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

Monica R. Gadelha, MD, PhD[1], Murray B. Gordon, MD[2], Mirjana Doknic, MD, PhD[3], Emese Mezősi, MD, PhD[4], Miklós Tóth, MD, PhD[5], Harpal Randeva, MBChB, PhD[6], Tonya Marmon, PhD[7], Rosa Luo, MS[8], Michael Monahan, MBA[8], Ajay Madan, PhD[8], Christine Ferrara-Cook, MD, PhD[8], Scott Struthers, PhD[8], Alan Krasner, MD[8].

[1]Neuroendocrinology Research Center/Endocrinology Division--Medical School and Hospital Universitario Clementino Fraga Filho--Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [2]Allegheny General Hospital, Pittsburgh, PA, USA, [3]Clinical Center of Serbia, Belgrade, Serbia, University of Pécs Medical School, Pécs, Hungary, [5]Semmelweis University, Budapest, Hungary, [6]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, United Kingdom, [7]Marmon Biostatistics, Seattle, WA, USA, [8]Crinetics Pharmaceuticals Inc., San Diego, CA, USA.

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 in patients with acromegaly switching from injected SRLs to once daily, oral paltusotine

Study Design

- ACROBAT Edge (NCT03789656) is a 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 period
- Primary endpoint: change from baseline in IGF-1 levels at week 13
- IGF-1 measured with IDS-ISYS assay (WHO 02/254)
- Primary efficacy analyses – Wilcoxon rank test

Subjects

- 5 groups (Gr) of adult patients (n=47) with acromegaly on stable SRL therapy for at least 3 months prior to paltusotine treatment:
  - Gr1 SRL monotherapy, IGF-1 >1, <2.5 x ULN, n=25
  - Gr2 SRL + cabergoline, IGF-1 IGF-1 >1, <2.5 x ULN, n=10
  - Gr3 SRL + cabergoline, IGF-1 <1 x ULN, n=5
  - Gr 4 pasireotide, IGF-1 <1 x ULN, n=4
  - Gr5 SRL & pegvisomant <1 x ULN, n=3
- Primary analysis performed on Group 1
- Groups 2-5 cohorts were included for exploratory and safety purposes

Group 1 Results

- 25 patients: median age 52 years (31-71); 44% female
- 20 (80%) had prior pituitary surgery
- At baseline 13 (52%) on octreotide; 92% on 30-40 mg dose, 12 (48%) on lanreotide; 58% on 120 mg dose
- 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

Figure 1. ACROBAT Edge Study Design

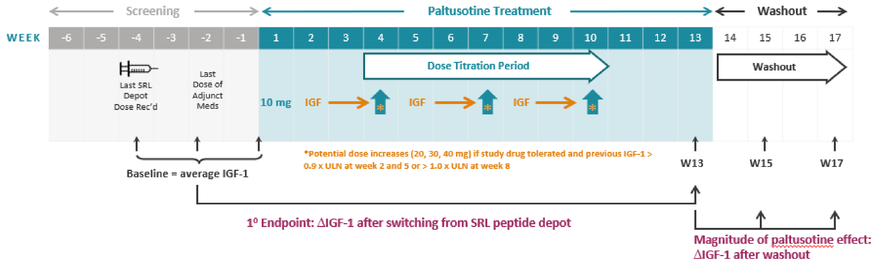


Figure 2. IGF-1 Levels After Switching to Paltusotine from Injected SRLs

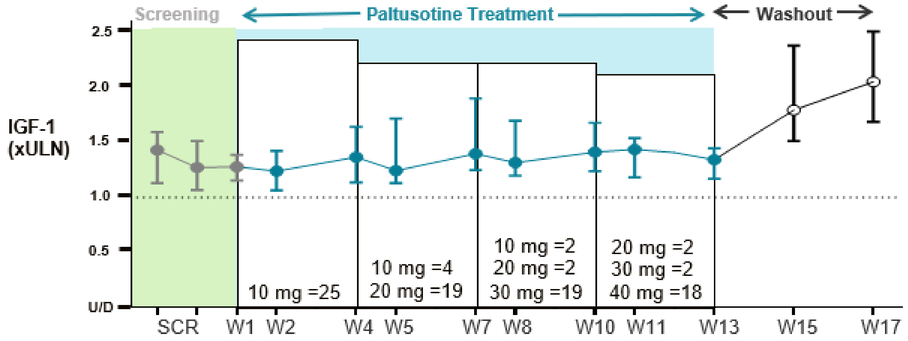
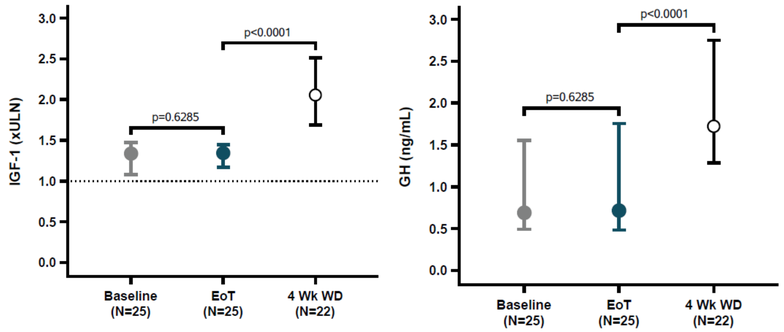


Figure 3. IGF-1 and GH Levels at baseline and at EOT



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

Primary Endpoint:

- 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

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%)/ 2 (4.3%)
Abdominal discomfort	4 (8.5%)
Abdominal distension	3 (6.4%)

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