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Clinical Research Article

ACROBAT Edge: Safety and Efficacy of Switching Injected SRLs to Oral Paltusotine in Patients With Acromegaly

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Abstract

Context: Paltusotine is a once-daily, oral, nonpeptide small-molecule somatostatin receptor type 2 (SST2) agonist in clinical development for treatment of acromegaly.

Objective: This work aimed to evaluate change in insulin-like growth factor I (IGF-I) levels in patients switched from octreotide long-acting release or lanreotide depot monotherapy to paltusotine.

Methods: A phase 2, open-label, prospective, multicenter, multinational, nonrandomized, single-arm exploratory study was conducted in which dosage uptitrations were performed in a double-blinded manner. At 26 global sites, patients with acromegaly switched to paltusotine from injected somatostatin receptor ligand (SRL)-based therapy. Patients received 13-week treatment with once-daily oral paltusotine (10-40 mg/d). The primary end point was change from baseline to week 13 in IGF-I for patients who switched from long-acting octreotide or lanreotide depot monotherapy to paltusotine (group 1). All patients underwent a 4-week paltusotine washout at end of treatment period (wk 13-17). IGF-I, growth hormone (GH), patient-reported outcome, and safety data were collected.

Results: Forty-seven patients enrolled. In group 1 (n = 25), IGF-I and GH showed no significant change between SRL baseline and end of paltusotine treatment at week 13 (median change in IGF-I = −0.03×upper limit of normal [ULN]; $P = .6285$; GH = −0.05 ng/mL; $P = .6285$). IGF-I and GH rose significantly in the 4 weeks after withdrawing paltusotine (median change in IGF-I = 0.55×ULN; $P < .0001$ [median increase 39%]; GH = 0.72 ng/mL; $P < .0001$ [109.1% increase]). No patients discontinued because of adverse events (AE); no treatment-related serious AEs were reported.

Conclusion: These results suggest once-daily oral paltusotine was effective in maintaining IGF-I values in patients with acromegaly who switched from injected SRLs. Paltusotine was well tolerated with a safety profile consistent with other SRLs.

Key Words: acromegaly, clinical trial, phase 2, somatostatin receptor type 2, somatostatin receptor ligands, paltusotine, somatotropinoma

Abbreviations: AE, adverse event; ASD, acromegaly symptom diary; ET, terminated treatment early; EoT, end of treatment; GH, growth hormone; IGF-1, insulin-like growth factor I; IQR, interquartile rage; LAR, long-acting release; LLOQ, lower limit of quantification; med, medication; NIBSC, National Institute for Biological Standards; PGI-I, Patient Global Impression of Improvement; SRL, somatostatin receptor ligands; SST2, somatostatin receptor type 2; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; V, visit.

Acromegaly is a chronic disease characterized by excessive secretion of growth hormone (GH) and its target hormone, insulin-like growth factor I (IGF-I), almost always caused by a pituitary adenoma (1). Prolonged exposure to increased levels of GH and IGF-I leads to progressive systemic complications including bone, cardiovascular, metabolic, cerebrovascular, and respiratory disease (2-7). Surgical removal of the adenoma is the preferred treatment for acromegaly. However, resection leads to remission in only about half of patients (8), and many require adjuvant pharmacotherapy to normalize GH and IGF-I levels (9).

The advent of somatostatin receptor ligand (SRL) therapy represented a major advance in the care of patients with acromegaly who were not cured by surgery (10, 11). Now, long-acting peptide injectable SRLs octreotide and lanreotide are considered first-line pharmacologic treatments for patients

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with acromegaly who have contraindications to surgery or who do not achieve remission after surgery (12). These treatments result in reduction of IGF-I and GH in approximately 90% of patients and disease control (defined as normalization of IGF-I levels) in about 20% to 40% of patients (13-18). In a recent study in SRL-treated patients, the IGF-I SD score was higher just before injection than at day 7 and day 14 after injection, indicative of waning in biochemical control before the next injection (19). There have been reports of worsening of some acromegaly symptoms, such as headache, toward the end of the 4-week SRL dosing period (20-24). Octreotide long-acting release (LAR) is administered via gluteal intramuscular injection using large-bore needles, which can be painful and the accuracy of delivery can vary (25). The effect of this variability of drug delivery on disease control is unknown. Lanreotide depot is administered in the clinic or at home via deep subcutaneous injection and can result in subcutaneous nodule formation (26, 27). For many patients, monthly hospital or clinic visits to receive the injection become a life-long necessity.

Many patients would welcome a treatment alternative that eliminates the requirement for travel, avoids painful injections, and maintains long-term efficacy (22, 28). To this end, a twice-daily oral formulation of octreotide was approved in the United States in 2020, based on a phase 3 study that showed maintenance of normalized IGF-I in 58.2% of patients with acromegaly who switched from long-acting peptide injectable SRL to oral octreotide vs 19.4% for those who switched to placebo ($P = .0079$) (11, 29-31).

Paltusotine (formerly CRN00808) is a nonpeptide, small-molecule, selective somatostatin receptor type 2 (SST2) agonist that was discovered using iterative medicinal chemistry based on the following selection criteria: (1) potent and selective stimulation of the SST2 receptor so as to avoid hyperglycemia that can result from SST5 stimulation (as seen with pasireotide) (32), (2) efficient absorption via the gastrointestinal tract to allow oral delivery, (3) a pharmacokinetic profile suitable for once-daily dosing, (4) low risk for substantial drug-drug interactions, (5) drug stability at room temperature, and (6) other drug-like characteristics including long-term safety in nonclinical toxicology studies (33, 34).

Paltusotine has more than a 4000-fold selectivity for SST2 compared to the other SST receptor subtypes (35), and no dose-limiting toxicities have been identified in preclinical toxicology studies (data on file). A phase 1 study (NCT03276858) in healthy male volunteers demonstrated an elimination half-life of approximately 30 hours, suitable for once-daily dosing, and that a single dose of paltusotine inhibited GH-releasing hormone–stimulated GH secretion (34). Multiple doses resulted in significant, dose-dependent suppression of IGF-I (19%-37% vs placebo), comparable to that seen with octreotide in healthy volunteers (34, 36). Paltusotine was well tolerated, with an adverse event (AE) profile comparable to octreotide and lanreotide depot (34, 36, 37).

In this first-in-disease study, we evaluated the safety, tolerability, and efficacy of once-daily, oral paltusotine in patients with acromegaly who switched from injectable long-acting SRLs.

Materials and Methods

Study Design

ACROBAT Edge (NCT03789656) was a phase 2, open-label, prospective, multicenter, multinational, nonrandomized, single-arm exploratory study in which dosage uptitrations were performed in a double-blinded manner. The study design comprised a 4- to 6-week screening period, 13-week treatment with paltusotine, and 4-week washout period (Fig. 1). During screening, serum IGF-I was measured at 2 of the 3 screening visits (visits 1b and 2) to assess eligibility (more details provided later). The last dose of depot SRL was administered at visit 1b (4 weeks before starting paltusotine), and any adjunctive treatment (eg, cabergoline, pegvisomant) was stopped at visit 2. Paltusotine was commenced at visit 3 (week 1) starting at 10 mg/day, uptitrated to a maximum 40 mg/day, discontinued at week 13, followed by a 4-week washout period until the final study visit at week 17. More details are provided later and in Fig. 1.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and all relevant local and federal regulatory guidelines. Institutional review boards or independent ethics committees at each study site approved the protocol, informed consent forms, and other study documents before the first patient was enrolled. All patients or a legal representative provided written informed consent before any screening procedures were started.

Participants

Key inclusion criteria

Patients were adults (aged 18-75 years, inclusive) with a confirmed acromegaly diagnosis on stable doses of acromegaly medication for at least 3 months who had a partial or complete response (defined in "Assignment to groups") to SRL-based therapy with octreotide LAR, lanreotide depot either as monotherapy (group 1) or in combination with either a dopamine agonist (groups 2 and 3) or pegvisomant (group 5). Group 4 comprised patients on pasireotide LAR monotherapy (see next sections for more details).

Those with adrenal insufficiency or hypothyroidism were receiving appropriate and stable replacement therapy for at least 3 months. Women and men with partners of childbearing potential were required to use effective forms of contraception between screening and the last study visit.

Key exclusion criteria

The study excluded patients naive to acromegaly treatment or who had received pituitary surgery in the 6 months before screening; uncontrolled cardiovascular, renal, or hepatic disease or diabetes mellitus; octreotide LAR doses greater than 40 mg every 4 weeks, lanreotide depot doses greater than 120 mg every 4 weeks, or pasireotide LAR doses greater than 60 mg every 4 weeks; or had an SRL dosing schedule less frequent than every 4 weeks.

Assignment to groups

Patients were enrolled into a primary analysis cohort (group 1) and exploratory cohorts (groups 2-5) according to prior SRL and IGF-I status. IGF-I was expressed relative to the upper limit of normal (ULN) of the age- and sex-related reference range. Patients in group 1 were partial responders to stable treatment with octreotide LAR or lanreotide depot monotherapy, with at least one screening IGF-I value greater than 1× ULN and the visit 2 value less than or equal to 2.5× ULN. Patients in group 2 were partial responders to a stable

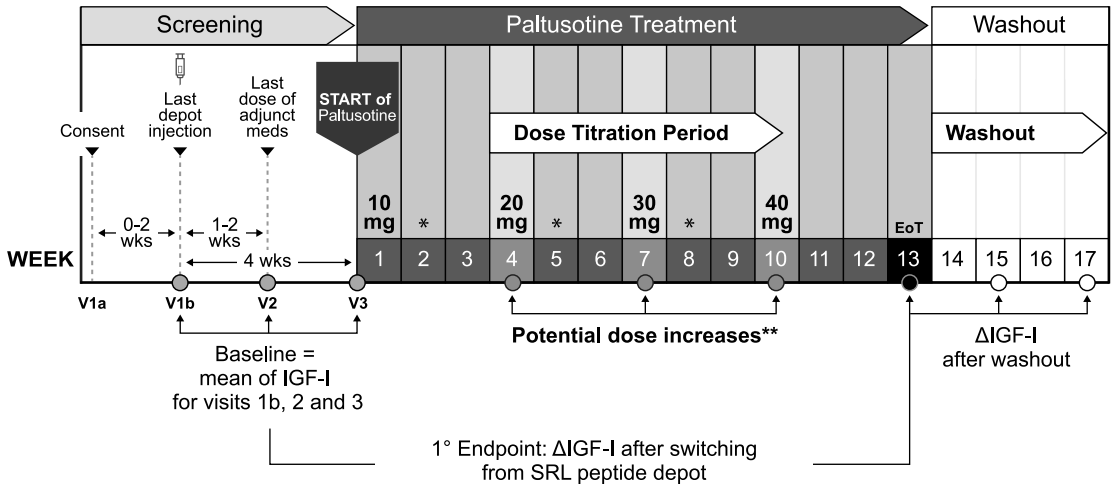

Figure 1. Study design. EoT, end of treatment; IGF-I, insulin-like growth factor I; med, medication; SRL, somatostatin receptor ligands; ULN, upper limit of normal; V, visit. *IGF-I measurements. **If study drug tolerated and previous IGF-I > 0.9×ULN at wk 2 and 5 or >1.0×ULN at wk 8.

combination of octreotide LAR or lanreotide depot plus a dopamine agonist (cabergoline), with the same IGF-I criteria as group 1. Patients in group 3 were complete responders (mean of screening IGF-I values < 1× ULN) to a stable combination of octreotide LAR or lanreotide depot plus a dopamine agonist, in all cases cabergoline. Patients in group 4 were complete responders to a stable dose of pasireotide LAR. Patients in group 5 were complete responders to a stable combination of octreotide LAR or lanreotide depot plus pegvisomant.

Procedures and Study Medication

Paltusotine was supplied in capsules (5 mg, 10 mg, and matching placebo) on blister cards containing rows of 4 capsules, with each row comprising the total daily blinded dose of paltusotine. Patients were instructed to take capsules with water once daily in the morning after an overnight fast of at least 6 hours, and to continue fasting for at least 2 hours after dosing. Patients used daily diaries to record confirmation of fasting before dosing and for 2 hours after dosing. Patients returned all unused study drug at each study visit, and an adherence check was conducted by counting returned capsules.

Enrolled patients began treatment with oral paltusotine 10 mg/day. The dose was uptitrated in a double-blind manner in 10-mg increments to a maximum 40 mg/day at weeks 4, 7, and 10 according to IGF-I levels measured at weeks 2, 5, and 8, respectively. Uptitrations were performed if the investigator confirmed that the patient was tolerating the current dose and the unblinded central IGF-I reader determined that IGF-I was greater than 0.9× ULN at weeks 2 and 5 or greater than 1.0× ULN at week 8. If the investigator and IGF-I reader both confirmed eligibility for a dose increase, the patient was assigned a blinded blister card containing the appropriate higher dose. Dose decreases to the prior dose level (eg, 20-10 mg, 10-5 mg) were to occur if patients did not tolerate the current dose. No dose changes were made if IGF-I suppression into the target range was achieved with a tolerated dose.

Serum IGF-I was measured at every study visit during the treatment (weeks 1-13) and washout periods (weeks 15 and 17; 2 and 4 weeks after withdrawing paltusotine, respectively). During the treatment period, IGF-I was measured before dosing (weeks 1, 4, 7, and 10) or 1 to 15 hours post dose (weeks 2, 3, 5, 6, 8, 9, 11, and 13). Assessments of GH were based on integrated values, defined as the mean of 3 samples collected at least 30 minutes apart over 2 hours and were undertaken during 2 screening visits; dosing visits at weeks 2, 5, 8, 11, and 13; and during the last study follow-up visit at week 17. Plasma concentrations of octreotide and lanreotide were also assessed throughout the study. Assessments of treatment safety and tolerability were based on clinical laboratory tests and vital signs measured at each study visit, and treatment-emergent AEs (TEAEs) monitored on an ongoing basis.

The protocol was amended to begin use of a daily acromegaly symptom diary (ASD) developed by Crinetics Pharmaceuticals in accordance with Food and Drug Administration patient-reported outcome guidance (38). Semi-structured interviews were used to elicit concepts important to patients with acromegaly in the development of the ASD. Symptoms experienced in the previous 24 hours were rated on an 11-point scale, from 0 (no symptom) to 10 (worst symptom). The total ASD score was computed by adding each of the individual symptom intensities (headache pain; joint pain; sweating; fatigue; weakness in legs; swelling; numbness or tingling), therefore the total ASD score can range from 0 to 70, with higher numbers indicating increased symptom burden. Based on patient interviews, the wording pertaining to the swelling item was modified slightly during the course of the study; the initial version referenced swelling in the "hands, arms or legs," while the final version refers to "swelling" in general. No adjustment for difference in the wording for this item was made in the analysis. Patient Global Impression of Improvement (PGI-I) scale was completed at week 13 (end of treatment).

Assays

Serum IGF-I and GH were measured centrally using Immunodiagnostic Systems iSYS (IGF-IRRINT, Boldon) immunoassays. Age- and sex-related reference standards for IGF-I were previously established by Bidlingmaier et al (39), using the iSYS assay and samples from 15 014 patients. The IGF-I assay used National Institute for Biological Standards

Table 1. Patient demographics and baseline characteristics

	Group 1 (n = 25)	Group 2 (n = 10)	Group 3 (n = 5)	Group 4 (n = 4)	Group 5 (n = 3)	Total (N = 47)
Age, y, median (range)	52.0 (31-71)	52.5 (31-70)	51.0 (43-69)	56.0 (46-67)	38.0 (35-66)	51.0 (31-71)
Female, n (%)	11 (44.0)	7 (70.0)	3 (60.0)	3 (75.0)	3 (100)	27 (57.4)
Mo since diagnosis, median (range)	98.2 (23.2-365.1)	116.2 (71.8-194.1)	86.3 (59.8-182.6)	130.4 (110.1-269.6)	84.4 (28.9-143.2)	112.5 (23.2-365.1)
Prior pituitary surgery, n (%)	20 (80.0)	9 (90.0)	4 (80.0)	2 (50.0)	2 (66.7)	37 (78.7)
Pretrial acromegaly treatments						
Lanreotide depot, n (%)	12 (48.0)	3 (30.0)	2 (40.0)	NA	2 (66.7)	19 (40.4)
Patients receiving 60/90/120 mg/mo, n	1/4/7	0/0/3	0/0/2	NA	1/1/0	2/5/12
Octreotide LAR, n (%)	13 (52.0)	7 (70.0)	3 (60.0)	NA	1 (33.3)	24 (51.1)
Patients receiving 10/20/30/40 mg/mo, n	1/0/9/3	0/0/7/0	0/1/1/1	NA	0/0/0/1	1/1/17/5
Cabergoline, n (%)	NA	10	5	NA	NA	15
Weekly dose, mg/wk, median (range)	NA	2.3 (0.5-3.5)	1.5 (0.5-2.0)	NA	NA	2 (0.5-3.5)

No patients had undergone pituitary radiotherapy.
Abbreviations: LAR, long-acting release; NA, not applicable.

(NIBSC) recombinant standard code 02/254 and yielded an intra-assay variability of 1.3% to 3.7%, an interassay variability of 3.4% to 8.7%, and a sensitivity of 8.8 ng/mL (39). The GH assay used NIBSC recombinant standard code 98/574 and yielded an intra-assay variability of 0.9% to 3.8%, an interassay variability of 1.1% to 3.4%, and a sensitivity of 0.04 ng/mL (40). The assays used to assess plasma concentrations of octreotide and lanreotide used a lower limit of quantification (LLOQ) of 100 pg/mL. Values less than the LLOQ were included in the analyses as LLOQ/2 (ie, 50 pg/mL).

Endpoints and Statistical Analyses

End points

The primary efficacy end point was the change in IGF-I from baseline to week 13 or end of paltusotine treatment (EoT, for patients who did not complete treatment) in patients in group 1. Exploratory end points included changes in IGF-I from baseline to each postbaseline time point, including 2 and 4 weeks (weeks 15 and 17, respectively) after treatment discontinuation of paltusotine at week 13, and from EoT to weeks 15 and 17; and changes over time in GH levels and total ASD and PGI-I scores. Safety and tolerability were assessed according to clinical laboratory tests, vital signs, and TEAEs.

Definition of baseline insulin-like growth factor I and growth hormone

Eligibility to participate in the study was based on 2 IGF-I measurements, taken at screening visits 1b (last SRL dose received) and 2 (1-2 weeks after visit 1b) (discussed earlier). For the purposes of efficacy assessments, baseline IGF-I was defined as the mean of all available values before the first dose of study drug (visits 1b, 2, and 3 [day 1, week 1]; see Fig. 1). Baseline GH was defined as the mean of all available measurements taken before the first dose of study drug (ie, at visits 1b and 2).

Determination of sample size

The study was planned to enroll approximately 45 patients, with at least 30 patients in groups 1 and 2 and up to 15 patients in groups 3 to 5. The primary objective of this study was to evaluate efficacy (IGF-I levels) in patients who are partial responders to octreotide LAR or lanreotide depot monotherapy. As such, this sample size was chosen to obtain sufficient clinical experience with paltusotine and descriptively assess treatment effects on IGF-I levels and was not formally powered for hypothesis testing.

Statistical analysis

The primary efficacy analysis was performed for group 1 (efficacy analysis set). Exploratory efficacy analyses were performed for groups 2 to 3 (previously treated with SRL plus dopamine agonist). All treated patients were included in safety analyses. Quantitative end points were summarized using descriptive statistics (eg, nonmissing sample size [n], median, interquartile range [IQR, ie, 25th percentile-75th percentile]). For categorical end points, the count and percentage of patients within each category were presented based on nonmissing data. The primary efficacy analysis and analyses of continuous exploratory end points used the Wilcoxon signed rank test.

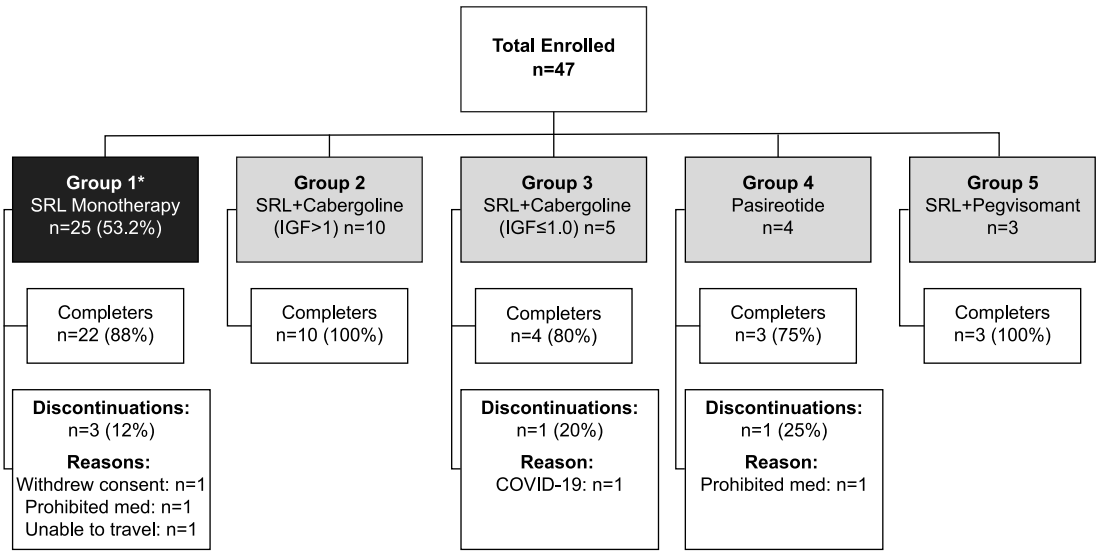

Figure 2. Patient disposition. IGF-I, insulin-like growth factor I; med, medication; SRL, somatostatin receptor ligands. *Efficacy analysis set.

Results

Study Population

ACROBAT Edge was conducted at 26 study sites in the United States, New Zealand, South America, United Kingdom, and Europe. The first patient was enrolled March 12, 2019. The last patient completed the last study visit August 31, 2020. A summary of demographics and baseline characteristics of all patients, by group, is presented in Table 1. No patient received radiation therapy before enrolling in the study. Most patients were taking the highest approved dose of injected SRL before enrolling in the study. In the overall population, the median (IQR) adherence to study treatment was 100% (95.7%-100%) based on days of dosing captured in the daily diaries.

A total of 47 patients (57% female, median age 51 years [range, 31-71 years]) were enrolled, including the 25 patients in group 1 used for the primary efficacy analyses (Fig. 2). Data for exploratory efficacy analyses were provided for patients in groups 2 and 3 (n = 15). Enrollment in groups 4 and 5 (n = 4 and 3, respectively) was too small to draw meaningful conclusions about paltusotine efficacy, but patients in all 5 groups contributed to the data on safety and tolerability. Overall, 89.4% of patients completed the study.

Two patients in group 1 discontinued treatment for the following reasons: use of a prohibited medication, and inability to travel to the study site. An additional group 1 patient completed treatment but withdrew consent during the washout period. One patient discontinued from group 3 (COVID-19–related restriction to site access), and one patient discontinued from group 4 (use of a prohibited medication). No patient withdrew because of an AE.

Efficacy

Group 1

Biochemistry. At baseline, median IGF-I for patients was 1.34× ULN (IQR: 1.08, 1.47× ULN) and remained relatively stable throughout the 13-week paltusotine treatment period (Table 2, Fig. 3); at week 13/EoT, median IGF-I was unchanged from baseline, with a median change of −0.03× ULN (IQR: −0.11 to 0.11× ULN; $P = .6285$) (see Table 2, Figs. 3 and 4a). Of 23 patients who completed the dosing period (2 discontinued during the treatment period), 20 (87%) achieved IGF-I levels at EoT within 20% of baseline or lower (Fig. 4B). Withdrawing paltusotine at week 13/EoT resulted in an increase in median IGF-I levels from EoT to week 17 of 39.0% (IQR: 28.8%-63.3%; $P < .0001$; Fig. 4A). Of 22 patients who completed the study including the washout phase (1 additional patient discontinued during the washout), 18 (82%) showed a meaningful (> 20%) rise from baseline in IGF-I 4 weeks after withdrawal of paltusotine (see Fig. 4B).

At baseline, median integrated GH levels in group 1 were 0.69 ng/mL (IQR: 0.49-1.55 ng/mL) and were unchanged at week 13/EoT (−0.05 ng/mL [IQR: −0.29 to 0.20]; $P = .6285$). Four weeks after withdrawing paltusotine, the group 1 integrated GH had significantly increased from EoT by a median of 109.1% (IQR: 34.7%-325.3%; $P < .0001$; Fig. 5).

Paltusotine dose. By week 13, 18/23 (78%) patients in group 1 who completed the treatment period titrated to the maximal dose of 40 mg/day, 2 ended treatment at 30 mg, 2 at 20 mg, and 1 at 10 mg/day (see Fig. 3). Dose increases were predominantly driven by elevated IGF-I at weeks 2, 5, and 8.

Exploratory groups

Biochemistry. For exploratory groups 2 and 3, the combined enrolled sample size (n = 15) was sufficient to allow pooled analyses of those patients previously treated with an SRL plus dopamine agonist (all treated with cabergoline). Median IGF-I levels were 1.21× ULN (IQR: 0.93-1.50× ULN) at baseline. After discontinuation of cabergoline and conversion from depot SRL to paltusotine, the median change from baseline in IGF-I levels at week 13/EoT was 0.28× ULN (IQR: 0.15-0.99× ULN; $P = .0020$; Fig. 6). At week 17, median IGF-I levels had increased from the week 13/EoT value by 22.1% (IQR: 3.7%-36.7%; $P = .0067$).

Changes in GH were consistent with these IGF-I findings. The median baseline GH for groups 2 and 3 was 1.04 ng/mL (IQR: 0.51-1.61 ng/mL). The median GH increase from baseline to week 13/EoT was 0.68 ng/mL (IQR: 0.10-1.58;

Table 2. Changes in insulin-like growth factor I and growth hormone for patients in groups 1 to 3

Biomarker	Group 1 (n = 25)			Groups 2-3 (n = 15)		
	Baseline	Wk 13/EoT	Wk 17 (4 wk after EoT)	Baseline	Wk 13/EoT	Wk 17 (4 wk after EoT)
IGF-I						
Median (IQR), ×ULN	1.34 (1.08, 1.47)	1.34 (1.17 to 1.45)	2.05 (1.69 to 2.51)	1.21 (0.93 to 1.50)	1.44 (1.09 to 2.08)	2.25 (1.71 to 2.92)
Change, median (IQR)	NA	−0.03 (−0.11 to 0.11)[a]	0.55 (0.41 to 1.02)[b]	NA	0.28 (0.15 to 0.99)[a]	0.30 (0.053 to 0.76)[b]
P	NA	.6285[a]	< .0001[b]	NA	.002[a]	.0166[b]
GH						
Median (IQR), ng/mL	0.69 (0.49 to 1.55)	0.72 (0.48 to 1.75)	1.72 (1.28 to 2.75)	1.04 (0.51 to 1.61)	1.46 (0.62 to 3.65)	2.48 (1.44 to 4.27)
Change, median (IQR)	NA	−0.049 (−0.29 to 0.20)[a]	0.72 (0.21 to 1.92)[b]	NA	0.68 (0.10 to 1.58)[a]	0.58 (0.03 to 1.94)[b]
P	NA	.6285[a]	< .0001[b]	NA	.0067[a]	.0676[b]

P value from Wilcoxon signed rank test.
Abbreviations: EoT, end of treatment; GH, growth hormone; IGF-I, insulin-like growth factor I; IQR, interquartile range: 25th percentile-75th percentile; NA, not applicable; ULN, upper limit of normal.
[a]Change from baseline.
[b]Change from wk 13/EoT.

P = .0067). Four weeks after withdrawing paltusotine, the integrated GH had significantly increased from week 13/EoT by a median of 15.0% (IQR: 1.8%-134.4%; *P* = .0419).

Doses for most patients in groups 2 and 3 were increased to 40 mg/day. Enrollment of patients using pretrial pasireotide LAR monotherapy (group 4, n = 4) or a combination of octreotide LAR or lanreotide depot plus pegvisomant (group 5, n = 3) was too small to reach conclusions regarding paltusotine efficacy in these populations.

Effect of residual long-acting octreotide and lanreotide

In the overall study population, 24 patients switched from octreotide LAR and 19 switched from lanreotide depot. The last SRL dose was received at visit 1b, which occurred 4 weeks before baseline. At visit 1b, the median plasma levels of octreotide and lanreotide pre injection were 590 pg/mL (IQR: 412-964 pg/mL) and 3150 pg/mL (IQR: 2650-4400 pg/mL), respectively. By week 7 (11 weeks after last dose of SRL), median octreotide plasma concentrations had decreased to below the LLOQ (50 pg/mL) and lanreotide concentrations had decreased to 1720 pg/mL (IQR: 1290-2640 pg/mL; 50.1% reduction from baseline). By week 13 (17 weeks after last dose of SRL), lanreotide concentrations further decreased to 824 pg/mL (IQR: 596-1460 pg/mL; 77.3% reduction from baseline).

To evaluate the potential effect of residual octreotide LAR and lanreotide depot on the change from baseline in IGF-I, sensitivity analyses evaluating the octreotide LAR vs lanreotide depot subsets were performed. The median change from baseline in IGF-I values at week 13/EoT in group 1 patients on pretrial lanreotide depot (−0.07× ULN [IQR: −0.16 to 0.01× ULN]; *P* = .0640) was similar to that in group 1 patients on pretrial octreotide LAR (0.01× ULN [IQR: −0.10 to 0.18× ULN]; *P* = .3757). Furthermore, in group 1 the median change in IGF-I levels between weeks 13/EoT and 17 in patients on pretrial lanreotide depot (0.53× ULN [IQR: 0.39-1.15× ULN]; *P* = .0015) was similar to that in those on pretrial octreotide LAR (0.67× ULN [IQR: 0.41-0.82× ULN]; *P* = .0039).

Patient-reported outcomes

Acromegaly symptom scores were observed to remain stable with no statistically significant change following conversion from SRL treatment to paltusotine. Out of a maximally symptomatic score of 70, median baseline total ASD scores were low (median [IQR] = 12.00 [4.21-23.93] n = 20), suggesting low symptom burden at baseline in this study population. Scores showed no significant change from baseline to week 13/EoT (median [IQR] = −0.43 [−5.0 to 2.4], n = 18). Changes in ASD scores during washout compared to EoT were not statistically significant.

Responses to the PGI-I indicated at week 13/EoT, 11 (23.4%) patients had "very much improved" or "much improved," whereas 26 (55.3%) patients had "minimally improved" or reported "no change" compared to before starting the study, while treated with depot SRLs. No patients reported any degree of worsening while treated with paltusotine.

Safety

Paltusotine was generally well tolerated. The most frequently (> 10%) reported AEs were headache, arthralgia, fatigue,

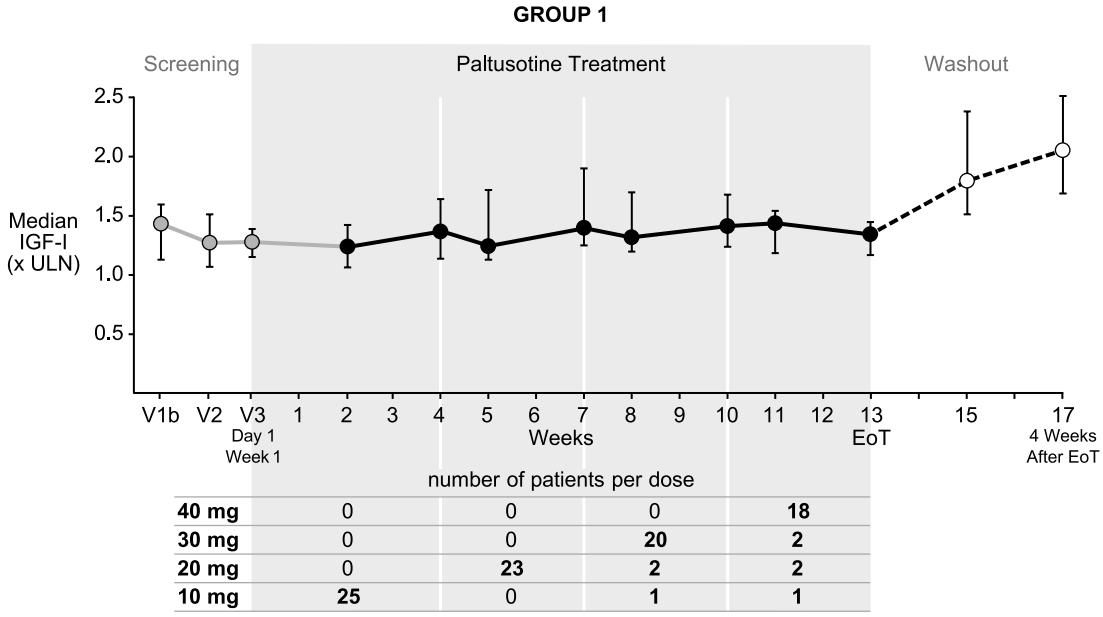

Figure 3. Median (interquartile range) IGF-I levels over time for patients in group 1. EoT, end of treatment; IGF-I, insulin-like growth factor I; ULN, upper limit of normal; V, visit. Efficacy analysis set.

hyperhidrosis, peripheral swelling and paresthesia, and diarrhea (Table 3). No patients required rescue treatment with standard acromegaly medications during the treatment period. No patients discontinued treatment because of TEAEs. One treatment-emergent serious AE (SAE) was reported (hospitalization with headache and rhinosinusitis), which the investigator assessed as unlikely to be related to the study drug. A second serious AE for preexisting (nontreatment emergent) nephrolithiasis was reported that resulted in hospitalization for lithotripsy, considered unrelated to the study drug. No safety signals were observed related to vital signs or clinical laboratory measurements, such as electrocardiogram abnormalities or increases in glycated hemoglobin A_{1c}, liver function tests, or amylase or lipase levels greater than 3× ULN. In particular, there was no evidence for a deterioration of glucose control as measured by serum glucose or glycated hemoglobin A_{1c} during the study.

Discussion

Paltusotine is a small-molecule SST2 agonist selected from the outset to manifest well-defined pharmacology, efficient oral bioavailability, and drug-like characteristics to be a once-daily oral alternative to depot SRL therapy both for acromegaly and neuroendocrine tumors. The previously reported phase 1 study of paltusotine demonstrated suppression of GH-releasing hormone–stimulated GH and IGF-I in healthy volunteers to an extent similar to that seen with octreotide (34, 36) The data reported in this first-in-patient study showed that acromegaly patients converted to paltusotine monotherapy maintained IGF-I and GH levels across 13 weeks of treatment at those previously achieved with injected SRL depots. This finding suggests that paltusotine at the maximum dose studied of 40 mg once daily was associated with a similar degree of IGF-I suppression as injected SRLs (see Fig. 4A).

Discontinuation of paltusotine at the completion of the scheduled 13 weeks of therapy resulted in a prompt and significant rise both in IGF-I and GH levels indicative that the patients had "active" acromegaly and that there was no substantial residual effect from the previous depot SRL therapy, which had been administrated approximately 21 weeks previously. Serum octreotide levels were undetectable by week 7 of paltusotine therapy (11 weeks after last dose of octreotide LAR) and reductions of more than 75% in lanreotide concentrations at week 13 (17 weeks after last pretrial lanreotide depot dose) were seen. Although some effect of this residual lanreotide cannot be ruled out definitively, these concentrations were insufficient to prevent robust increases in IGF-I and GH after paltusotine withdrawal. It should be noted that previous registrational lanreotide depot clinical trials in patients with acromegaly generally allowed for a 3-month washout time (15, 41).

In addition to the primary analysis population (group 1, n = 25), acromegaly patients using more intensive pretrial regimens (groups 2-5) were explored in this study. Following the combination of data from cohort 2 (elevated IGF-I at study entry) and cohort 3 (IGF-I < 1 × ULN at study entry) patients who had received octreotide LAR or lanreotide depot plus cabergoline before the trial (n = 15) showed a small but statistically significant increase in median IGF-I concentrations when switched from combination therapy to paltusotine monotherapy, followed by a significant and more robust increase in IGF-I during the 4 weeks after discontinuation of paltusotine of 22% (see Fig. 6). The modest initial rise in IGF-I is consistent with the previously reported effect of cabergoline therapy in acromegaly (42), while the increase seen on discontinuation of paltusotine is consistent with the effect seen in patients on SRL monotherapy (group 1) at study entry. Only 3 and 4 patients respectively were recruited into groups 4 (pasireotide LAR monotherapy) and 5 (depot SRL plus pegvisomant), respectively, and no efficacy analysis was undertaken. Data from all 47 patients were included in the safety analysis.

All patients commenced paltusotine at 10 mg once daily and most patients were titrated to the maximum dose of 40 mg by the EoT period (week 13), paralleling the reductions

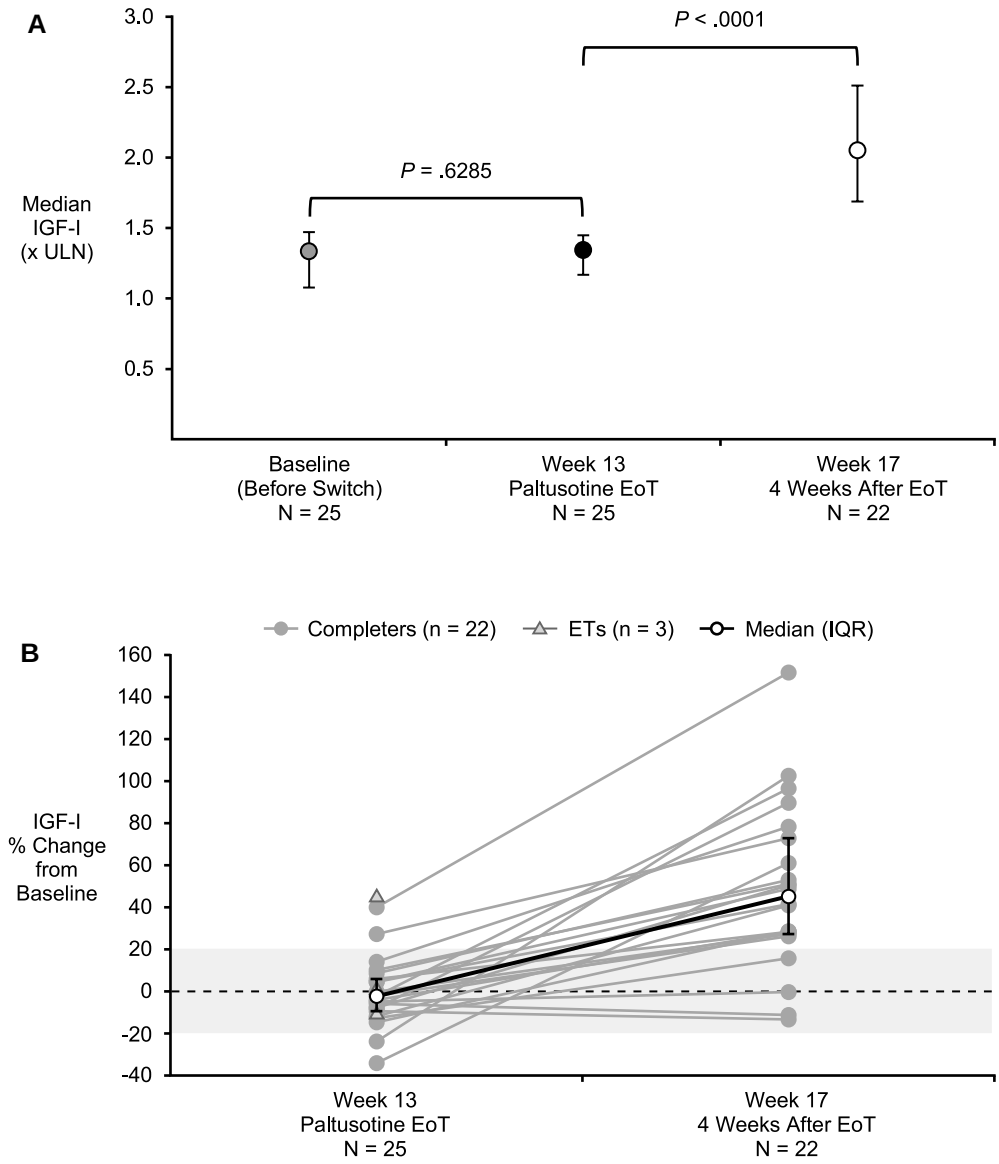

Figure 4. Median IGF-I levels for patients in group 1 at baseline, treatment week 13 (end of treatment, EoT), and 4 weeks after EoT (week 17). A, Median ± IQR IGF-I levels for patients in group 1 at baseline, week 13 (EoT), and 4 weeks after EoT (week 17). B, Percentage change in IGF-I from baseline to EoT and 4 weeks after EoT for individual patients in group 1. ETs, patients who terminated treatment early; IGF-I, insulin-like growth factor I; IQR, interquartile range; ULN, upper limit of normal. Efficacy analysis set. Baseline was calculated as a mean of the measurements from screening visits 1b and 2 and predose week 1. Data are presented as median (interquartile range: 25th percentile-75th percentile) EoT was defined as week 13 (visit 14) or the last on-treatment value for those who discontinued treatment. Four weeks after EoT was defined as week 17 or at least 22 days after the last dose. The shaded area represents expected biologic variability associated with IGF-1 measurements. *P* values were based on nonparametric Wilcoxon sign rank test of whether the median change was different from zero.

in the serum concentrations of depot SRLs. At week 13, 18 of the 23 patients who completed the treatment period were on the 40 mg/day dose. Analyses of pooled data from the various studies in humans, combined with exposure-response modeling, suggest a paltusotine dose of 40 mg/day is likely to achieve IGF-I suppression consistent with that achieved by depot SRLs for most patients with acromegaly (43). The capsules used in this study are not suitable for delivering larger doses of paltusotine. In the phase 3 PATHFNDR studies of paltusotine in acromegaly (NCT05192382 and NCT04837040), a spray-dried, dispersion immediate-release tablet will be used that will allow a higher dose of 60 mg for individuals in whom a therapeutic drug concentration is not achieved with the starting 40 mg dose. In addition, adoption of the spray-dried, dispersion tablet will enable the interval between taking the tablet and eating to be reduced from the 2 hours specified in this study to 1 hour (44).

This study includes the first use of the ASD, which is an exploratory tool being developed according to Food and Drug Administration recommendations. As might be expected with the maintenance of IGF-I levels, patient-reported acromegaly symptoms including the ASD remained stable after switching from depot SRLs to paltusotine. Preliminary data suggest a utility for the ASD in further clinical trials (Martin et al in review). Double-blind, placebo-controlled trials are needed to better evaluate the magnitude and duration of acromegaly symptom control associated with paltusotine therapy. The ability of ASD to capture changes in patient symptoms with treatment-induced changes in IGF-I will also be evaluated in phase 3 trials.

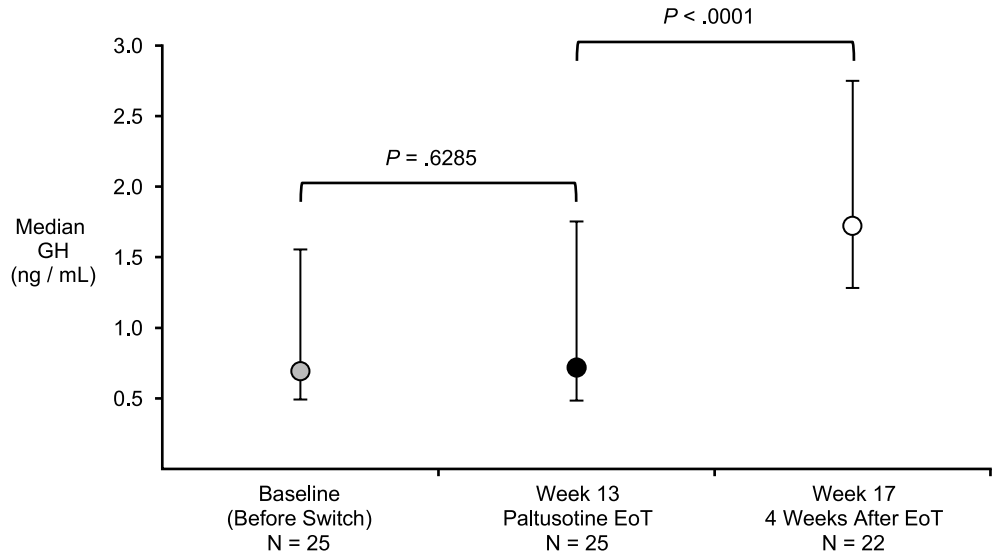

Figure 5. Median ± IQR GH levels for patients in group 1 at baseline, treatment week 13 (end of treatment, EoT), and 4 weeks after EoT (week 17). Efficacy analysis set. Baseline was calculated as a mean of the integrated GH measurements from screening visits 1b and 2 and treatment week 1. Data are presented as median (interquartile range: 25th percentile-75th percentile). EoT was defined as week 13 (visit 14) or the last on-treatment value for those who discontinued treatment. EoT was defined as week 17 or result at least 22 days after last dose. *P* values were based on the nonparametric Wilcoxon sign rank test of whether the median change is different from zero. EoT, end of treatment; GH, growth hormone.

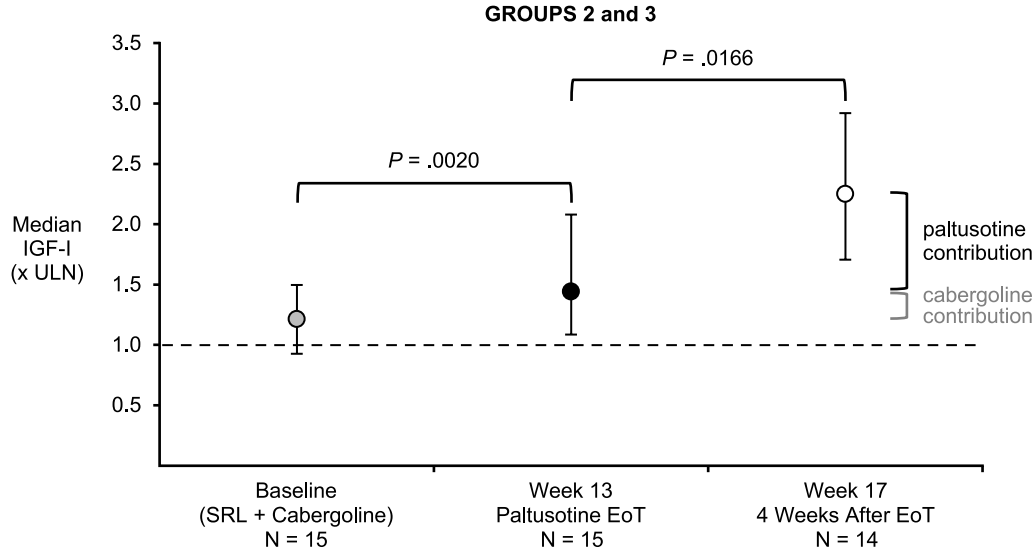

Figure 6. Median ± IQR IGF-I levels for patients treated with SRL + cabergoline (groups 2 and 3) at baseline, treatment week 13 (end of treatment, EoT) and 4 weeks after EoT (week 17). Baseline was calculated as a mean of the measurements from screening visits 1b and 2 and treatment week 1. Data are presented as median (interquartile range: 25th percentile-75th percentile). EoT was defined as week 13 (visit 14) or the last on-treatment value for those who discontinued treatment. Four weeks after EoT was defined as week 17 or at least 22 days after the last dose. *P* values were based on the nonparametric Wilcoxon sign rank test of whether the median change was different from zero. EoT, end of treatment; IGF-I, insulin-like growth factor I; SRL, somatostatin receptor ligands; ULN, upper limit of normal.

Paltusotine was well tolerated in this study with no patients withdrawing because of AEs. The most frequently reported AEs were headache, arthralgia, fatigue, hyperhidrosis, peripheral swelling and paresthesia, and diarrhea. These symptoms are characteristic of underlying acromegaly or are known side effects of SRL therapy (37, 45).

The limitations of the data presented here are its short duration (13 weeks) and the absence of medically untreated patients with active acromegaly. The ongoing open-label ACROBAT Advance extension study (NCT04261712) has provided insights into the long-term safety, tolerability, and efficacy of paltusotine, with the initial readouts being consistent with the safety and efficacy data presented here (46). The phase 3 PATHFNDR studies are designed to provide further, placebo-controlled insights into paltusotine safety and efficacy in patients currently controlled with pharmacotherapy, and in medically naive or otherwise not medically treated patients.

In conclusion, the results of this study suggest that once-daily, oral paltusotine was effective at maintaining IGF-I values in patients with acromegaly who switch from injected SRL therapy. Paltusotine appears to be well tolerated

Table 3. Treatment-emergent adverse events occurring in more than 5% of patients in groups 1 to 5 (safety set)

TEAE[a]	No. (%) of patients (N = 47)
Headache[b]	15 (31.9)
Arthralgia	13 (27.7)
Fatigue	10 (21.3)
Hyperhidrosis	9 (19.1)
Paresthesia	7 (14.9)
Peripheral swelling	7 (14.9)
Diarrhea	5 (10.6)
Abdominal discomfort	4 (8.5)
Abdominal pain	4 (8.5)
Abdominal distension	3 (6.4)
Back pain	3 (6.4)
Dyspepsia	3 (6.4)
Sleep apnea syndrome	3 (6.4)

Abbreviation: TEAE, treatment-emergent adverse event.
[a]By Medical Dictionary for Regulatory Activities version 21.1 (MedDRA)-preferred term.
[b]One serious TEAE of headache was reported, deemed by the investigator to be unlikely related to paltusotine treatment. See text for additional detail.

with a safety profile consistent with the SRL class of therapeutics. These data have informed the design of the phase 3 PATHFNDR clinical program in acromegaly and initial studies in patients with neuroendocrine tumors. If the efficacy and safety of paltusotine are confirmed, it is possible that paltusotine represents an alternative to injectable SRLs as a treatment for patients with acromegaly.

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Disclosures

M. R. Gadelha has served as an advisory board member for Ipsen, Novartis Pharmaceuticals, Novo Nordisk, Recordati Rare Diseases, and Crinetics Pharmaceuticals; as a research investigator for Crinetics Pharmaceuticals, Recordati Rare Diseases, and Novartis Pharmaceuticals; and as a speaker for Crinetics Pharmaceuticals, Novartis Pharmaceuticals, Ipsen, Novo Nordisk, and Recordati Rare Diseases. M. B. Gordon received research support from Ascendis, Camurus, Chiasma, Corcept, Crinetics, Ipsen, Novartis, Opko, Pfizer, Strongbridge, and Novo Nordisk and served as a scientific consultant for Crinetics, Recordati Rare Diseases, HRA Pharma and Novo Nordisk. M. Doknic, E. Mezősi, and H. Randeva have served as research investigators for Crinetics Pharmaceuticals. M. Tóth has received consulting fees from Novartis, Ipsen, Recordati and Pfizer, and has served as a research investigator for Crinetics Pharmaceuticals. A. Madan was Chief Development Officer of Crinetics Pharmaceuticals at the time of manuscript development and is now a Drug Development consultant, San Diego, CA, to Crinetics Pharmaceuticals. T. Marmon, President, Marmon Biostatistics, Seattle, WA, served as a Biometrics consultant to Crinetics Pharmaceuticals. T. Jochelson, President, Rancho Clinical Research Consulting, Rancho Santa Fe, CA, served as a Clinical Research consultant to Crinetics Pharmaceuticals. A. Madan, T. Marmon and T. Jochelson have received consulting fees from Crinetics Pharmaceuticals. R. Luo, M. Monahan, C. Ferrara-Cook, R. S. Struthers and A. Krasner are employees of Crinetics Pharmaceuticals.

Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

Clinical Trial Information

ClinicalTrials.gov registration number NCT03789656 (registered December 27, 2018).

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