>AUC0-inf, ng·h/mL</td>
<td>23,490 (51.2)</td>
<td>24,870 (10.4)</td>
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Table 3. Summary of Plasma PK Parameters of Sebetralstat After a Single Oral Dose

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Figure 1. Plasma Concentration of Sebetralstat 600 mg

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

Table 4. Summary of Plasma PK Parameters of Sebetralstat After a Single Oral Dose

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Figure 3. Mean Plasma Concentration of Sebetralstat 600 mg

Figure 4. Mean Plasma Concentration of Sebetralstat 600 mg

Conclusions

Sebetralstat had comparable PK, PD, and safety profiles in healthy Japanese and White adults.

References


Acknowledgments

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