**ACROBAT Edge Phase 2 Study: Safety and Efficacy of Switching Injected Long-Acting Somatostatin Receptor Ligands (SRLs) to Once Daily Oral Paltusotine**

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**Introduction**

- Paltusotine is an oral, non-peptide, once daily somatostatin type 2 (SST2) receptor agonist
- Data from healthy volunteers (Phase 1) indicate inhibition of GH and lowering of IGF-1

**Study Design (Figure 1)**

- **ACROBAT Edge** (NCT03789656) single-arm, open-label, dose-blinded study
- Patients switched from injectables SRLs to oral, once daily paltusotine
- **Pre-specified primary endpoint:** change from baseline in IGF-1 levels at week 13
- **Exploratory endpoint:** change from baseline in GH levels at week 13
- IGF-1 measured with IDS-6YS assay (WHO 02/254)
- Primary efficacy analysis — Wilcoxon Signed Rank test

**Subjects**

- 5 groups of adult patients (n=47) with acromegaly on stable SRL therapy for at least 3 months:
  - **Group 1** SRL monotherapy, IGF-1 >1, <2.5 x ULN, n=25
  - median age 52 years (31-71), 44% female;
  - 20% (80%) had prior pituitary surgery;
  - 13 (52%) on octreotide; 92% on lanreotide (58% on 120 mg)
  - **Group 2** SRL+ cabergoline, IGF-1 >1, <2.5 x ULN, n=10
  - **Group 3** SRL+ cabergoline, IGF-1 <1 x ULN, n=5
  - **Group 4** pasireotide, IGF-1 <1 x ULN, n=4
  - **Group 5** SRL + pegvisomant <1 x ULN, n=3
  - Primary analysis performed on Group 1
  - Groups 2-5shorts were included for exploratory and safety purposes

**Pre-specified Primary Endpoint (Figure 2 and 3)**

- No change in IGF-1 ≤ 0.034 [-0.107, 0.107], median (IQR), p=0.6 in patients converting from depot SRL monotherapy to paltusotine

**Figure 1. ACROBAT Edge Study Design**

**Figure 2. IGF-1 Levels After Switching to Paltusotine from Injected SRLs**

**Figure 3. IGF-1 and GH Levels at baseline, EOT and after 4 weeks of withdrawal**

**Group 1 Results (Figure 3)**

- 20/23 patients (87%) achieved IGF-1 levels at week 13 that were within 20% of baseline
- 18/22 (82%) patients who completed the study showed a ≥20% rise from baseline in IGF-1 four weeks after withdrawal of paltusotine

**Safety**

- No study discontinuation due to adverse events
- No patients required rescue treatment with injectable SRLs
- No treatment related SAEs; 2 non-treatment related SAEs (headache and nephrolithiasis)

**Common Acromegaly Symptoms**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients (N=47) n (%)</th>
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<tbody>
<tr>
<td>Headache</td>
<td>15 (31.9%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (27.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (21.3%)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>9 (19.1%)</td>
</tr>
<tr>
<td>Peripheral swelling</td>
<td>7 (14.9%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>7 (14.9%)</td>
</tr>
<tr>
<td>Sleep apnoea syndrome</td>
<td>3 (6.4%)</td>
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</tbody>
</table>

**Common SRL Side Effects**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients (N=47) n (%)</th>
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<tbody>
<tr>
<td>Diarrhoea</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>Abd pain/Abd pain upper</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>3 (6.4%)</td>
</tr>
</tbody>
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**Conclusions**

- Once daily oral paltusotine maintained IGF-1 levels after switching from injected SRL monotherapy
- Both IGF-1 and GH levels promptly rose after withdrawing paltusotine which characterized the magnitude of therapeutic activity of oral paltusotine
- Paltusotine appears to be well tolerated with a safety profile similar to that of SRLs currently in use