Long-Term Treatment with Oral Paltusotine for Acromegaly: Results from the ACROBAT Advance study

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Introduction

- Paltusotine is a once daily, oral, nonpeptide, somatostatin receptor agonist highly selective for subtype 2 receptor currently being evaluated for the treatment of acromegaly and carcinoid syndrome.
- ACROBAT Advance (NCT04261712) is an ongoing, phase 2, non-randomized, multi-center, open-label, long-term extension study to evaluate long-term paltusotine safety and efficacy data.

Subjects

- Eligible subjects have participated in the previously reported phase 2 parent studies, ACROBAT Edge (EudraCT 2018-002230-20) or Evolve (EudraCT 2018-001833-42).
- The study enrolled 43 (88%) of 49 eligible subjects.
- Paltusotine therapy: initiated at 10 mg/day and titrated up to maximum dose of 40 mg/day based on IGF-1 and tolerability. Combination therapy allowed for subjects not reaching therapeutic targets with 40 mg/day of paltusotine monotherapy.
- Interim results from a data snapshot as of June 16, 2022 are presented.

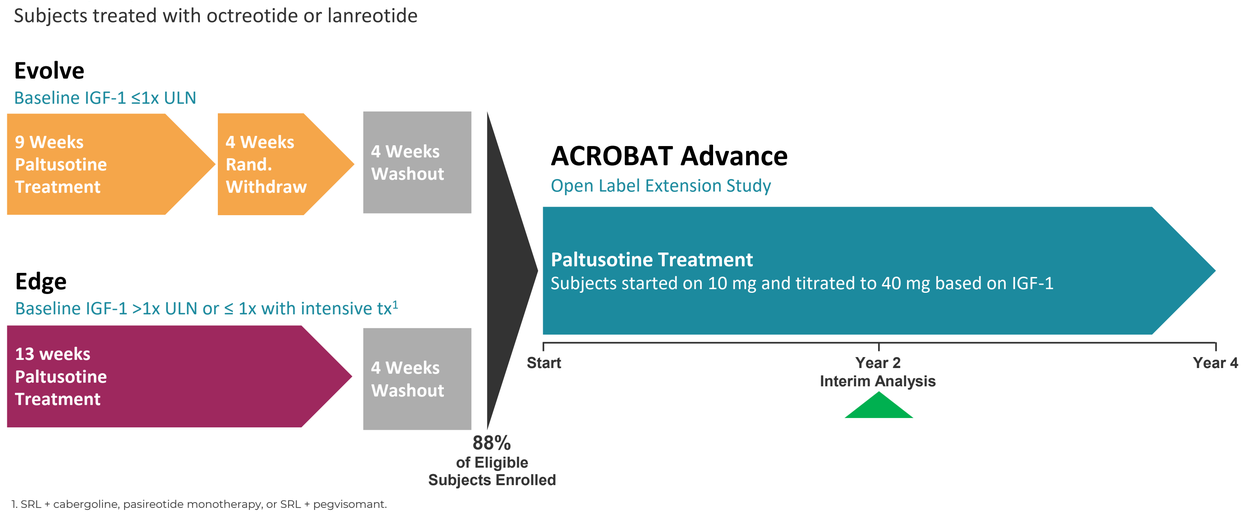
Table 1. Baseline Characteristics

	All Subjects N=43
Age, Mean (SD)	53.0 (11.61)
Sex, Female, n (%)	24 (55.8)
Months since diagnosis, Mean (SD)	129.4 (78.42)
Prior pituitary surgery, n (%)	37 (86.0)
Pre-trial medical treatment[1]	
Lanreotide, n - 60/90/120 mg/month	1/2/14
Octreotide, n - 20/30/40 mg/month	3/17/3
Pasireotide (Edge), n - 40/60 mg/month	1/1
SRL + Cabergoline (Edge), n	10
Pegvisomant (Edge), n - 20 mg/week	1

1. Pre-trial is defined as prior to parent trial for direct rollovers and prior to ACROBAT Advance for delayed rollovers

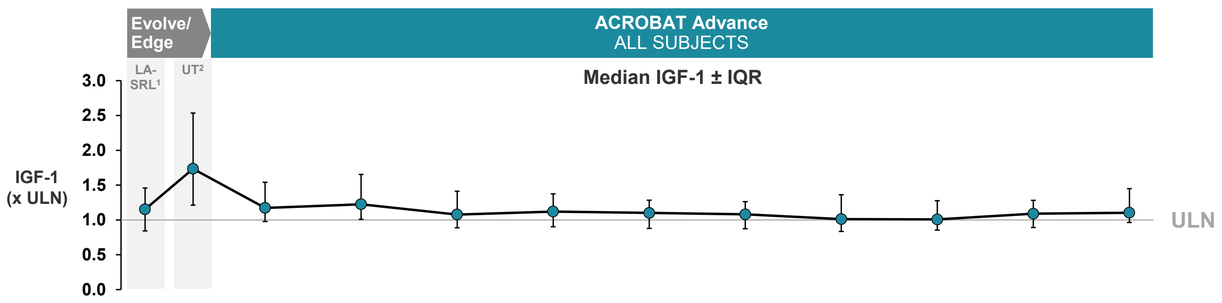
Results

Figure 1. Subjects from Parent Trials Enrolled into ACROBAT Advance



1. SRL + cabergoline, pasireotide monotherapy, or SRL + pegvisomant.

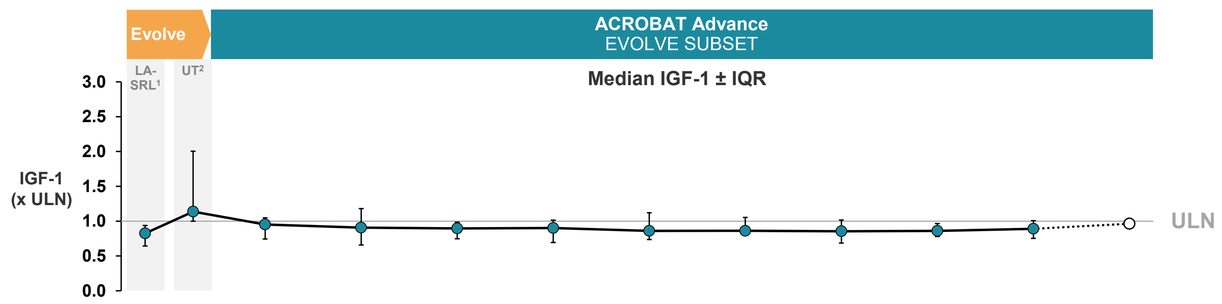
Figure 2. IGF-1 Levels IGF-1 Maintained at Injected LA-SRL Baseline Levels After Switching to Paltusotine from Injected SRLs (all subjects)



Week	3	15	31	39	47	51	64	77	90	103
N 43 43	43	42	39	37	38	37	31	27	21	10
Cumulative Discons.	0	0	2	3	3	3	5	6	6	6
Median Paltusotine Dose (mg)	10	30	40	40	40	40	40	40	40	40
Cabergoline Use (n)	0	1	4	8	14	15	13	11	10	5

1. Baseline (screening) from Evolve/Edge studies while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve/Edge studies.
Pegvisomant was added in two Edge subjects. One subject was on pegvisomant at Weeks 77 and 90. The other subject does not have measured IGF-1 after starting pegvisomant.

Figure 3. IGF-1 Maintained at Injected LA-SRL Baseline Levels in Subjects Who Previously Participated in ACROBAT Evolve (Controlled with LA-SRL Monotherapy at Baseline)



Week	3	15	31	39	47	51	64	77	90	103
N 11 11	11	11	11	11	11	11	8	7	4	1
Cumulative Discons.	0	0	0	0	0	0	2	3	3	3
Median Paltusotine Dose (mg)	10	20	20	30	30	30	20	20	15	20
Cabergoline Use (n)	0	0	0	0	1*	0	0	0	0	0

1. Baseline (screening) from Evolve/Edge studies while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve studies.
* Subject discontinued due to investigator decision 4 weeks after starting cabergoline. At the time of discontinuation, this subject's IGF-1 was 1.0xULN. IGF-1 for 2 additional Evolve subset subjects who discontinued from the study were 1.2x and 0.9xULN at the time of discontinuation.

Subject's Treatment Preference

- At 52 weeks in the study (or at the last visit for those who discontinued the study), participants were asked to choose their preferred treatment option.
- Thirty-two (89%) of respondents preferred once daily paltusotine, two (5.5%) had no preference, and two (5.5%) preferred the previous injections.

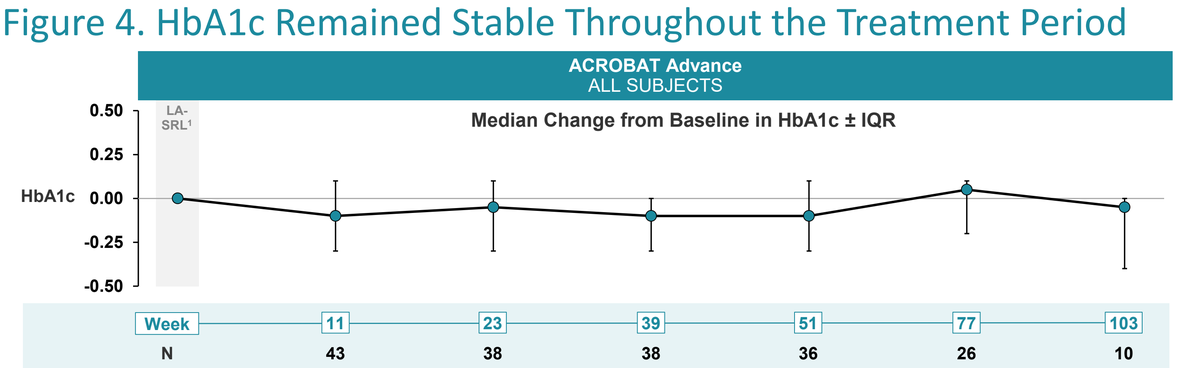
Paltusotine Was Well Tolerated

Table 2. TEAEs Occurring in ≥3 Subjects

TEAEs	Any Dose N=43 n (%) m
Headache	13 (30.2) 20
Arthralgia	11 (25.6) 22
Fatigue	8 (18.6) 13
Corona virus infection	7 (16.3) 7
Diarrhea	5 (11.6) 5
Hyperhidrosis	5 (11.6) 7
Myalgia	5 (11.6) 6
Paresthesia	5 (11.6) 8
Anxiety	4 (9.3) 5
Dizziness	4 (9.3) 4
Peripheral swelling	4 (9.3) 9
Hypertension	3 (7.0) 3
Hypotension	3 (7.0) 4

- During the study, there were 6 nontreatment-related TESAEs in 5 subjects: gallstone pancreatitis, worsening of coronary artery disease followed by sinus arrest post coronary artery bypass surgery, renal mass, deep vein thrombosis, and arthralgia (elective surgery for worsening of pre-existing hip pain).
- There were 6 discontinuations: 3 from the Evolve group (physician decision, subject preference, and inability to fulfill study procedures) and 3 from the Edge group (1 adverse event- headache, 1 pregnancy, 1 withdrawn consent).
- Of 36 subjects who had pituitary MRIs performed during the study, 33 showed no change in comparison with baseline. Two subjects had slight pituitary tumor size reductions. One subject with no visible tumor at baseline was found to have a 5-mm lesion 13 months following the baseline MRI.
- No safety signals seen in clinical laboratories, including HbA1c, LFTs, ECGs, no amylase/lipase elevations >3x ULN.

Figure 4. HbA1c Remained Stable Throughout the Treatment Period



Week	11	23	39	51	77	103
N	43	38	38	36	26	10

1. LA-SRL timepoint is last HbA1c while on injected SRL therapy.

Conclusions

- Once daily, oral paltusotine lowered and maintains IGF-1 at levels comparable to prior injected SRL therapy for up to 103 weeks. This was seen in all subsets of subjects representing a wide range of baseline disease control.
- Paltusotine was well tolerated in this phase 2 study with a safety profile similar to that of injected SRLs, including when used in combination with adjunctive therapy.
- Most subjects prefer once-daily oral paltusotine over injected SRLs.

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