

Long-Term Safety and Efficacy of Once-Daily Oral Paltusotine in Combination With Cabergoline for the Treatment of Patients With Acromegaly

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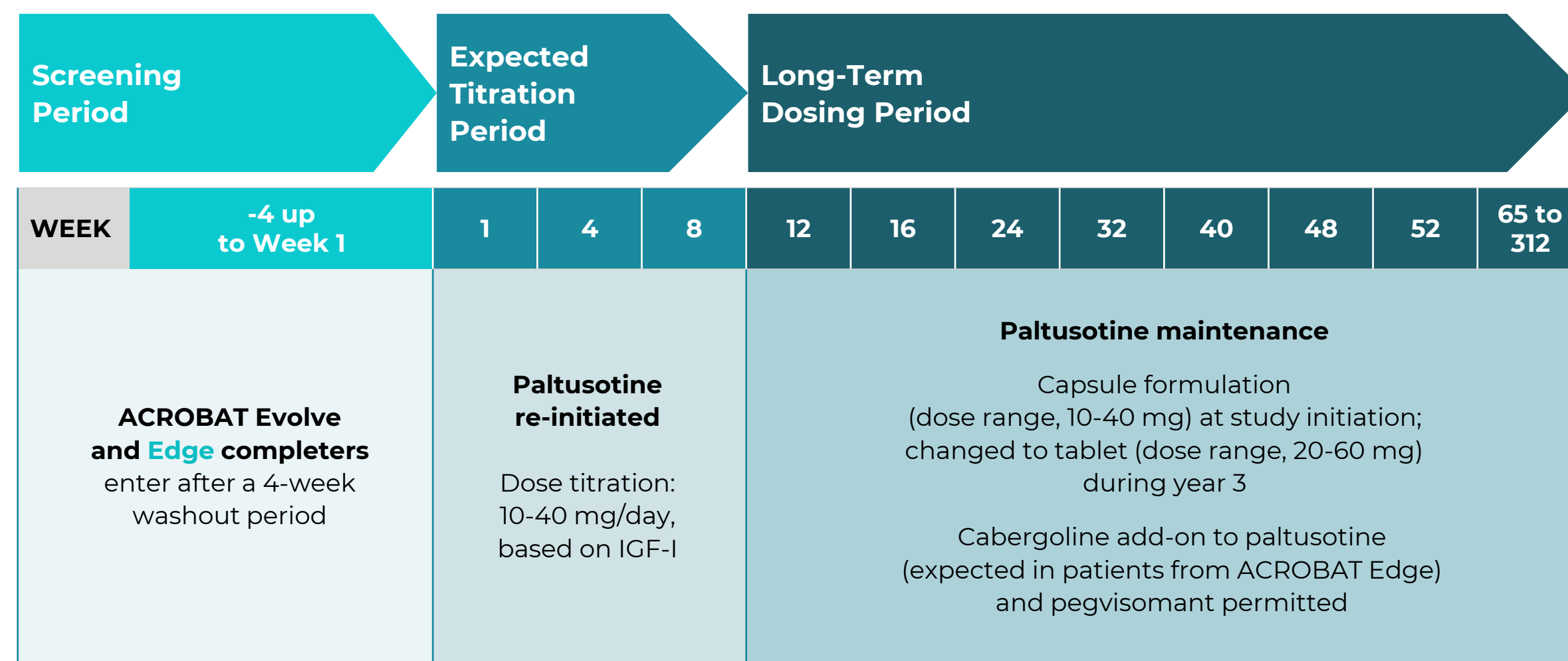
BACKGROUND

- Paltusotine, a nonpeptide, selective somatostatin 2 receptor agonist, is approved in the United States and Europe as a once-daily oral treatment for adults with acromegaly^{1,2}
- The dopamine receptor agonist cabergoline may be used as an off-label, add-on therapy in patients with acromegaly that is not fully controlled by an injected depot somatostatin receptor ligand (SRL)^{3,4}
- This analysis evaluated the safety and efficacy of paltusotine in combination with cabergoline in patients with acromegaly who have been followed for up to 4 years in the ACROBAT Advance study

METHODS

- ACROBAT Advance is an ongoing, single-arm, phase 2, open-label extension study (NCT04261712) that enrolled patients with acromegaly who completed a phase 2 parent study
 - Adjunctive treatment (eg, cabergoline, pegvisomant) was allowed as of Week 12 in patients who did not attain normal insulin-like growth factor 1 (IGF-I) levels on the maximum dose of paltusotine

ACROBAT Advance Study Design



- This analysis included patients from the ACROBAT Edge parent study who received at least 1 dose of cabergoline in the ACROBAT Advance study
 - Patients in ACROBAT Evolve had normal IGF-I levels on SRL monotherapy, without adjunctive medication; therefore, this analysis included only patients from ACROBAT Edge, consistent with their prior injection-based treatment history
 - At enrollment in ACROBAT Edge, all patients were candidates for combination drug therapy: patients were either suboptimally controlled on an injected depot SRL (octreotide or lanreotide) alone or in combination with cabergoline, or they required combination therapy or pasireotide to achieve normal IGF-I levels⁵

- The analysis population comprised 25 patients who received cabergoline in the ACROBAT Advance study, 4 of whom also received pegvisomant

Patient Characteristics at Enrollment in ACROBAT Advance

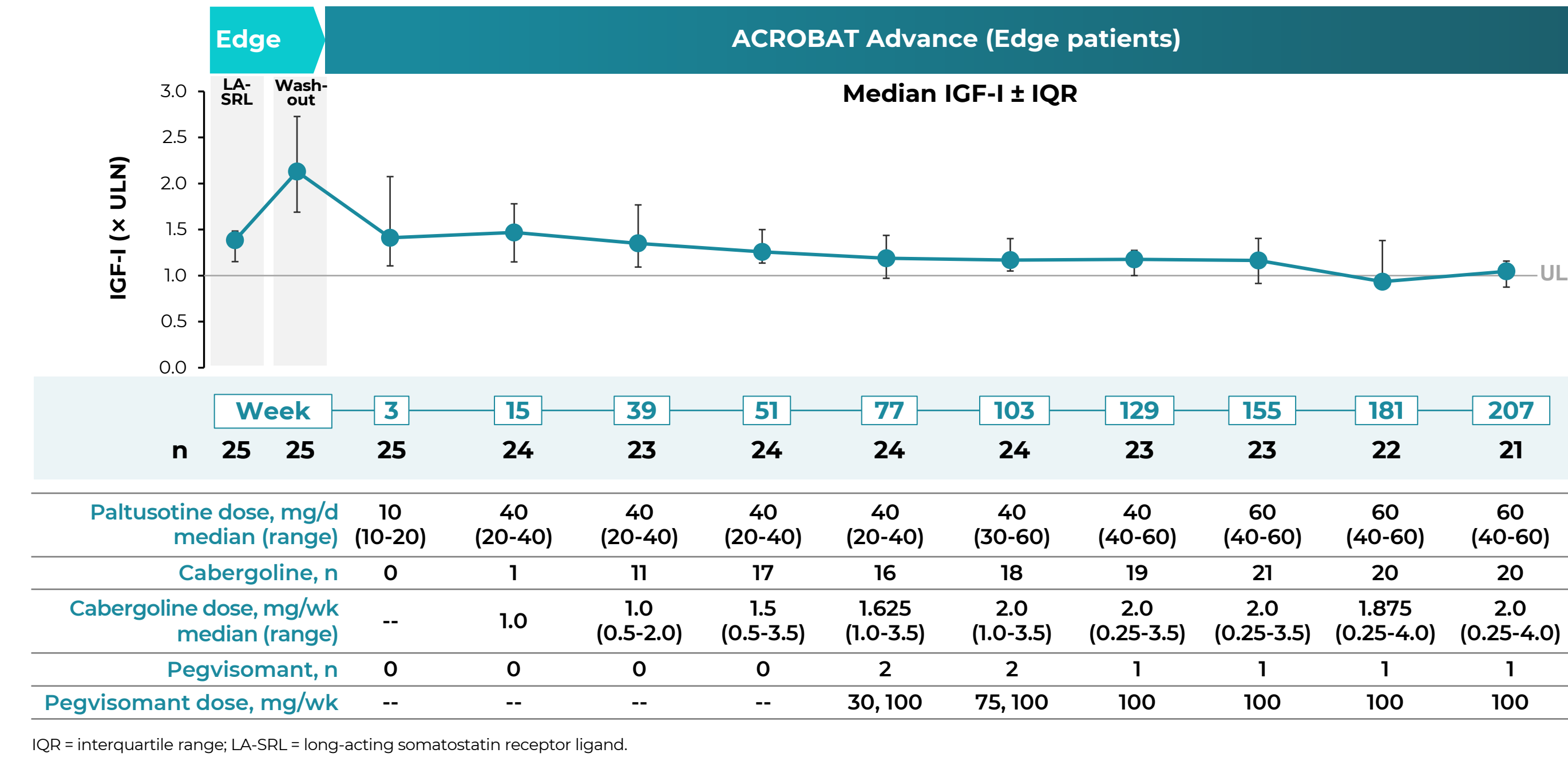
Characteristic	Patients (N=25)
Age, years, mean ± SD	53.0 ± 9.4
Female, n (%)	12 (48.0)
Time since diagnosis, years, mean ± SD	8.9 ± 4.0
Prior pituitary surgery, n (%)	20 (80.0)
Pre-trial medical treatment*	
Lanreotide depot: dose of 60/90/120 mg/month, n	1/2/9
Octreotide LAR: dose of 20/30/40 mg/month, n	1/8/2
Pasireotide LAR: dose of 40/60 mg/month, n	3/2
Injected SRL + cabergoline, n	12

*Acromegaly medications used before the parent study and/or before enrollment in ACROBAT Advance.

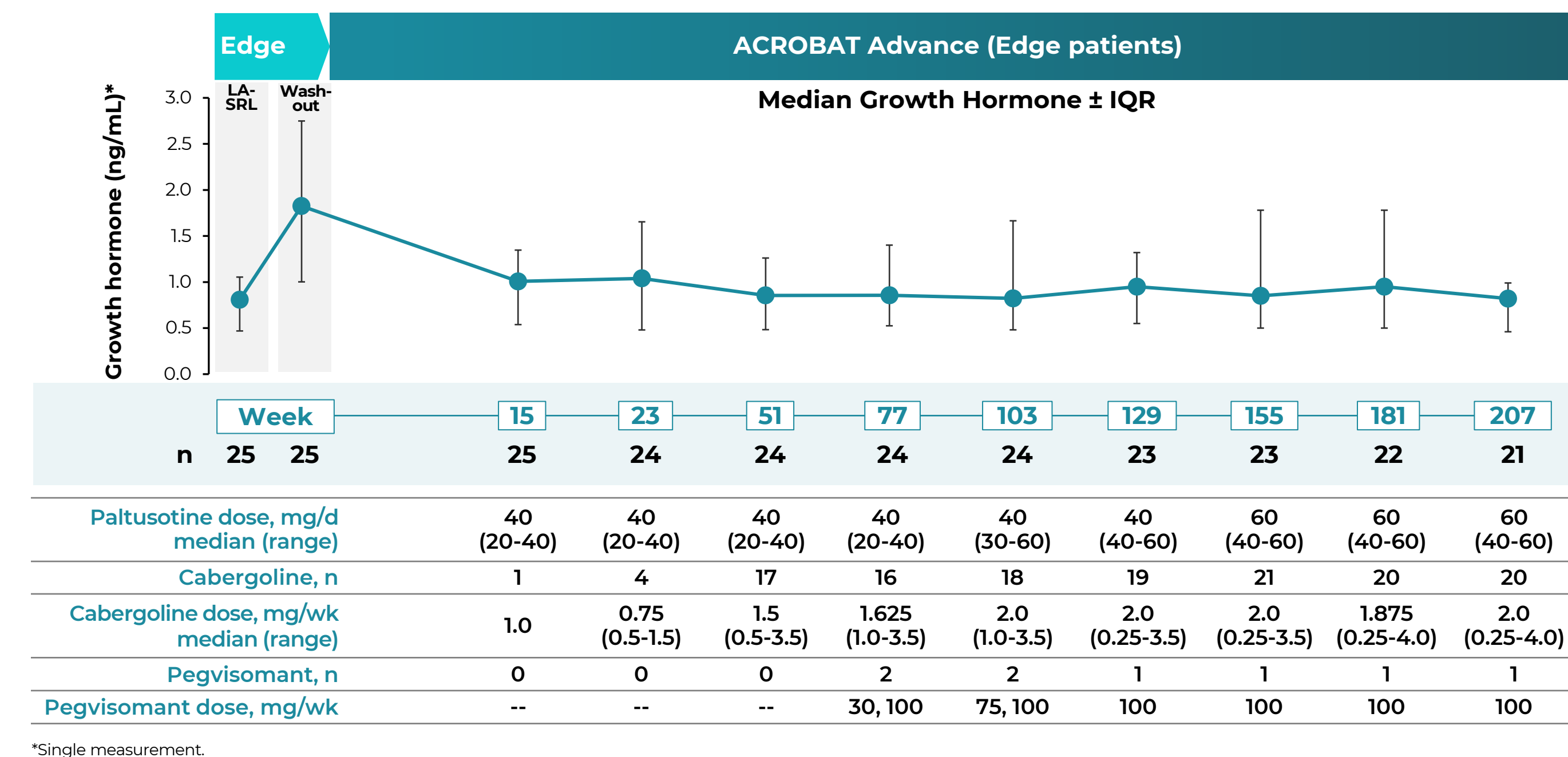
- In ACROBAT Advance, IGF-I levels during paltusotine monotherapy were comparable to the ACROBAT Edge study baseline values (on injected depot SRL) and decreased to normal or near-normal levels over time when adjunctive medications were added
 - In the 4 patients who received pegvisomant, the median cabergoline dose level was 2.75 mg/week (range, 1.5-4.0) when pegvisomant (dose range, 30-100 mg/week) was added
- Relative to paltusotine monotherapy, all 25 patients experienced a reduction in IGF-I levels with adjunctive cabergoline
- Twenty-one patients (84%) showed IGF-I normalization at ≥1 time point after starting adjunctive cabergoline
 - In the 4 patients without IGF-I normalization, the maximum cabergoline dose ranged from 1 mg/week to 4 mg/week
- Acromegaly symptoms were stably controlled in patients receiving paltusotine and adjunctive cabergoline

RESULTS

IGF-I Levels in Patients With Adjunctive Cabergoline



Growth Hormone Levels Remained Stable in Patients With Adjunctive Cabergoline



Safety

- The most commonly reported adverse events during adjunctive cabergoline use were diarrhea in 7 (28.0%) patients and arthralgia in 6 (24.0%) patients
- One serious drug-related adverse event (cholelithiasis) was reported in a patient on paltusotine 40 mg/day and cabergoline 1.5 mg/week

CONCLUSIONS

- During up to 4 years of follow-up, paltusotine monotherapy was at least as effective as prior octreotide or lanreotide depot injections for achieving stable, long-term IGF-I and symptom control
- The requirement for adjunctive treatment was consistent with prior treatment history (uncontrolled on injected depot octreotide or lanreotide or requiring combination therapy or pasireotide for IGF-I control)
- Combination treatment with paltusotine and adjunctive medication was well tolerated and associated with additive IGF-I reduction

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AUTHOR DISCLOSURES

MRC reports serving as a PI of research grants from Alexion, Crinetics Pharmaceuticals, Inc., Debiopharm, and Recordati; an occasional consultant for Camurus, Crinetics Pharmaceuticals, Inc., Novo Nordisk, and Recordati; and a speaker for Camurus, Crinetics Pharmaceuticals, Inc., Novo Nordisk, and Recordati. MBG reports receiving research support from Ascendis, Camurus, Chiasma, Corcept, Crinetics Pharmaceuticals, Inc., Ipsen, Novartis, Novo Nordisk, Opko, Pfizer, and Strongbridge and serving as a scientific consultant for Crinetics Pharmaceuticals, Inc., HRA Pharma, Novo Nordisk, and Recordati. MD reports serving as a PI of a research grant from Crinetics Pharmaceuticals, Inc., and an advisory board member for Pfizer in CEE. EM reports serving as a PI of a research grant from Crinetics Pharmaceuticals, Inc., and a speaker and consultant for Lilly, Novartis, Novo Nordisk, and Recordati. MT reports serving as a PI of a research grant from Crinetics Pharmaceuticals, Inc., and a speaker and occasional consultant for Camurus, Ipsen, Lilly, Novartis, Pfizer, and Recordati. HR reports no conflicts of interest. CLB reports serving as a PI of research grants from Crinetics Pharmaceuticals, Inc.; having received consulting fees, honoraria, and meeting support from Crinetics Pharmaceuticals, Inc., Ipsen, and Recordati; and serving on an advisory board for Crinetics Pharmaceuticals, Inc. CD, AC, and AK are employees of Crinetics Pharmaceuticals, Inc. TJ is a consultant for Crinetics Pharmaceuticals, Inc.