P399

Paltusotine Maintains IGF-I, GH, and Symptom Control in Patients With Acromegaly Switched From Injected Octreotide or Lanreotide Monotherapy: Topline Results From PATHFNDR-1, a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study

Monica R. Gadelha, MD, PhD[1]; Alessandra Casagrande, MD, PhD[2]; Christian J. Strasburger, MD[3]; Martin Bidlingmaier, MD[4]; Peter J. Snyder, MD[5]; Mirtha Guitelman, MD[6]; Cesar L. Boguszewski, MD, PhD[7]; Michael Buchfelder, MD, PhD[8]; Ilan Shimon, MD[9]; Gerald Raverot, MD, PhD[10]; Miklós Tóth, MD, PhD, DSci[11]; Emese Mezosi, MD, PhD, DSci[12]; Mirjana Doknic, MD[13]; Xiaolin Fan, PhD[2]; David R. Clemmons, MD[14]; Michael Keeley, PhD[2]; Peter J. Trainer, MD[2]; R. Scott Struthers, PhD[2]; Alan Krasner, MD[2]; Beverly M.K. Biller, MD[15]

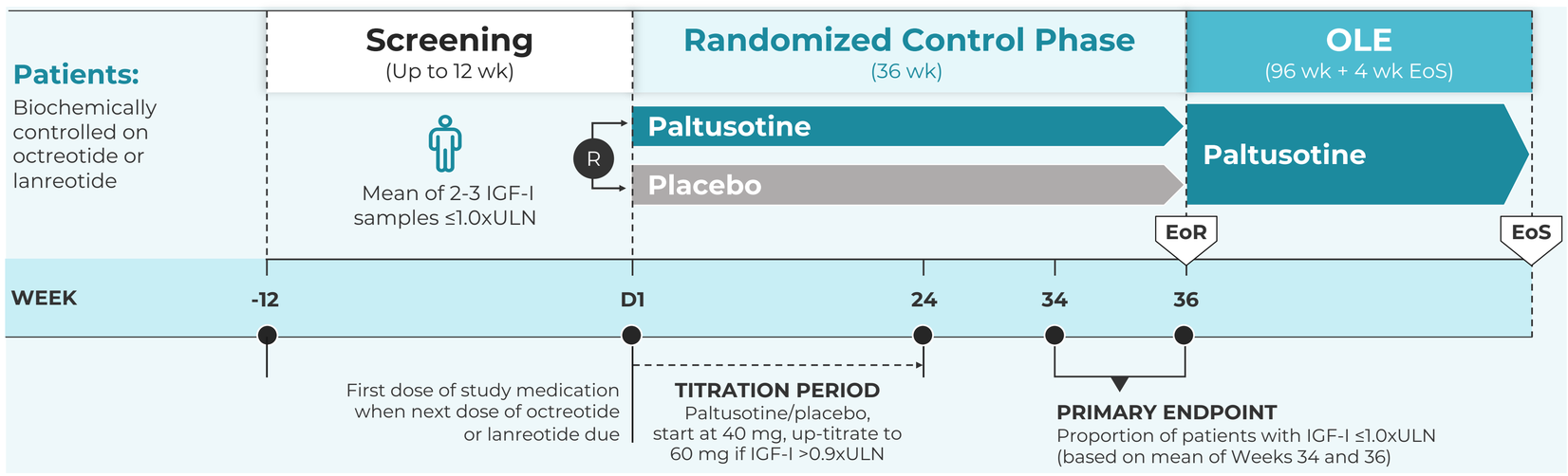
BACKGROUND

- Paltusotine is a once-daily, oral, selectively targeted somatostatin receptor type 2 agonist in development for the treatment of acromegaly and carcinoid syndrome
- PATHFNDR-1 (NCT04837040) evaluated the efficacy and safety of paltusotine in patients with acromegaly who had achieved biochemical control with octreotide or lanreotide injections and were switched to oral paltusotine

METHODS

- Enrolled patients had IGF-I ≤1 × ULN on a stable (≥12 weeks) dose of octreotide or lanreotide
- Patients randomized 1:1 to paltusotine 40 mg/day or placebo for 36 weeks
  - During the first 24 weeks, paltusotine dose titrated (range, 20-60 mg) based on IGF-I levels and tolerance
- IGF-I and GH measured centrally using iSYS immunoassays
- Acromegaly symptoms assessed with Acromegaly Symptom Diary (higher scores greater symptom burden)[1]
- Tumor volume measured by MRI scans, read centrally

Study Design



EoR = end of the randomized control phase; EoS = end of study; OLE = open-label extension; R = randomization.

CONCLUSIONS

- Once-daily oral paltusotine was effective for maintaining biochemical and symptom control in patients switched from octreotide or lanreotide
- Paltusotine was well tolerated, with no severe or serious adverse events

Patient Characteristics

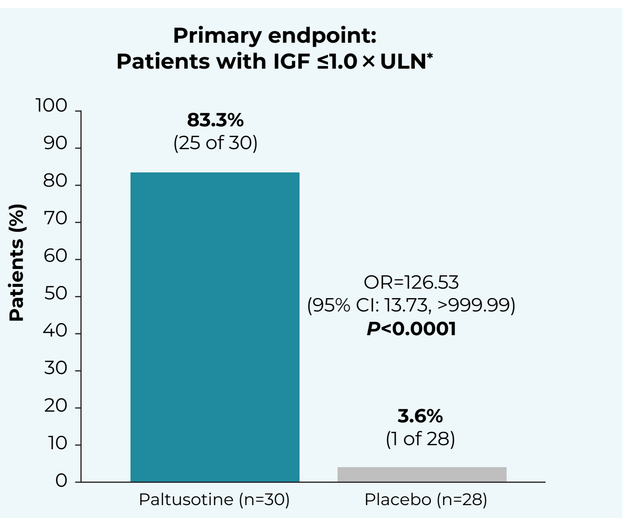
Parameters	Paltusotine (n=30)	Placebo (n=28)
Age, years, mean (SD)	55.9 (14.6)	53.9 (12.9)
Female sex, n (%)	15 (50.0)	17 (60.7)
Duration of acromegaly (since diagnosis), n (%)		
<10 years	5 (16.7)	15 (53.6)
≥10 to <20 years	19 (63.3)	11 (39.3)
≥20 years	6 (20.0)	2 (7.1)
Previous pituitary surgery	26 (86.7)	24 (85.7)
Prior injected somatostatin receptor ligand, n (%)*		
Octreotide	18 (60.0)	16 (57.1)
Lanreotide	12 (40.0)	12 (42.9)
Baseline IGF-I, ×ULN, mean (SD)	0.83 (0.14)	0.82 (0.16)
Screening GH, ng/mL, mean (SD)†	0.92 (1.02)	0.89 (0.83)

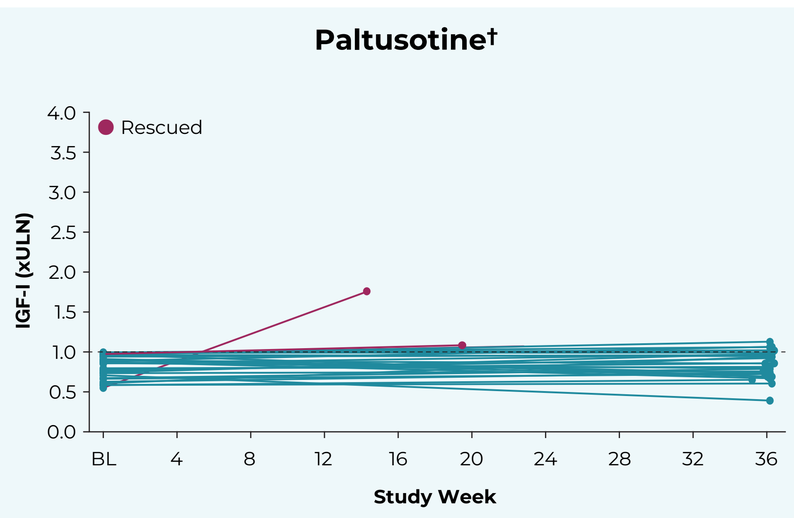
*Randomization stratified by prior medication.
†Mean of 5 samples; screening value served as baseline.

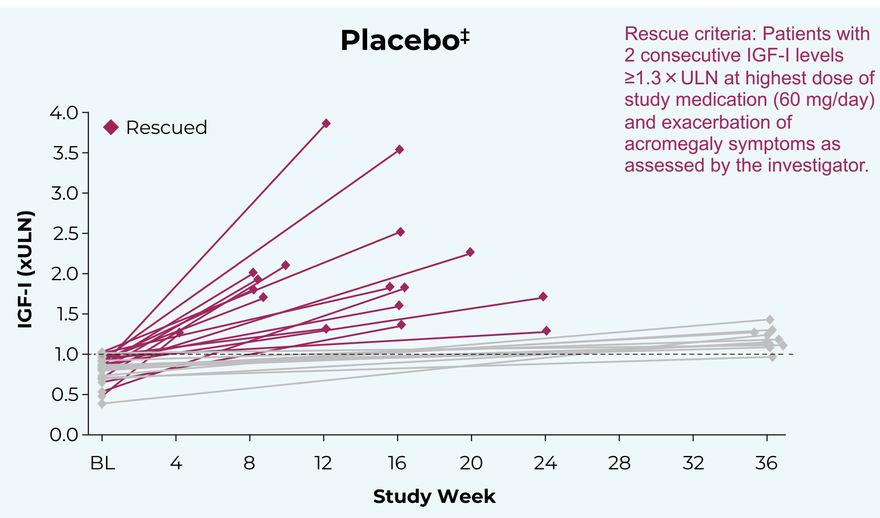
- 1 patient in the placebo group discontinued the study due to "patient decision"

RESULTS

Primary Endpoint Met



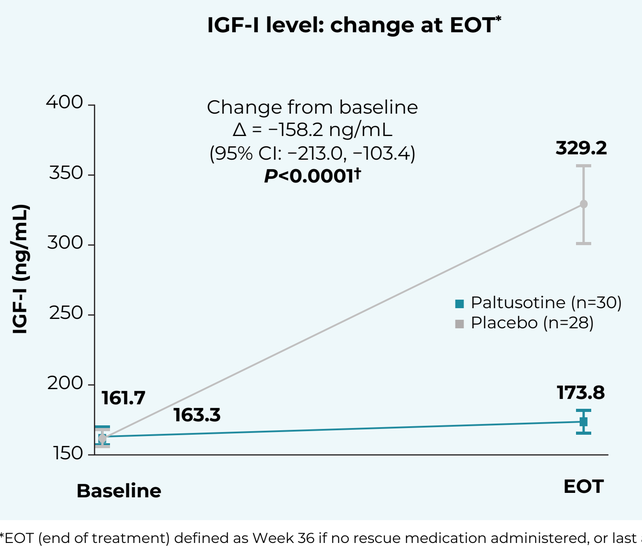


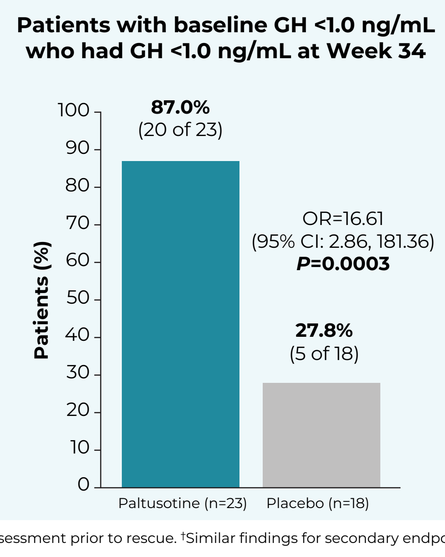


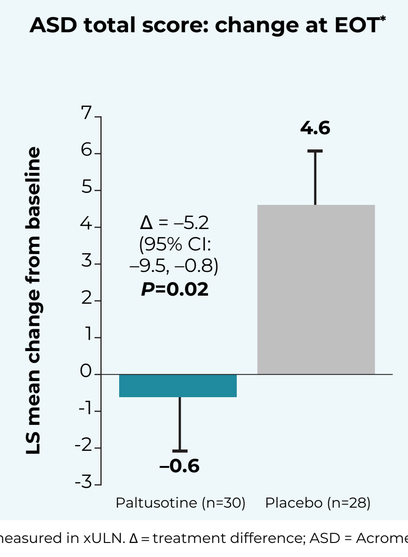
Rescue criteria: Patients with 2 consecutive IGF-I levels ≥1.3 × ULN at highest dose of study medication (60 mg/day) and exacerbation of acromegaly symptoms as assessed by the investigator.

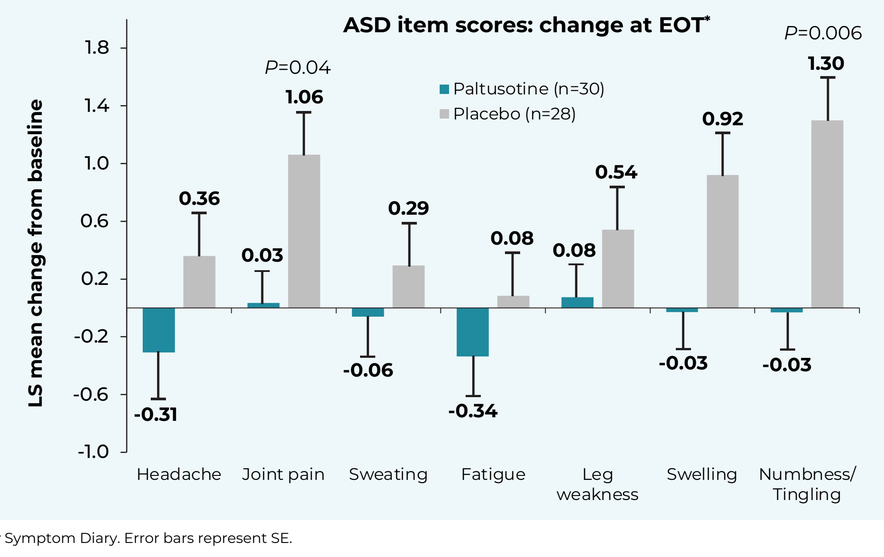
*Based on mean of 2 measurements (Weeks 34 and 36) in the randomized treatment period. Patients considered to have failed to meet the primary outcome if IGF-I >1.0 × ULN based on the mean of the last 2 measurements, IGF-I missing at both Weeks 34 and 36, treatment discontinued (for any reason) prior to EOR, other acromegaly treatment administered, or uptitration in dose after Week 24. †2 of 30 patients received rescue medication (1 per protocol and 1 who discontinued study treatment due to adverse events). ‡17 of 28 patients received rescue medication (per protocol).

All Secondary Endpoints Met









*EOT (end of treatment) defined as Week 36 if no rescue medication administered, or last assessment prior to rescue. †Similar findings for secondary endpoint measured in xULN. Δ = treatment difference; ASD = Acromegaly Symptom Diary. Error bars represent SE.

Safety

Adverse Events, n (%)*	Paltusotine (n=30)	Placebo (n=28)
Any adverse event	24 (80.0)	28 (100)
Severe adverse event	0	3 (10.7)
Serious adverse event	0	1 (3.6)†
Common somatostatin receptor ligand side effects‡		
Diarrhea	7 (23.3)	4 (14.3)
Abdominal pain	5 (16.7)	3 (10.7)
Nausea	3 (10.0)	2 (7.1)
Constipation	2 (6.7)	4 (14.3)
Other adverse events‡		
COVID-19	0	6 (21.4)

Adverse Events, n (%)*	Paltusotine (n=30)	Placebo (n=28)
Common acromegaly symptoms‡		
Arthralgia	8 (26.7)	16 (57.1)
Headache	6 (20.0)	10 (35.7)
Peripheral swelling	2 (6.7)	10 (35.7)
Fatigue	2 (6.7)	5 (17.9)
Muscle weakness	1 (3.3)	3 (10.7)
Paresthesia	0	7 (25.0)
Asthenia	0	4 (14.3)
Hyperhidrosis	0	4 (14.3)
Pain in extremity	0	3 (10.7)

*Adverse events that emerged or worsened during study treatment; including events with onset after rescue medication was administered. Adverse events were coded using MedDRA version 24.0. †Acute cholecystitis, judged by study investigator as not treatment related. ‡Adverse events occurring in >10% of patients in either treatment group.

- Incidence of adverse events considered related to acromegaly was notably lower for paltusotine (30.0%) compared with placebo (85.7%)
- There were no clinically significant changes in pituitary tumor size
- No safety signals were observed in vital signs, electrocardiograms, or laboratory test results during treatment with paltusotine

REFERENCE
1. Martin S, et al. *J Patient Rep Outcomes*. 2023;7(1):15.

ACKNOWLEDGMENTS
The authors thank the site investigators, study coordinators/nurses, clinical staff, and patients who participated in the study. This study was funded by Crinetics Pharmaceuticals, Inc. Technical editorial and medical writing assistance were provided under the direction of the authors by Janetricks C. Okeyo, PhD, Crinetics Pharmaceuticals, Inc., and Nancy Holland, PhD, Synchrony Medical Communications, LLC, West Chester, PA, USA; funding for this support was provided by Crinetics Pharmaceuticals, Inc.

[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]Crinetics Pharmaceuticals, Inc., San Diego, CA, USA; [3]Department of Medicine for Endocrinology, Diabetes and Nutritional Medicine, Charite-Universitätsmedizin, Campus Mitte, Berlin, Germany; [4]Neuroendocrine Research Group, Department of Internal Medicine, Ludwig-Maximilians University, Munich, Germany; [5]Division of Endocrinology, Diabetes, and Metabolism, Perelman School of Medicine University of Pennsylvania, Philadelphia, PA, USA; [6]División Endocrinología, Hospital Carlos G Durand, Buenos Aires, Argentina; [7]Department of Internal Medicine, Endocrine Division (SEMPR), University Hospital, Federal University of Parana, Curitiba, Brazil; [8]Neurosurgery Department, University of Erlangen, Erlangen, Germany; [9]Institute of Endocrinology, Rabin-Beilinson Medical Center, Faculty of Medicine, Tel Aviv University, Israel; [10]Endocrinology Department, Reference Center for Rare Pituitary Diseases HYPO, "Groupement Hospitalier Est" Hospices Civils de Lyon, yon Cedex, France; [11]Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary; [12]Department of Medicine, University of Pécs Medical School, Pécs, Hungary; [13]Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia; Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [14]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [15]Neuroendocrine and Pituitary Tumor Clinical Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Crinetics Pharmaceuticals

DISCLOSURES:

MRG reports being a principal investigator (PI) of research grants from Crinetics and Recordati; occasional consultant for Crinetics, Ipsen, Novo Nordisk, and Recordati; and speaker for Ipsen, Novo Nordisk, and Recordati. AC, XF, MK, PJT, RSS, and AK are employees and stock shareholders of Crinetics Pharmaceuticals. CJS reports being a PI of a research grant from Crinetics; and occasional consultant for Amolyt Pharma, Consilient Health, Novo Nordisk, Recordati, and Sandoz-Hexal. M Bidlingmaier reports being a PI of research grants from Amolyt, Camurus, Chiasma, Crinetics, IDS, Ionis, Lumos, and OPKO; occasional consultant for Crinetics, Ionis, Novo Nordisk, Pfizer, Roche, and Sandoz; and speaker for Euroimmun, Novo Nordisk, and Pfizer. PJS, M Buchfelder, and EM report being a PI of a research grant from Crinetics. MG reports being a PI of research grants from Crinetics; and occasional consultant and speaker for Recordati, Sanofi Aventis, and Varifarma. CLB reports being a PI of a research grant from Crinetics; and speaker and consultant for Ipsen, Novo Nordisk, and Recordati. IS reports being a PI of a research grant from Crinetics and Debiopharm; and speaker and consultant for Medison and Pfizer. GR reports being a PI of a research grant from Crinetics; occasional consultant for Amolyt, Crinetics, Ipsen, Novo Nordisk, Pfizer, and Recordati; and speaker for Ipsen, Pfizer, and Recordati. MT reports being a PI of a research grant from Crinetics; and speaker and consultant for Ipsen, Lilly, Novartis, and Recordati. MD reports being a PI of a research grant from Crinetics; and advisory board member for Pfizer in CEE. DRC is a consultant for Crinetics. BMKB reports being a PI of research grants from Crinetics and Ionis; and occasional consultant for Amryt, Camurus, Crinetics, and Recordati.