Paltusotine Shows Long-term Safety and IGF-1 Maintenance in the ACROBAT Advance Study

Mônica R. Gadelha for the ACROBAT Study Group

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ACROBAT Study Author Group

Monica R. Gadelha, MD, PhD[1]; Murray B. Gordon, MD[2]; Mirjana Doknic, MD, PhD[3]; Emese Mezősi, MD, PhD, DSci[4]; Miklós Tóth, MD, PhD, DSci[5]; Cesar Boguszewski[6] ;Harpal Randeva, MBChB, FRCP, FAcadTM, PhD[7]; Marcello D. Bronstein, MD, PhD[8]; Christine Ferrara-Cook, MD, PhD[9]; Alessandra Casagrande, MD, PhD[9]; Alan Krasner, MD[9].

[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, [4]University of Pécs Medical School, Pécs, Hungary, [5]Semmelweis University, Budapest, Hungary, [6]SEMPR, Endocrine Division, Department of Internal Medicine, Federal University of Parana, Curitiba, Brazil[7]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, United Kingdom, [8]Neuroendocrine Unit, Division of Endocrinology and Metabolism, Hospital das Clinicas, University of Sao Paulo, Sao Paulo, Brazil,

[9]Crinetics Pharmaceuticals Inc., San Diego, CA, USA.

Disclosures

- ✓ Principal investigator - clinical trials: Crinetics, Novartis and Recordati Rare Diseases
- ✓ Speaker fee: Crinetics, Novo Nordisk, Ipsen, Recordati Rare Diseases, Novartis
- ✓ Advisory board member: Recordati Rare Diseases, Crinetics, Ipsen, Novo Nordisk
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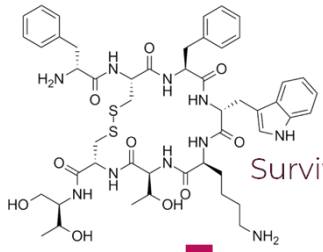
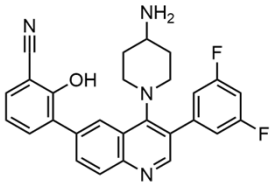
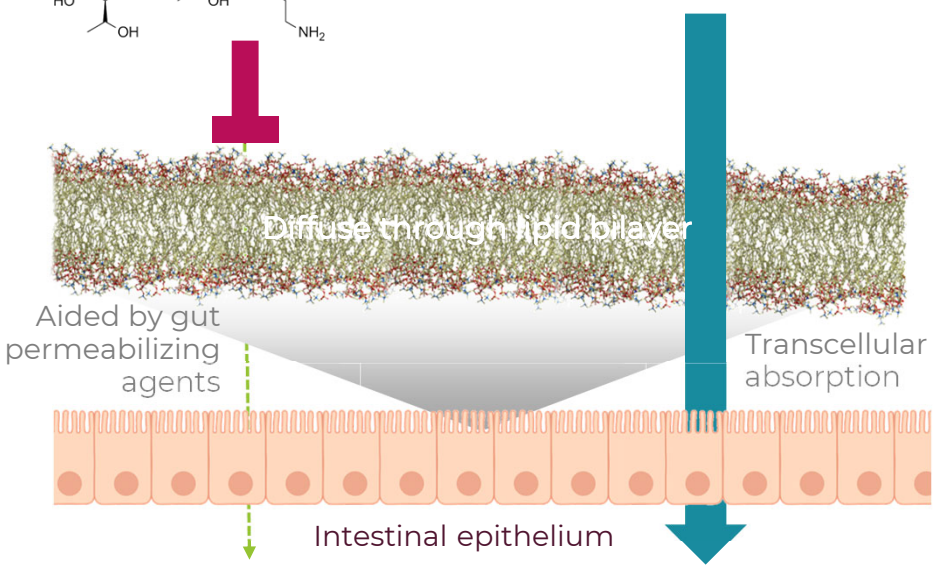
Paltusotine: an oral, small non-peptide somatostatin agonist, highly selective to SST2

Peptide: Octreotide



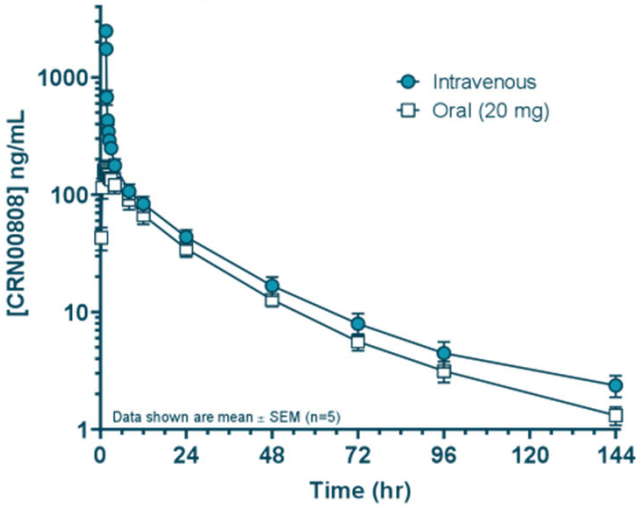
Nonpeptide: paltusotine





Oral Bioavailability 70%

(CRN00808-06; Healthy humans)



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

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

Subjects 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

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

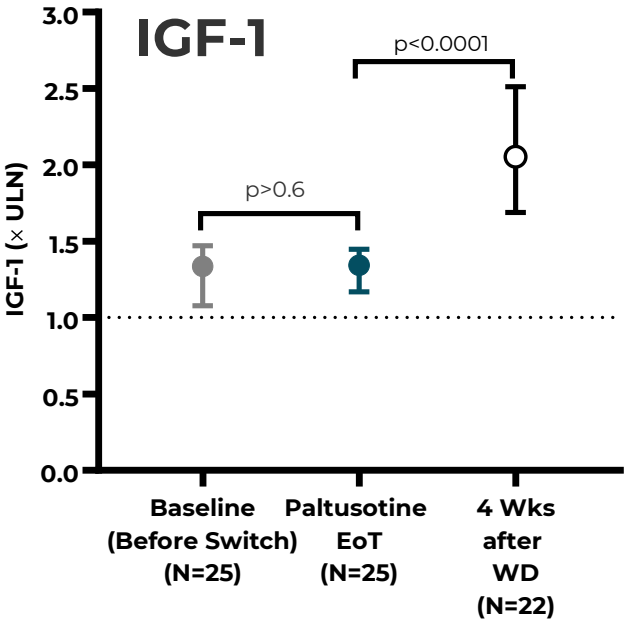
n=25

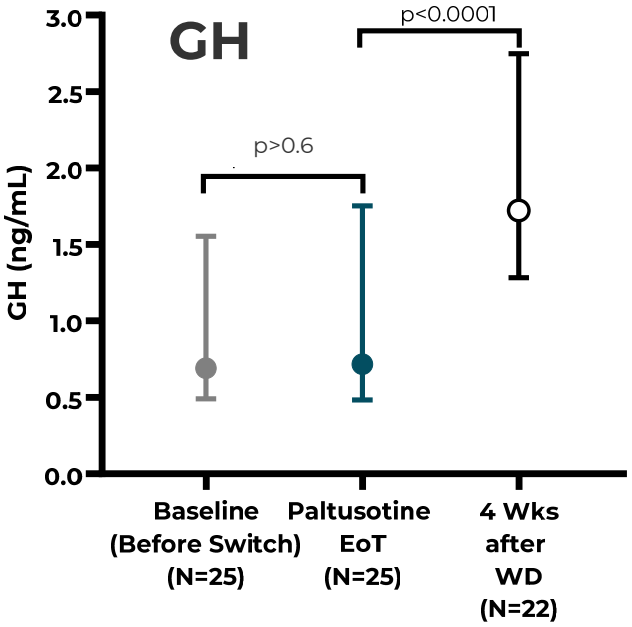
	Screening						Paltusotine Treatment													Washout			
WEEK	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
							10 mg			20 mg			30 mg			40 mg							

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

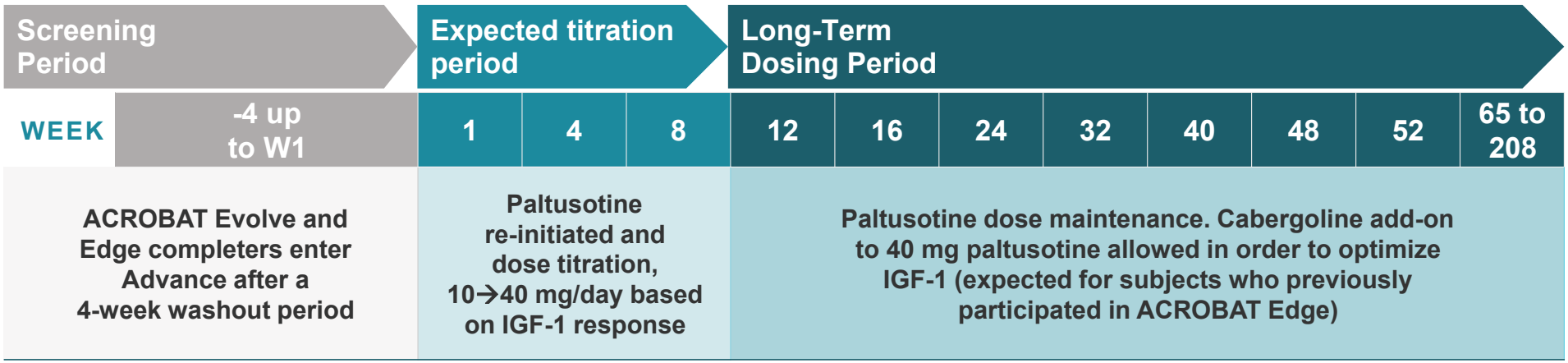
Results from the Primary Population (Group 1) of the Edge study





Data presented are median (Interquartile Range [IQR]: 25th percentile, 75th percentile) EoT = End of Treatment defined as Week 13 (Visit 14) or last on treatment value carried forward (LOCF). Wks after WD is defined as Week 17 or result at least 22 days after last dose.
Note: p-values are based on non-parametric Wilcoxon Sign Rank test of whether the median change is different from zero.

ACROBAT Advance:
Open label extension study design



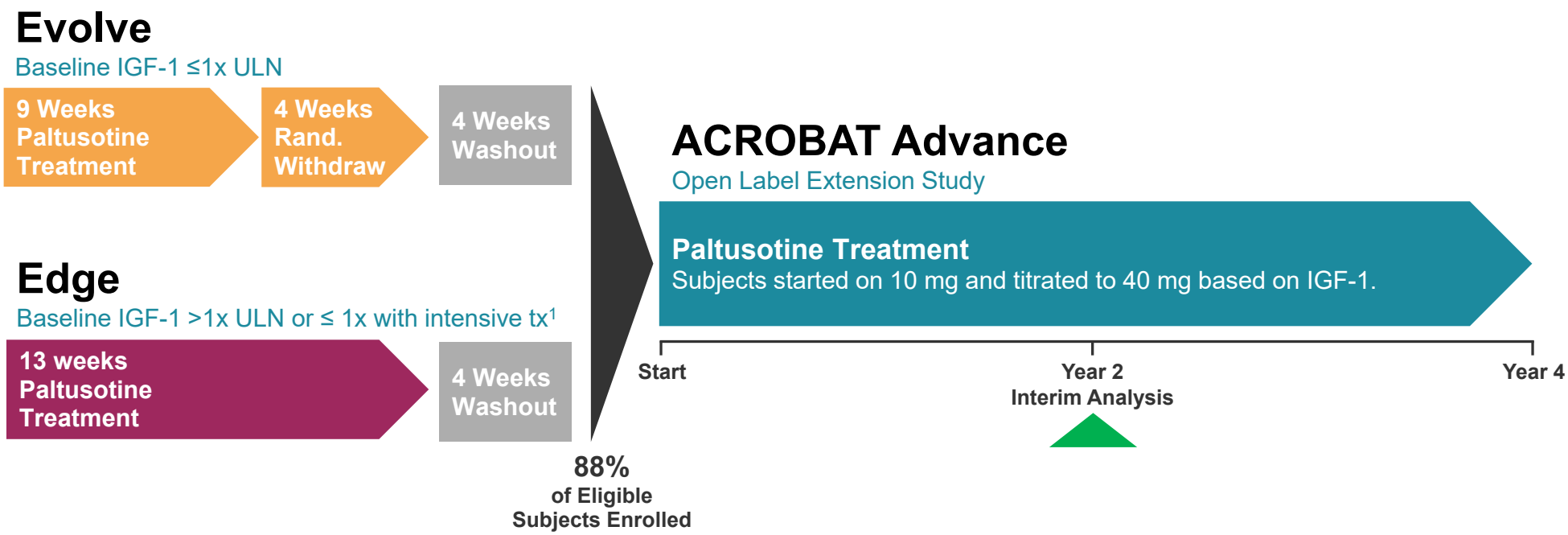
Baseline Characteristics ACROBAT Advance

	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.

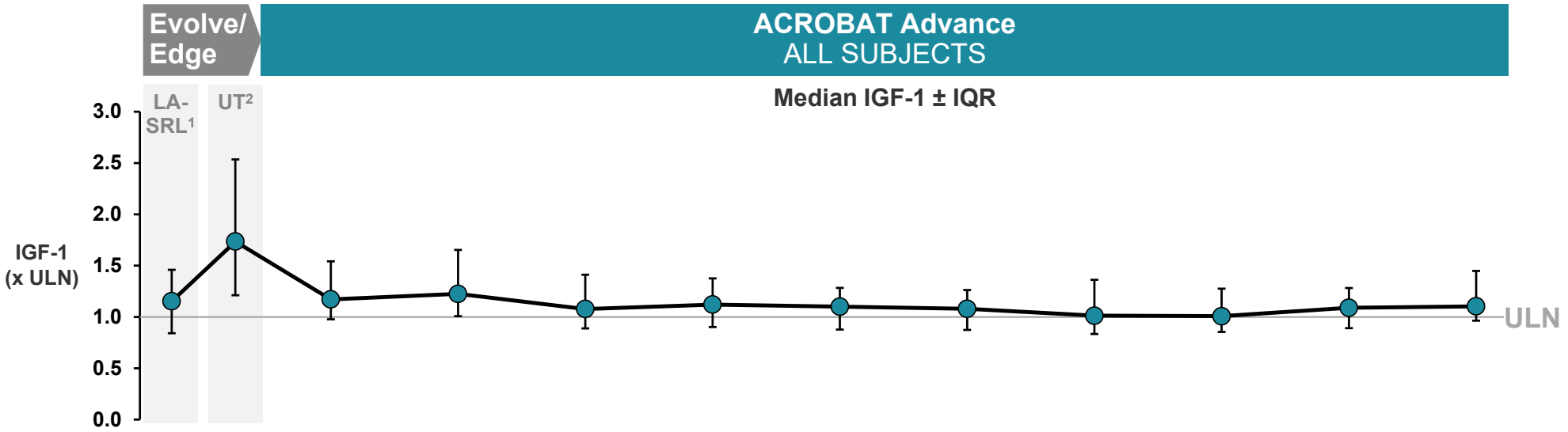
Subjects from Parent Trials Enrolled into ACROBAT Advance

Primary Population
Subjects treated with octreotide or lanreotide



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

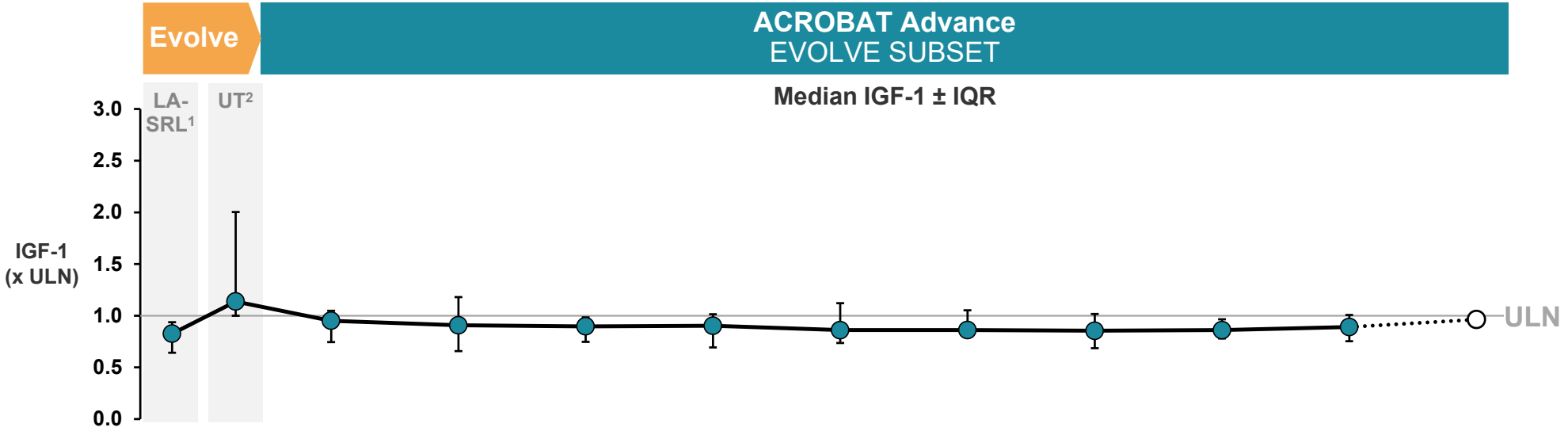
IGF-1 Levels IGF-1 Maintained at Injected LA-SRL Baseline Levels After Switching to Paltusotine from Injected SRLs (all subjects)



Week	LA-SRL[1]	UT[2]	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
Med. 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.

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	LA-SRL[1]	UT[2]	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
Med. 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.

Subjects' 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

Safety Summary

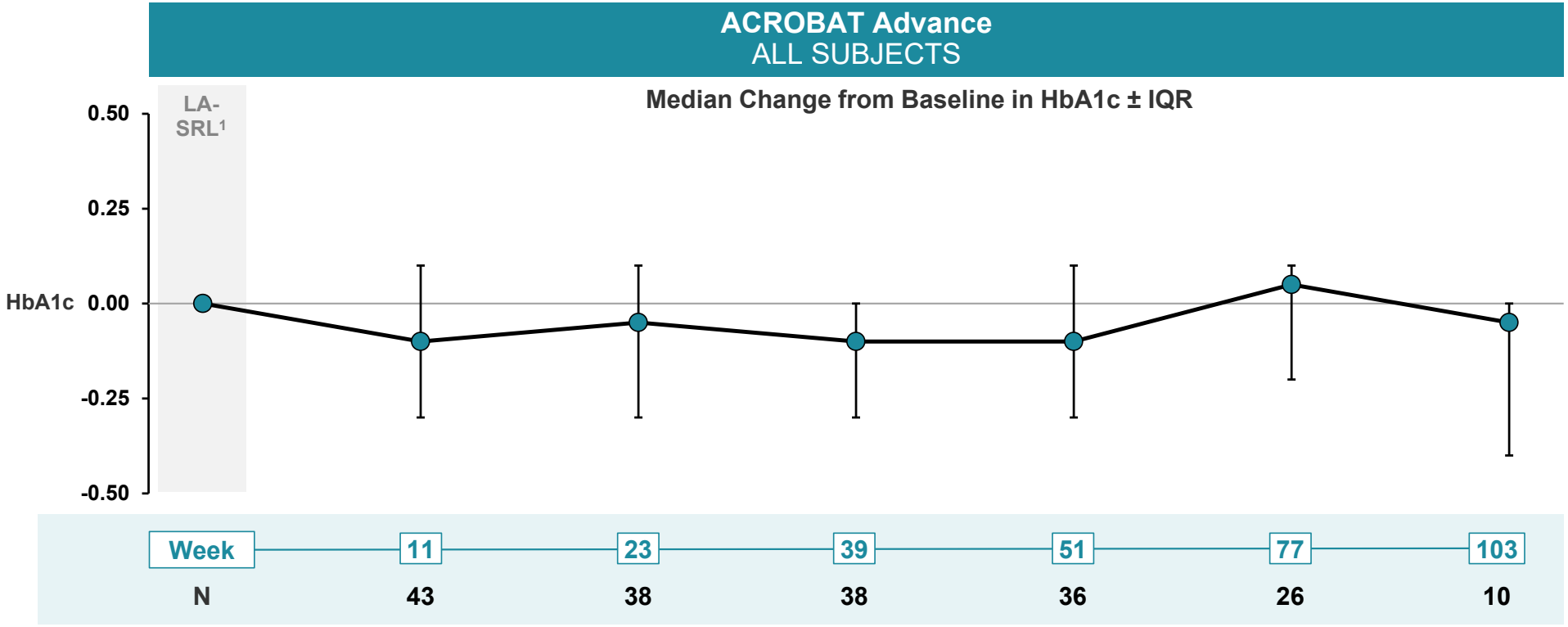
TEAEs Occurring in ≥3 subjects

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.

n = The number of unique subjects per preferred term. m = The number of occurrences for each preferred term. TEAE= treatment emergent adverse events.
The safety population is comprised of all subjects who have received at least one dose in ACROBAT Advance.

HbA1c Remained Stable Throughout the Treatment Period



1. Baseline (screening) from Evolve/Edge studies 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.

Acknowledgements

Thank you to the patients, nurses and investigators who made this study possible!