Long-Term Efficacy and Safety of Oral, Once-Daily Paltusotine Treatment in Acromegaly: Two-Year Interim Results From the ACROBAT Advance Study

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SfE BES 2022 - Conflict of Interest

Name: Harpal Randeva

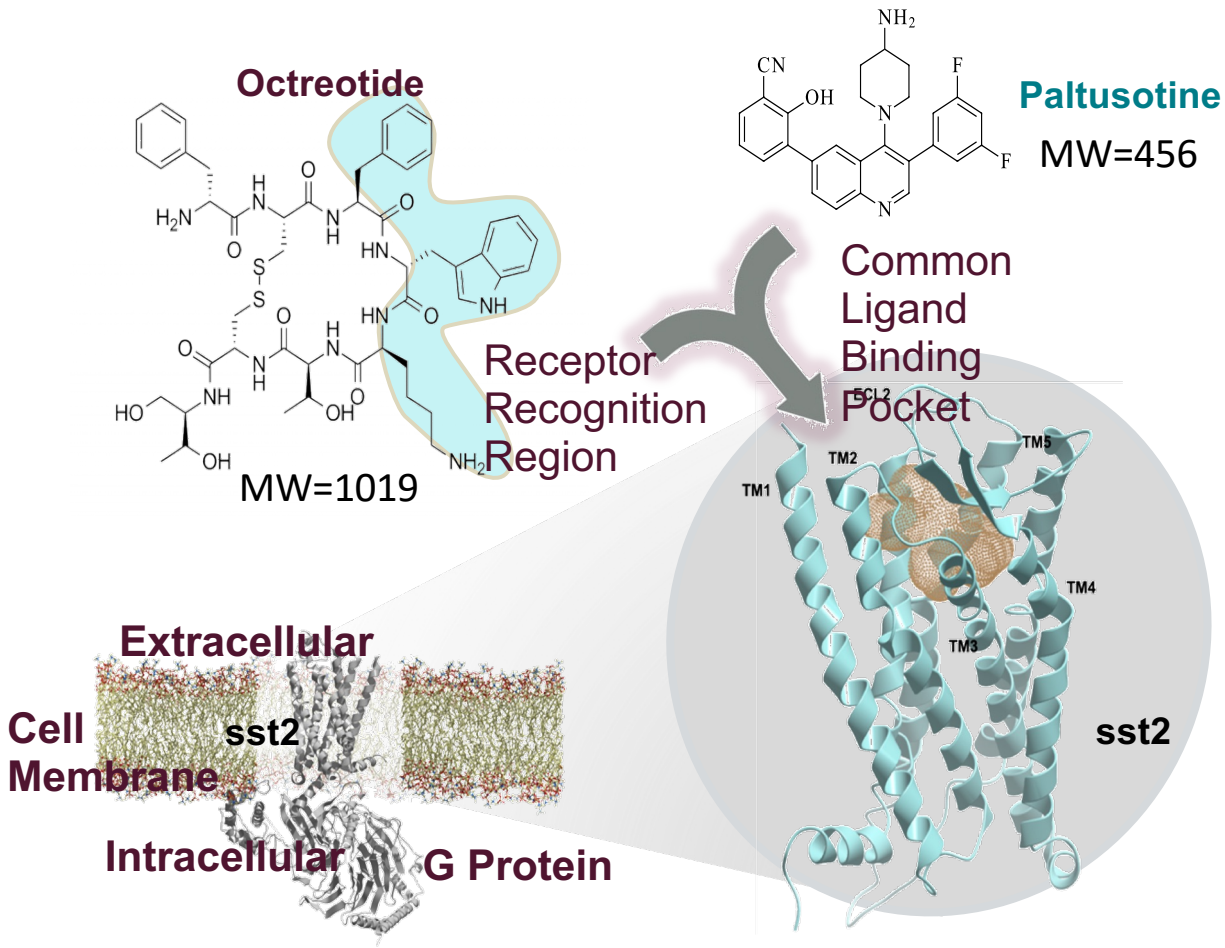
√ I have the following potential conflicts of interest to report:

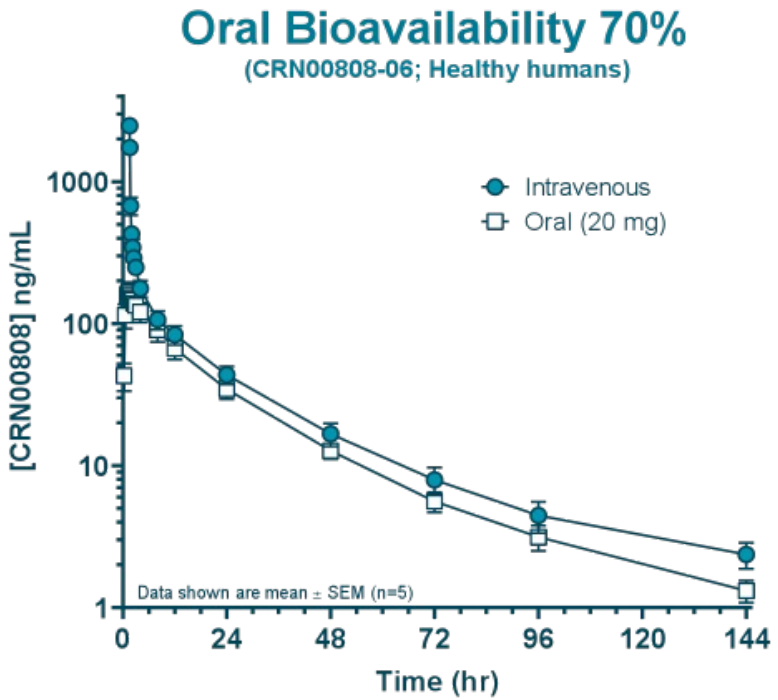
√ Research Contracts

Presenter: Peter Trainer, VP Clinical Endocrinology, Crinetics Pharmaceuticals

Employee and stockholder

Paltusotine an oral, small non-peptide somatostatin agonist, highly selective to SST2





Paltusotine (CRN00808)	
High Oral Bioavailability	70%
Long Observed Half Life	42-50 h

One-a-day dosing

ACROBAT Edge & Evolve: Phase 2 studies in acromegaly

EDGE Results - ENDO 2021 Presentation

Evolve—Median Dose 20 mg/day

Primary Population

Patients treated with octreotide or lanreotide & baseline **IGF-1 ≤1x ULN**

n=13

	Screening	Paltusotine Treatment												Randomized Withdrawal if IGF ≤ 1.0				Washout			
WEEK	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
							10 mg			20 mg			30 mg										

Evolve enrollment stopped April 2020, based on positive Edge results

Edge—Median Dose 40 mg/day

Primary Population

Patients treated with octreotide or lanreotide & baseline **IGF-1 >1x ULN**

n=25

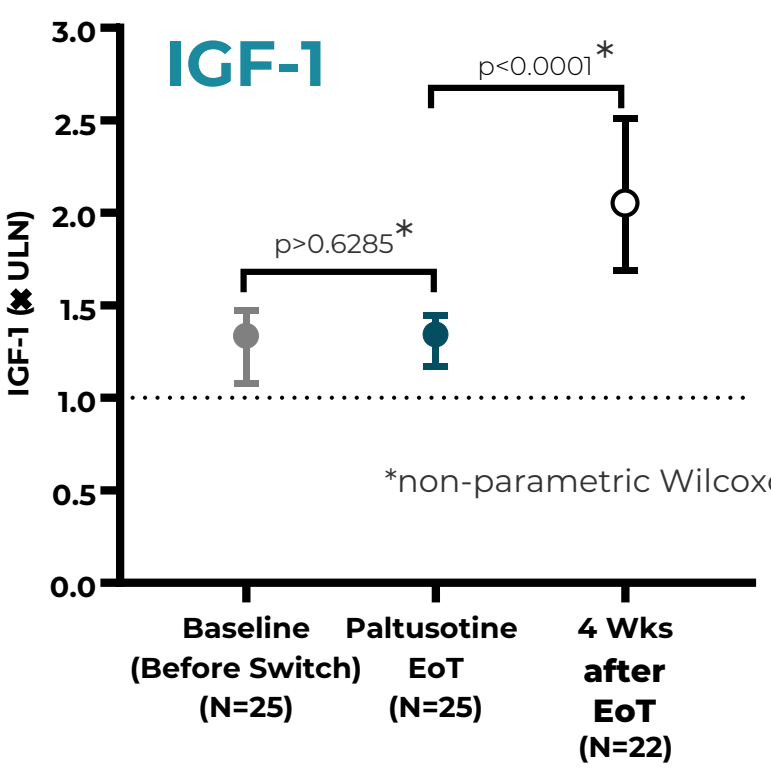
	Screening	Paltusotine Treatment																Washout			
WEEK	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
							10 mg			20 mg			30 mg			40 mg							

Exploratory population (groups 2-5; n=22): uncontrolled subjects on SRL + CAB or ≤ IGF-1 1x with intensive therapy

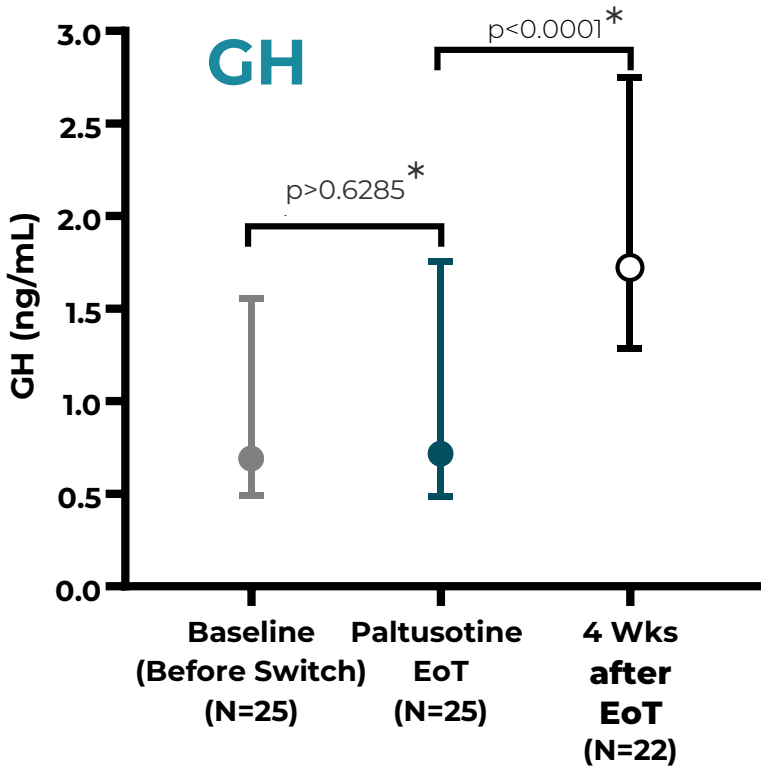
ACROBAT Edge: Paltusotine maintained IGF-1 and GH levels for 13 weeks after switching from injected SRL peptide depots

Results from the Primary Population (Group 1) of the Edge study

median (Interquartile Range [IQR]: 25th, 75th percentiles)



*non-parametric Wilcoxon Sign Rank test



EoT = End of Treatment defined as Week 13 or last on treatment value carried forward (LOCF).

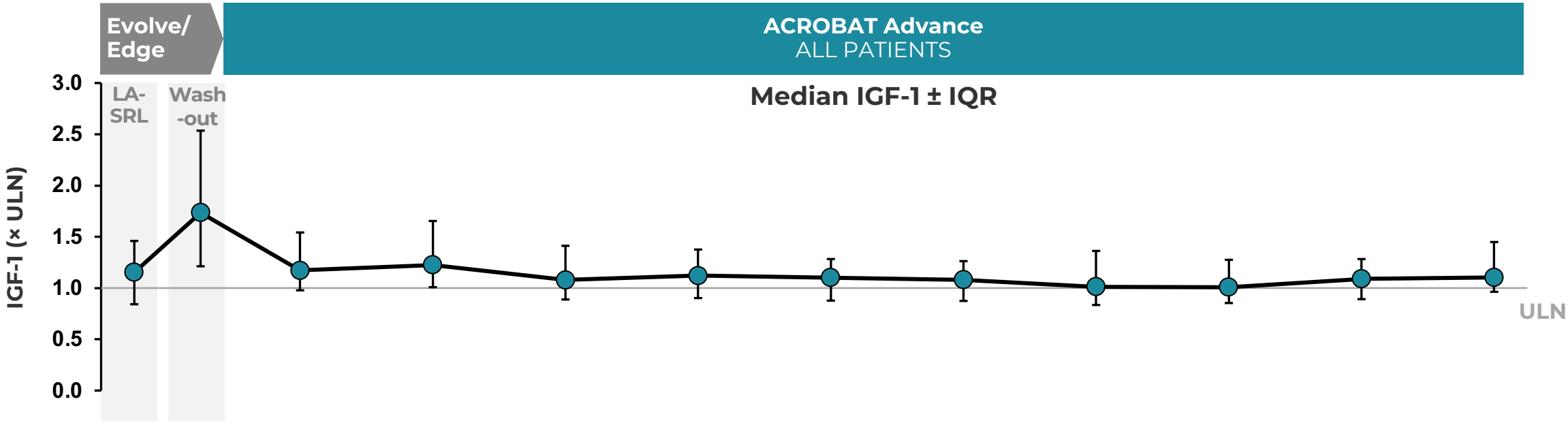
ACROBAT Advance: Open label extension study design

To evaluate long-term safety and efficacy of paltusotine in the treatment of patients with Acromegaly

Interim results; for up to 2 years

	Screening Period	Expected titration period			Long-Term Dosing Period							
WEEK	-4 up to W1	1	4	8	12	16	24	32	40	48	52	65 to 208
	ACROBAT Evolve and Edge completers enter after a 4-week washout period	Paltusotine re-initiated Dose titration: 10→40 mg/day based on IGF-1			Paltusotine dose maintenance Cabergoline add-on permitted to paltusotine 40 mg (expected in patients from ACROBAT Edge) and pegvisomant							

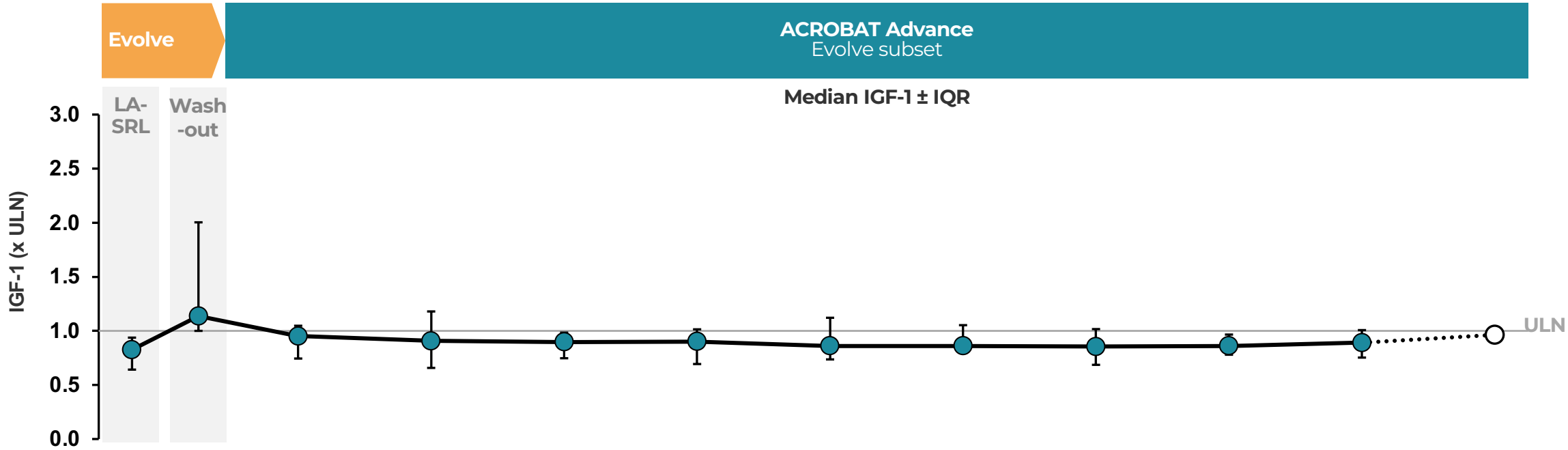
IGF-1 Maintained at Baseline Levels After Switching to Paltusotine From Injected SRLs (All Patients)



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 discontinuations	0	0	2	3	3	3	5	6	6	6
Medium 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

- 94% of the patients receiving adjunctive medication in Advance study either had IGF-1 sub-optimally controlled or required combination therapy or pasireotide in order to achieve normal IGF-1 at the parent study baseline
- Includes 1 patient treated with pegvisomant

IGF-1 Maintained at Baseline Levels in Patients Who Previously Participated in ACROBAT Evolve



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 discontinuations			0	0	0	0	0	0	2	3	3	3
Medium 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

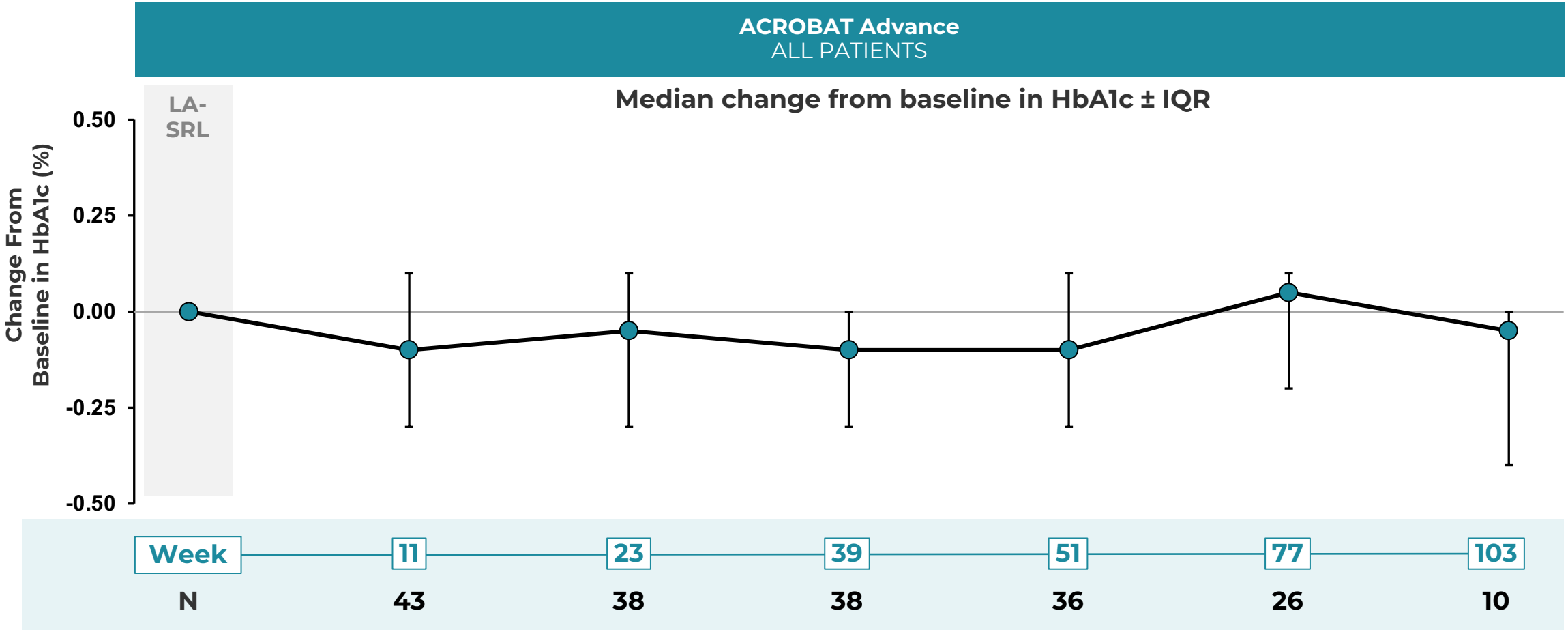
*Patient discontinued due to investigator decision 4 weeks after starting cabergoline. At the time of discontinuation, IGF-1 1.0xULN. 2 additional patients discontinued, IGF-1 values were 1.2x and 0.9x ULN at the time of discontinuation.

Safety Summary

Adverse events, n (%) m	Any dose (N=43)
Any AE	36 (83.7) 249
AEs Occurring in ≥3 patients	
Headache	13 (30.2) 20
Arthralgia	11 (25.6) 22
Fatigue	8 (18.6) 13
Coronavirus 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

- 6 serious AEs in 5 patients: gallstone pancreatitis, worsening of coronary artery disease followed by sinus arrest, renal mass, deep vein thrombosis, and arthralgia (elective hip replacement)
  - No serious AEs were treatment-related
- 6 discontinuations from the study: 3 from Evolve group (physician decision; patient preference; inability to fulfill study procedures) & 3 from Edge group (AE [headache]; pregnancy; withdrew consent)
- 36 patients had pituitary MRIs
  - 33 showed no change in tumor size
  - 2 patients had slight reduction in pituitary tumor size
  - 1 patient 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, and ECG, and no amylase/lipase elevations >3x ULN

HbA1c Remained Stable Throughout Paltusotine Treatment Period



Conclusions

- Once daily, oral paltusotine lowered and maintained IGF-1 at levels comparable to prior injected SRL therapy for up to 103 weeks
  - This was observed in all subsets of patients 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
- At Week 52, thirty-two (88.9%) of the 36 respondents preferred once daily paltusotine treatment

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