INTRODUCTION

Insulin-like growth factor-I (IGF-I) and growth hormone (GH) levels are the primary biochemical markers of disease activity in acromegaly.
- Individual patient’s measurements may vary significantly during stable treatment.
- Despite these common fluctuations, biochemical treatment response in acromegaly clinical trials is typically monitored using single-point analyses.
- Accordingly, longitudinal evaluations may assess patient status more accurately and so more closely reflect real-world clinical practice.

- In a recent phase 3 trial, oral octreotide capsules (OOC) demonstrated sustained response (IGF-I <1.3 x upper limit of normal [ULN]) and GH <2.5 ng/mL for up to 13 months in patients with acromegaly previously managed with somatostatin receptor ligand (SRL) injections.
  - This result was based on composite landmark analyses of IGF-I and GH at specific time points.
  - This approach does not account for natural variation in IGF-I levels over time and fails to incorporate the time course of IGF-I measurements recorded at each visit.
- Time-weighted average (TWA) response
  - Represents an integrated measure of efficacy.
  - Is calculated by dividing the area under the plasma concentration-time curve (AUC) by the total amount of time under observation.
- Here we report of post hoc TWA IGF-I and GH analyses from the OOC phase 3 trial.

RESULTS

- While IGF-I varied between visits, more patients gained response by TWA analysis versus landmark analysis, and some patients were nonresponders due to GH elevation despite IGF-I <1.3 xULN (Figure 3).
- Through the end of core treatment and extension periods, response rates by TWA were greater than those calculated per original trial criteria (Table).

Proportion of responders based on conventional landmark analysis versus TWA IGF-I + GH composite, n/N (95% CI) [39% CI]

<table>
<thead>
<tr>
<th>Study period</th>
<th>Study population</th>
<th>Proportion of responders</th>
<th>Proportion of responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Landmark response rate</td>
<td>TWA response rate</td>
<td></td>
</tr>
<tr>
<td>Core treatment</td>
<td>Modified intention-to-treatment cohort</td>
<td>98/151 (64.9)</td>
<td>108/151 (71.5)</td>
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<tr>
<td></td>
<td>Fixed-dose population</td>
<td>87/110 (79.9)</td>
<td>92/110 (83.6)</td>
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<tr>
<td>Core + extension</td>
<td>Fixed-dose population</td>
<td>82/110 (74.6)</td>
<td>92/110 (83.6)</td>
</tr>
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<td></td>
<td>Responders at start of fixed dose</td>
<td>77/91 (84.6)</td>
<td>86/91 (94.5)</td>
</tr>
</tbody>
</table>

*Using all data collected during core treatment.
*Considering all data collected during the fixed-dose period.
*Using all data collected during the core and extension periods.
*Using all data collected during the fixed-dose and extension periods.

CONCLUSIONS

- Based on a composite using TWA IGF-I and TWA GH, OOC demonstrated a greater response versus the single-point analysis at end of treatment.
- Analyses incorporating all evaluations over time may provide assessments of overall treatment response that are more accurate and more clinically meaningful than single-point evaluations.
- The phase 3 IMPROVED trial will assess treatment response with a TWA assessment of IGF-I values over multiple time points.

REFERENCES


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