Once daily, oral nonpeptide somatostatin receptor type 2 (SST2) specific agonist paltusotine was associated with long-term toleration and efficacy in patients with acromegaly enrolled in ACROBAT Advance, a phase 2 open label extension study

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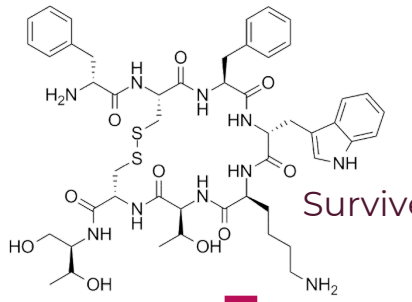
Disclosure

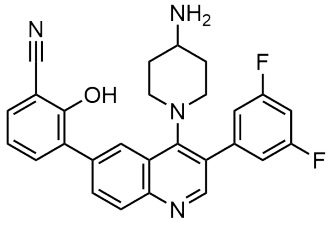
- ✓ Principal investigator - clinical trials: Crinetics, Novartis and Recordati Rare Diseases
- ✓ Speaker fee: Crinetics, Novo Nordisk, Ipsen, Recordati Rare Diseases, Novartis
- ✓ Advisory board member: Recordati Rare Diseases, Crinetics, Ipsen, Novo Nordisk

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

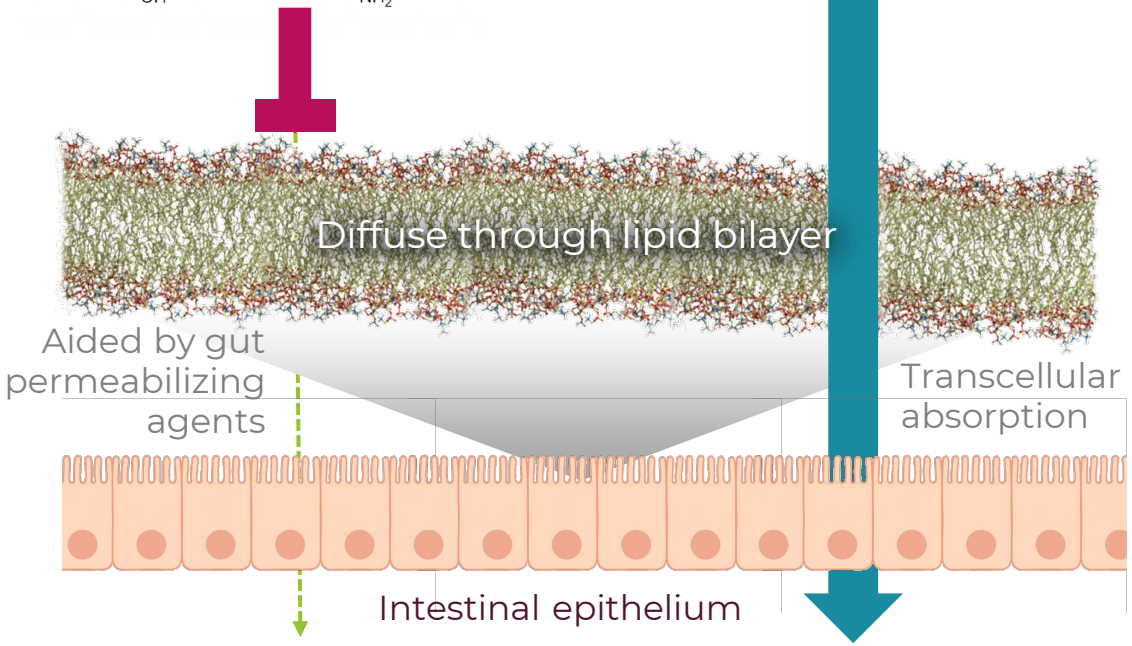
Peptide: Octreotide



Nonpeptide: paltusotine

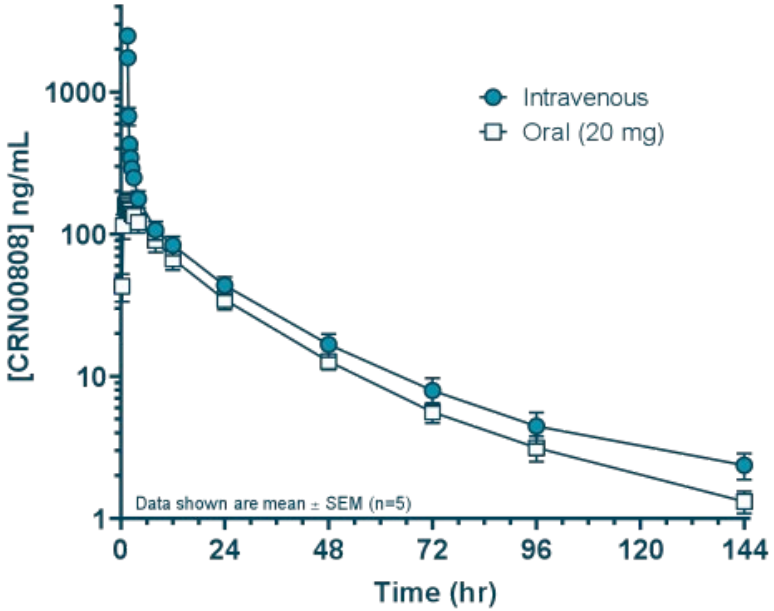


Survive proteolysis



Oral Bioavailability 70%

(CRN00808-06; Healthy humans)



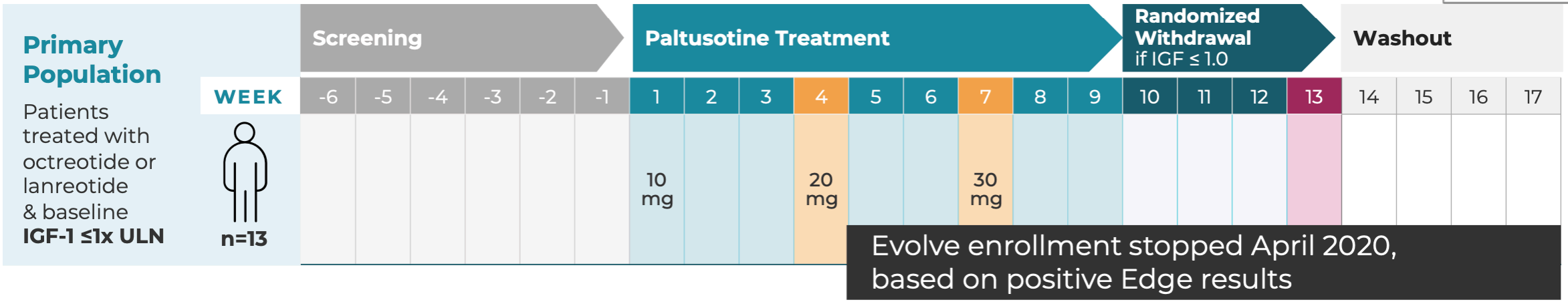
Paltusotine (CRN00808)	
High Oral Bioavailability	**70%**
Long Observed Half Life	**42-50 hr.**

One-a-day dosing

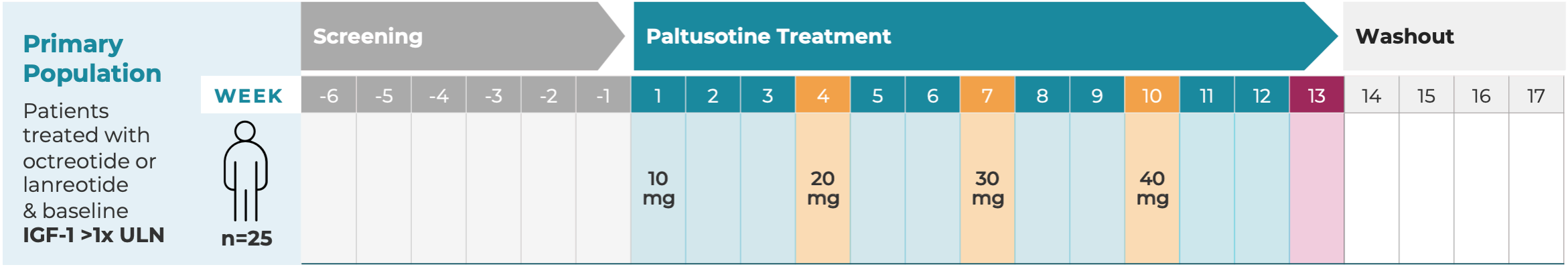
ACROBAT Edge & Evolve: Phase 2 studies in acromegaly

EDGE Results - ENDO 2021 Presentation

Evolve—Median Dose 20 mg/day



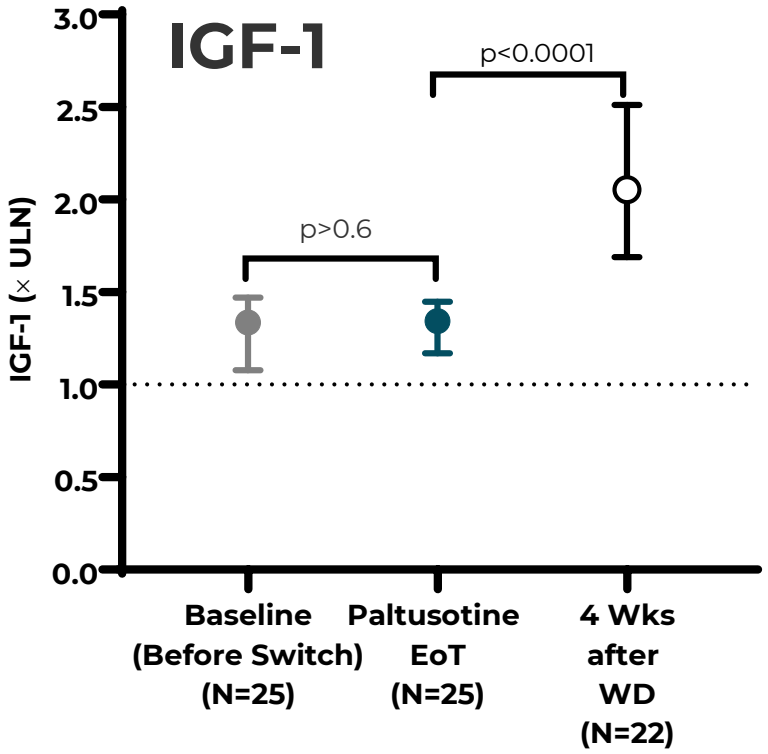
Edge—Median Dose 40 mg/day

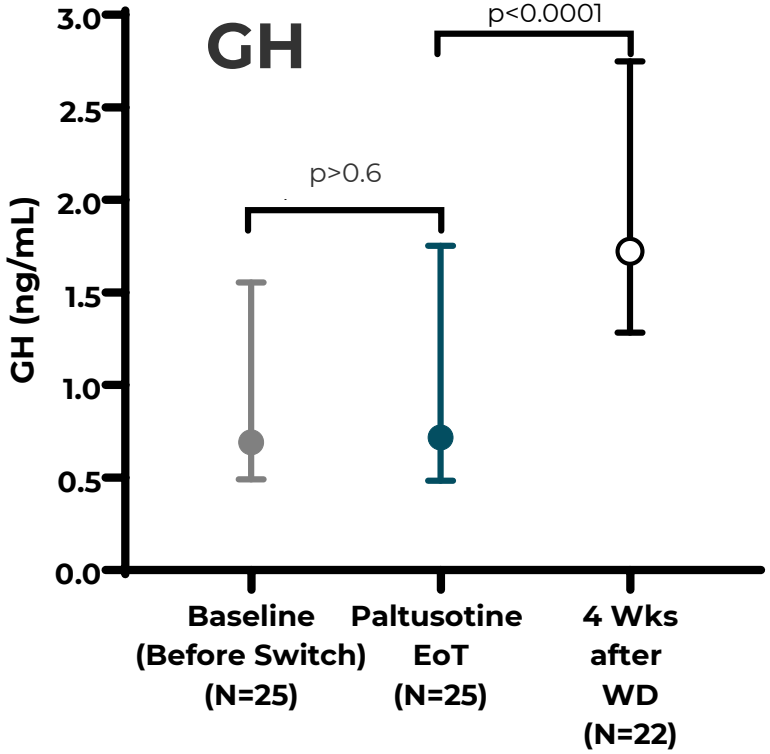


Exploratory population (groups 2-5; n=22): uncontrolled patients on SRL + CAB or ≤ IGF-1 1x with intensive therapy

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.

EVOLVE and EDGE → ACROBAT Advance

ongoing open label extension study of EVOLVE and EDGE plan to last for 4 years.

Population entering parent trials

Patients treated with LA-SRLs

Evolve

Baseline IGF-1 ≤1x ULN

9 Weeks Paltusotine Treatment → **4 Weeks Rand. Withdraw** → **4 Weeks Washout**

Edge

Baseline IGF-1 >1x ULN or ≤ 1x with intensive tx[1]

13 weeks Paltusotine Treatment → **4 Weeks Washout**

Eligible patients:
Patients that completed the previous phase 2 studies

ACROBAT Advance

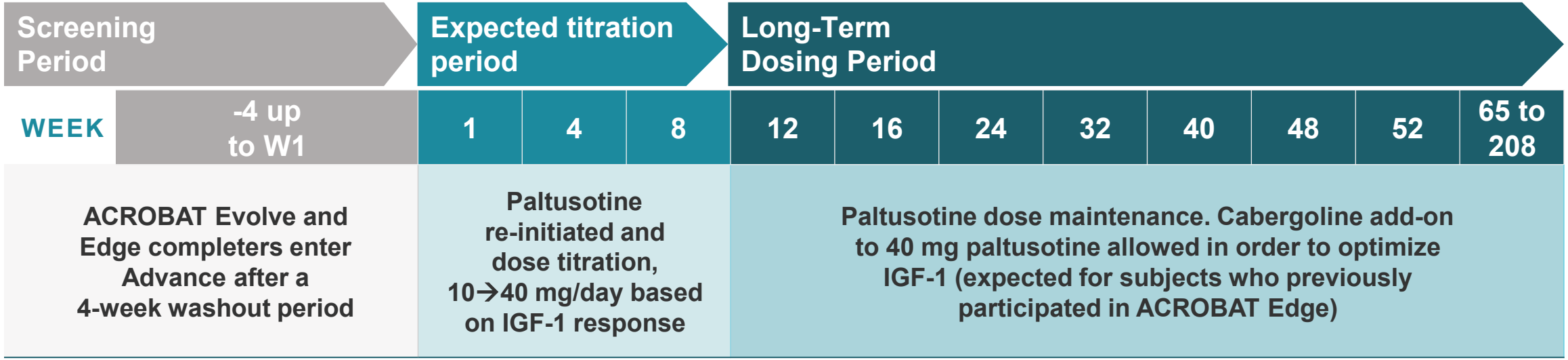
Open Label Extension Study

Up to 4 years of Paltusotine Treatment

Patients started on 10 mg and titrated to 40 mg based on IGF-1

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

ACROBAT Advance: Open label extension study design



Baseline characteristics (data cut off: Aug, 2021)
ACROBAT Advance patients

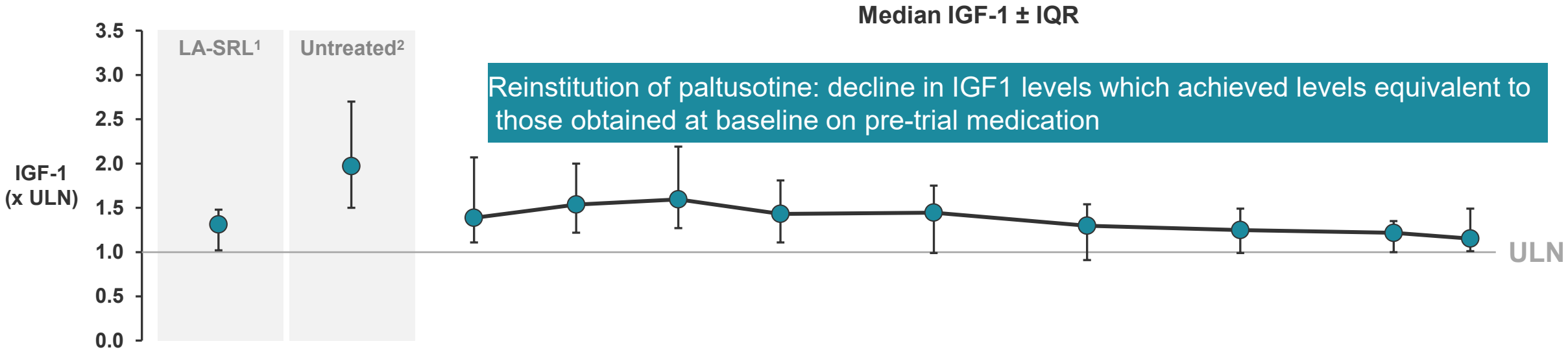
	All Patients N=41
Age, Mean (SD)	**53.2 (11.5)**
Sex, Female, n (%)	**23 (56.1)**
Months since diagnosis, Mean (SD)	**129.7 (79.8)**
Prior pituitary surgery, n (%)	**35 (85.4)**
Pre-trial medical treatment[1]	
Lanreotide, n - 60/90/120 mg/month	**1/2/13**
Octreotide, n - 20/30/40 mg/month	**3/16/3**
Pasireotide (Edge), n - 40/60 mg/month	**1/1**
SRL + Cabergoline (Edge), n	**10**
Pegvisomant (Edge), n - 20 mg/week	**1**

long standing diagnosis

1. Pre-trial is defined as prior to parent trial for direct rollovers and prior to ACROBAT Advance for delayed rollovers.
As of the time of this data cut off (Aug, 2021) the study has enrolled 41 of 49 eligible patients (84%).

IGF-1 levels on paltusotine treatment for up to 51 weeks (from patients previously enrolled in EDGE study)

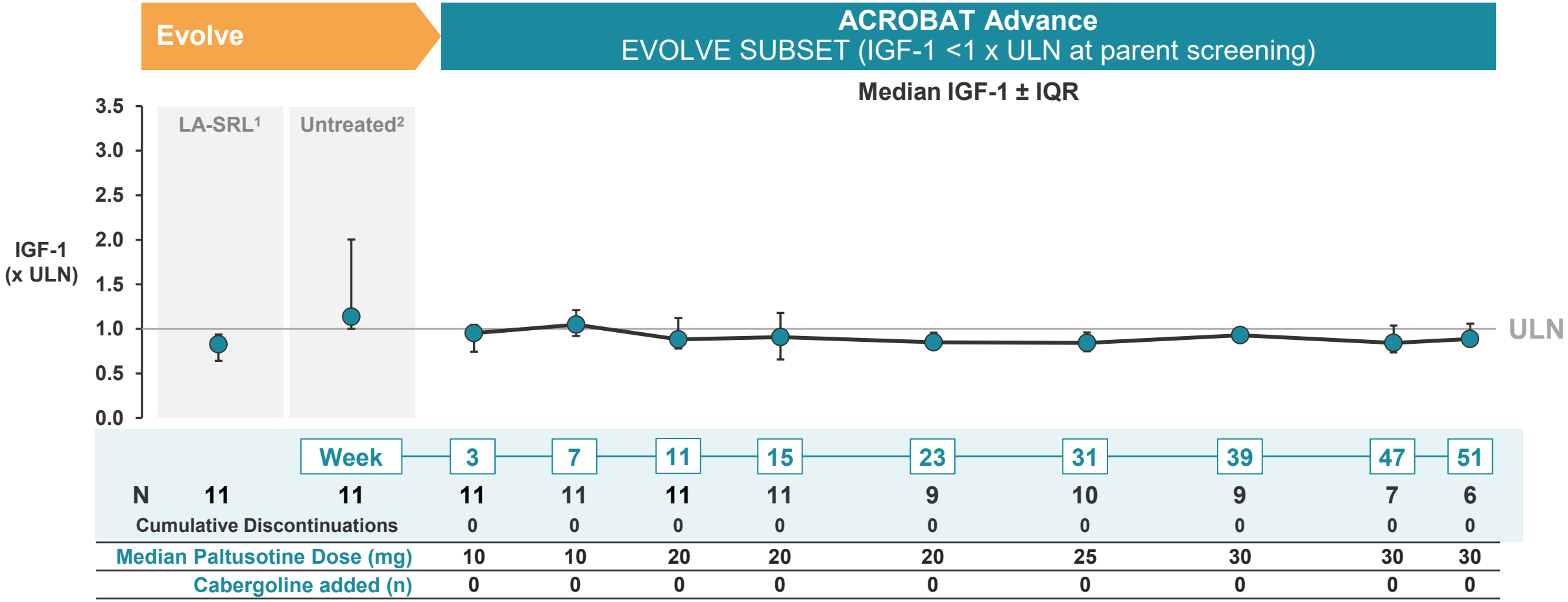
Edge → **ACROBAT Advance**
EDGE SUBSET (IGF-1 >1x ULN or ≤1x with intensive tx at parent screening)



Week		3	7	11	15	23	31	39	47	51
N	30	30	30	28	27	26	24	21	19	17	17
Cumulative Discontinuations			0	0	0	0	2	2	3	3	3
Median Paltusotine Dose (mg)			10	20	20	35	40	40	40	40	40
Cabergoline added (n)			0	0	0	1	1	3	4	9	10

1. Baseline (screening) from Edge study while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Edge study.
ACROBAT Advance DATA through August 31, 20

IGF-1 levels on paltusotine treatment for up to 51 weeks (from patients previously enrolled in EVOLVE study)



Week		3	7	11	15	23	31	39	47	51
N	11	11	11	11	11	11	9	10	9	7	6
Cumulative Discontinuations		0	0	0	0	0	0	0	0	0	0
Median Paltusotine Dose (mg)		10	10	20	20	20	25	30	30	30
Cabergoline added (n)		0	0	0	0	0	0	0	0	0

1. Baseline (screening) from Evolve study while on injected SRL therapy. 2. End of 4-week wash-out from paltusotine at end of Evolve study.
ACROBAT Advance DATA through August 31, 2021

Paltusotine was well tolerated

The most common AE were consistent with symptoms of acromegaly or GI symptoms expected with SRL

TEAEs Occurring in ≥3 Patients

TEAEs	Any Dose N=41 n (%)
Headache	**12 (29.3)**
Arthralgia	**9 (22.0)**
Fatigue	**6 (14.6)**
Paresthesia	**5 (12.2)**
Hyperhidrosis	**5 (12.2)**
Diarrhea	**5 (12.2)**
Peripheral swelling	**4 (9.8)**
Corona virus infection	**4 (9.8)**
Apnea	**3 (7.3)**
Anxiety	**3 (7.3)**
Dizziness	**3 (7.3)**
Hypoglycemia	**3 (7.3)**
Hypotension	**3 (7.3)**

- No safety signals seen in clinical laboratories, including no amylase/lipase elevations >3x ULN, HbA1c, LFTs, ECGs
- 3 non-treatment related SAEs in 2 patients
  - Gallstone pancreatitis
  - Worsening of coronary artery disease followed by sinus arrest post coronary artery bypass surgery
- There were 4 discontinuations
  - 1 adverse event (headache)
  - 1 pregnancy
  - 1 withdrawn consent
  - 1 patient preference (discontinued after the Week 51 IGF-1 measurement)

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

Conclusions

- Once daily, oral paltusotine lowered and maintained IGF-1 at levels comparable to prior injected SRL therapy for up to 51 weeks
- Combination therapy, expected in subjects who completed ACROBAT Edge, was utilized appropriately in the study
- Paltusotine was well tolerated with a safety profile similar to that of injected SRLs, including when used in combination with cabergoline
- The phase 3 studies (PATHFNDR) for paltusotine have been initiated, as ACROBAT Advance continues to accumulate long-term safety and efficacy data

Acknowledgements

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