# Longitudinal assessment of response to treatment with oral octreotide capsules in patients with acromegaly: post hoc analysis of a phase 3 trial

151-GP

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## INTRODUCTION

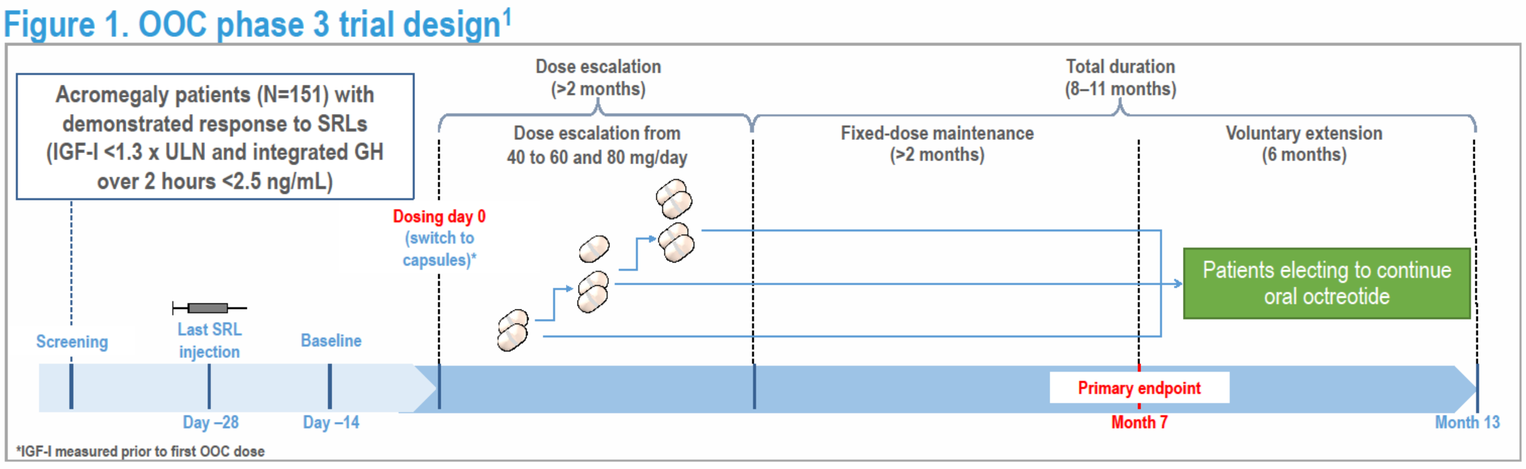
- Insulin-like growth factor-I (IGF-I) and growth hormone (GH) levels are the primary biochemical markers of disease activity in acromegaly
  - Individual patients' measurements may vary significantly during stable treatment
  - Despite these common fluctuations, biochemical treatment response in acromegaly 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[1]
  - 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 post hoc TWA IGF-I and GH analyses from the OOC phase 3 trial

## METHODS

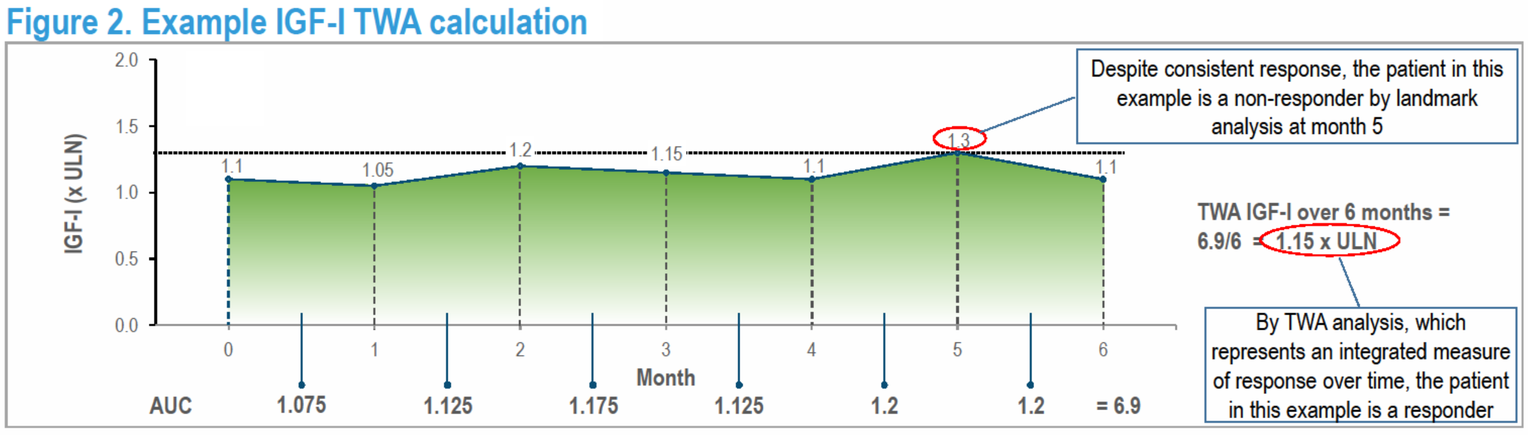
The OOC phase 3 study design has been described previously[1]

- Multicenter, open-label, maintenance-of-response, baseline-controlled withdrawal trial (**Figure 1**)
- IGF-I was assessed monthly; mean integrated GH was assessed upon dose escalation and at the beginning and end of each study period
- Primary endpoint was a composite including IGF-I and GH at the end of core treatment (up to 7 months)
- In this post hoc analysis comparing conventional (landmark) and TWA response:
  - Longitudinal IGF-I and GH are expressed as integrated TWA incorporating all measurements and accounting for missing data (**Figure 2**)
  - Response is defined as a composite including TWA IGF-I <1.3 x ULN and TWA GH <2.5 ng/mL

### Figure 1. OOC phase 3 trial design[1]

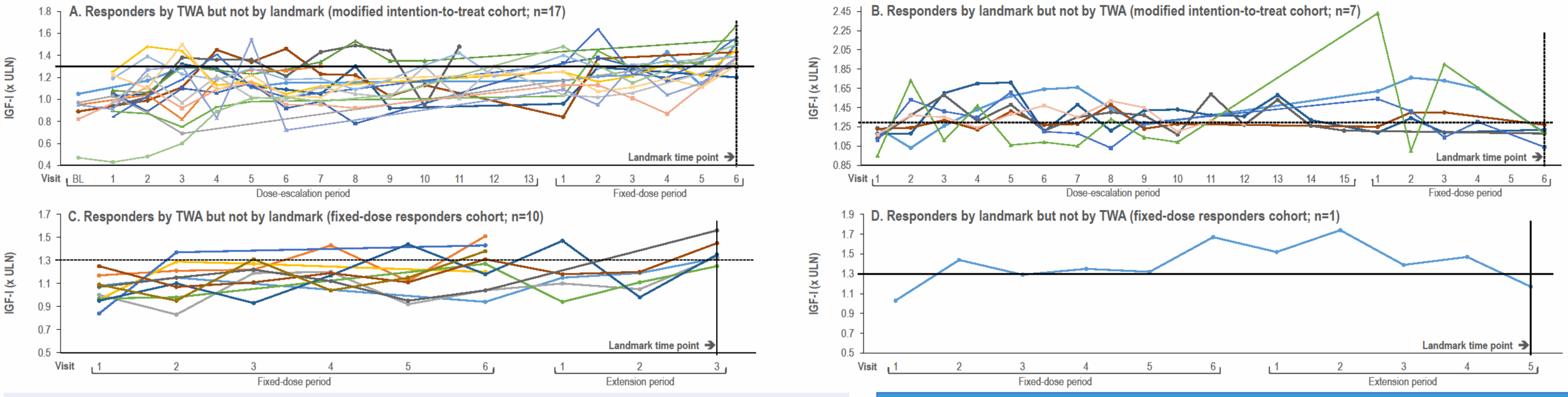



### Figure 2. Example IGF-I TWA calculation




## RESULTS

### Figure 3. IGF-I by study visit in patients with discrepant TWA and landmark response status




- 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]**

| Study period | Study population | Proportion of responders | |
|---|---|---|---|
| | | Landmark response rate | TWA response rate |
| Core treatment | Modified intention-to-treat population[a] | 98/151 (**64.9**); [58.4–74.2] | 108/151 (**71.5**); [65.6–80.4] |
| | Fixed-dose population[b] | 87/110 (**79.0**); [70.3–86.3] | 92/110 (**83.6**); [75.4–90.0] |
| Core + extension | Fixed-dose population[c] | 82/110 (**74.6**); [65.4–82.4] | 92/110 (**83.6**); [75.4–90.0] |
| | Responders at start of fixed dose[d] | 77/91 (**84.6**); [75.5–91.3] | 86/91 (**94.5**); [87.6–98.2] |

[a]Using all data collected during core treatment; [b]Considering all data collected during the fixed-dose period; [c]Using all data collected during the core and extension periods; [d]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 MPOWERED trial[2] will assess treatment response with a TWA assessment of IGF-I values over multiple time points**

## REFERENCES

1. Melmed S *et al. J Clin Endocrinol Metab* 2015;100:1699–1708.
2. ClinicalTrials.gov. NCT02685709. Available at: https://clinicaltrials.gov/ct2/show/NCT02685709.

## ACKNOWLEDGMENT

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