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Objective:
- To compare PK properties of somavaratan between pre-pubertal children with GHD enrolled in Japanese and US trials

Methods:
- The PKPD analysis included J14VRS subjects randomized to receive a single dose of somavaratan (2.8, 2.7, or 4.0 mg/kg; n = 8 each) and VERTICAL subjects from corresponding dose groups
- Serum PK (peak concentration [Cmax], AUC, total body clearance [CL]) and PD (IGF-I SDS, IGFBP-3 AUC) were evaluated using non-compartmental methods from samples collected on days 1 (pre-dose), ~4, 8, 15, and 30 (and day 22 for VERTICAL)

Results:
- Demographics and Baseline Characteristics are shown in Table 1
- Patients in VERTICAL were older and had higher body weights than patients in J14VRS

Table 1. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1.8 mg/kg</th>
<th>2.7 mg/kg</th>
<th>4.0 mg/kg</th>
<th>1.8 mg/kg</th>
<th>2.7 mg/kg</th>
<th>4.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean)</td>
<td>7.6 (4.0-10.9)</td>
<td>7.6 (4.0-10.5)</td>
<td>7.0 (3.3-9.5)</td>
<td>7.6 (4.0-10.1)</td>
<td>7.3 (3.5-9.9)</td>
<td>7.8 (3.5-9.8)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/1</td>
<td>6/2</td>
<td>4/8</td>
<td>7/1</td>
<td>6/2</td>
<td>4/8</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6 (77%)</td>
<td>6 (77%)</td>
<td>5 (76%)</td>
<td>6 (77%)</td>
<td>6 (77%)</td>
<td>5 (76%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>18.6 (3.3-9.5)</td>
<td>19.1 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
</tr>
<tr>
<td>Weight, kg (mean range)</td>
<td>18.6 (3.3-9.5)</td>
<td>19.1 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
<td>17.0 (3.3-9.5)</td>
</tr>
</tbody>
</table>

Conclusions:
- In line with the body weight effect on somavaratan PK parameters in both studies, the data continue to support weight-based dosing
- After adjusting for differences in body weight, differences in exposure between Japanese and US populations did not merit changes in dosing principles
- PD response to somavaratan was comparable between the two study populations
- Based on the results of this analysis, PK/PD of somavaratan appears to be insensitive to ethnic factors
- The Phase 3 study in Japan continues to enroll patients receiving somavaratan 3.5 mg/kg twice monthly

References:

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Figure 1. Somavaratan Structure-Function vs Prepubertal Children with GHD in the US, but little is known about the impact of ethnic factors on outcomes

Figure 2. VERTICAL and J14VRS Pediatric GH Study Design

Figure 3. Somavaratan AUC0-14 in Japanese and US Subjects

Figure 4. (A) Cmax/dose and (B) Clearance by Body Weight

Figure 5. Baseline-Adjusted AUC0-14 for (A) IGF-I SDS and (B) IGFBP-3 in Japanese and US Subjects By Dose Group