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 GHRH-induced GH secretion and lowering of serum IGF-1
- We report the impact on IGF-1 of patients with acromegaly switching from injected SRLs to once daily, oral paltusotine

Study Design (Figure 1)

- ACROBAT Edge (NCT03789656) single-arm, open-label, dose-blinded study
- Patients switched from injectables SRLs to oral, once daily paltusotine (first generation capsule formulation) for 13-weeks, followed by a 4-week washout
- 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-ISYS assay (WHO 02/254)
- Primary efficacy analyses – 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 yeas (31-71); 44% female;
    - 20 (80%) had prior pituitary surgery;
    - 13 (52%) on octreotide; 92% on 30-40 mg; 12 (48%) 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 2-5 cohorts were included for exploratory and safety purposes

Pre-specified Primary Endpoint (Figure 2 and 3)

- No change in IGF-1 levels at week 13 compared to baseline [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

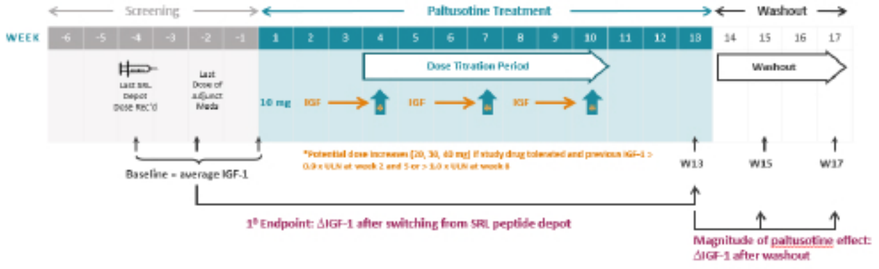


Figure 2. IGF-1 Levels After Switching to Paltusotine from Injected SRLs

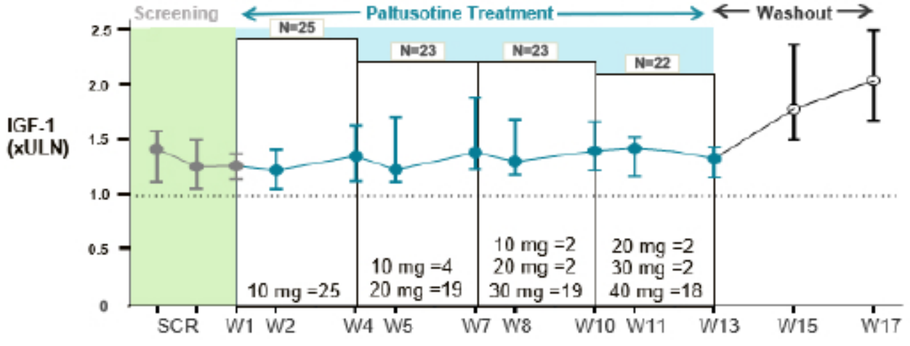
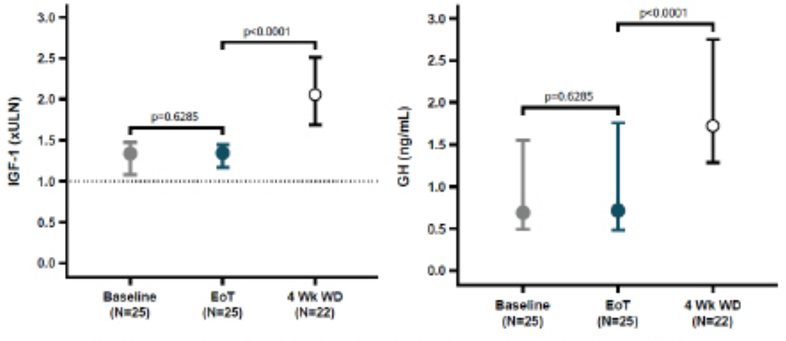


Figure 3. IGF-1 and GH Levels at baseline, EOT and after 4 weeks of withdrawal



EoT = End of Treatment (Week 13 or last on treatment value carried forward); WD = withdrawal Time since EOT

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)

Treatment Emergent Adverse Events ≥ 5%*	Patients (N=47) n (%)
Common Acromegaly Symptoms	
Headache	15 (31.9%)
Arthralgia	13 (27.7%)
Fatigue	10 (21.3%)
Hyperhidrosis	9 (19.1%)
Peripheral swelling	7 (14.9%)
Paraesthesia	7 (14.9%)
Sleep apnoea syndrome	3 (6.4%)
Common SRL Side Effects	
Diarrhoea	5 (10.6%)
Abd pain/Abd pain upper	4 (8.5%)
Abdominal discomfort	4 (8.5%)
Abdominal distension	3 (6.4%)

*TEAEs include any AE that newly appears, increases in frequency, or worsens in severity following initiation of study drug through 28 days after last dose.

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