Hereditary angioedema (HAE) is a rare genetic disease characterized by C1 inhibitor deficiency, which causes abnormal functioning of the kallikrein-kinin system, leading to unpredictable, unprovoked edema and angioedema attacks. The clinical manifestation of HAE in patients with C1 inhibitor deficiency most often occurs in the setting of C1-inhibitor deficiency (C1-INH). 

- The consumption of a normal meal prior to a single dose of sebetralstat did not alter the sebetralstat PK or PD under fasting conditions.

- A phase 2, randomized, double-blind, placebo-controlled, crossover trial in 68 adult patients (NCT04208412) evaluated the safety, tolerability, and efficacy of multiple doses of sebetralstat in HAE patients with C1 inhibitor deficiency and with subsequent predicted exposure in adolescent patients to be included in the phase 3 clinical trials of sebetralstat.

**Methods**

**Study Population and Design**

- The analysis included sebetralstat plasma concentration data from the following 3 clinical trials of sebetralstat: 
  - A phase 1 trial in 68 healthy adult male volunteers (88 total doses) to evaluate the safety, tolerability, PK, and food effects of single ascending doses of sebetralstat (NCT04406847).
  - A phase 1 trial in 30 healthy adult volunteers (90 total doses) to evaluate the safety, tolerability, PK, and multiple dosing of sebetralstat (NCT04349800). 
  - A phase 2, randomized, double-blind, placebo-controlled, crossover trial in 42 patients (NCT04349800) of sebetralstat under fasting conditions.

**Model Development**

- The population PK model was developed using nonlinear mixed-effects modeling using NONMEM® 7.4 (X-Clinical). 
- The model was graphically developed using data from the phase 1 single ascending dose trial to describe the time course of sebetralstat concentrations in healthy adults.
- The final model was externally validated using data from the phase 1 multiple ascending doses and phase 2 trials and independently assessed by interpreting the time course of covariances.

**Results**

**Predicted Exposure in Adolescents and Adults**

- The range of the predicted overall exposure (AUC from 0 to 24 h) in adolescents was within the previously observed adult values, with a slight difference in the expected lower body weight of adolescents.

**Predicted Exposure in Adolescents and Adults**

- The PK of sebetralstat in the adult adolescent population was predicted to be higher than in adults, indicating a higher predicted dose of sebetralstat, reflecting the expected lower body weight of adolescents.

**Figure 1. Predicted Observed Sebetralstat Concentration vs Time Plots in Healthy Adult Volunteers and Patients With HAE by (A) Dose and (B) Food Status – Final Population PK Model**

**Table 1. Demographics of Analyzed and Simulated Populations**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult Volunteers (N=77)</th>
<th>Adolescents (N=40)</th>
<th>Patients With HAE (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.0 (SD 15.1)</td>
<td>16.0 (SD 1.0)</td>
<td>30.0 (SD 9.2)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>46/31</td>
<td>16/24</td>
<td>28/9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>80.0 (SD 14.0)</td>
<td>70.0 (SD 12.0)</td>
<td>69.6 (SD 8.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.0 (SD 7.0)</td>
<td>165.0 (SD 4.0)</td>
<td>165.0 (SD 4.0)</td>
</tr>
</tbody>
</table>

**Figure 2. Predicted Plasma Sebetralstat Exposure at a 600-mg Dose After Fasting in Adolescents and Adults**

- The PK of sebetralstat in the healthy adult volunteers and patients with HAE was well described by a two-compartment population model with mixed zero- and first-order absorption and a long time associated with the zero-order absorption process and first-order elimination.

**Conclusion**

- The population PK model predicted that overall sebetralstat exposure in an adolescent population would be similar to that in adults for a single 600-mg dose.
- The model supports the use of the same doses of sebetralstat for adolescents and in adults in phase 3 clinical trials.