

Dose selection for paltusotine, a once daily oral nonpeptide, somatostatin receptor 2 ligand, for the treatment of patients with carcinoid syndrome (CS)



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BACKGROUND

- Long-acting somatostatin receptor ligands (LA-SRLs) are first line therapy for neuroendocrine tumor (NET) syndromes including acromegaly and the carcinoid syndrome (CS).
- In acromegaly, two phase 2 studies: EDGE (NCT 03789656) and EVOLVE (NCT 03792555) suggested that patients injected with SRLs can switch to once daily oral paltusotine (CRN00808).
- Paltusotine is a nonpeptide, small molecule, somatostatin type 2 (SST2) receptor ligand (SRL) with 70% bioavailability, while maintaining stable serum IGF-1 levels.
- However, CS patients may require higher doses of an orally administered drug due to:
 - Malabsorption, which can be associated with CS
 - Potential differences in clearance and volume of distribution of paltusotine between CS and acromegaly

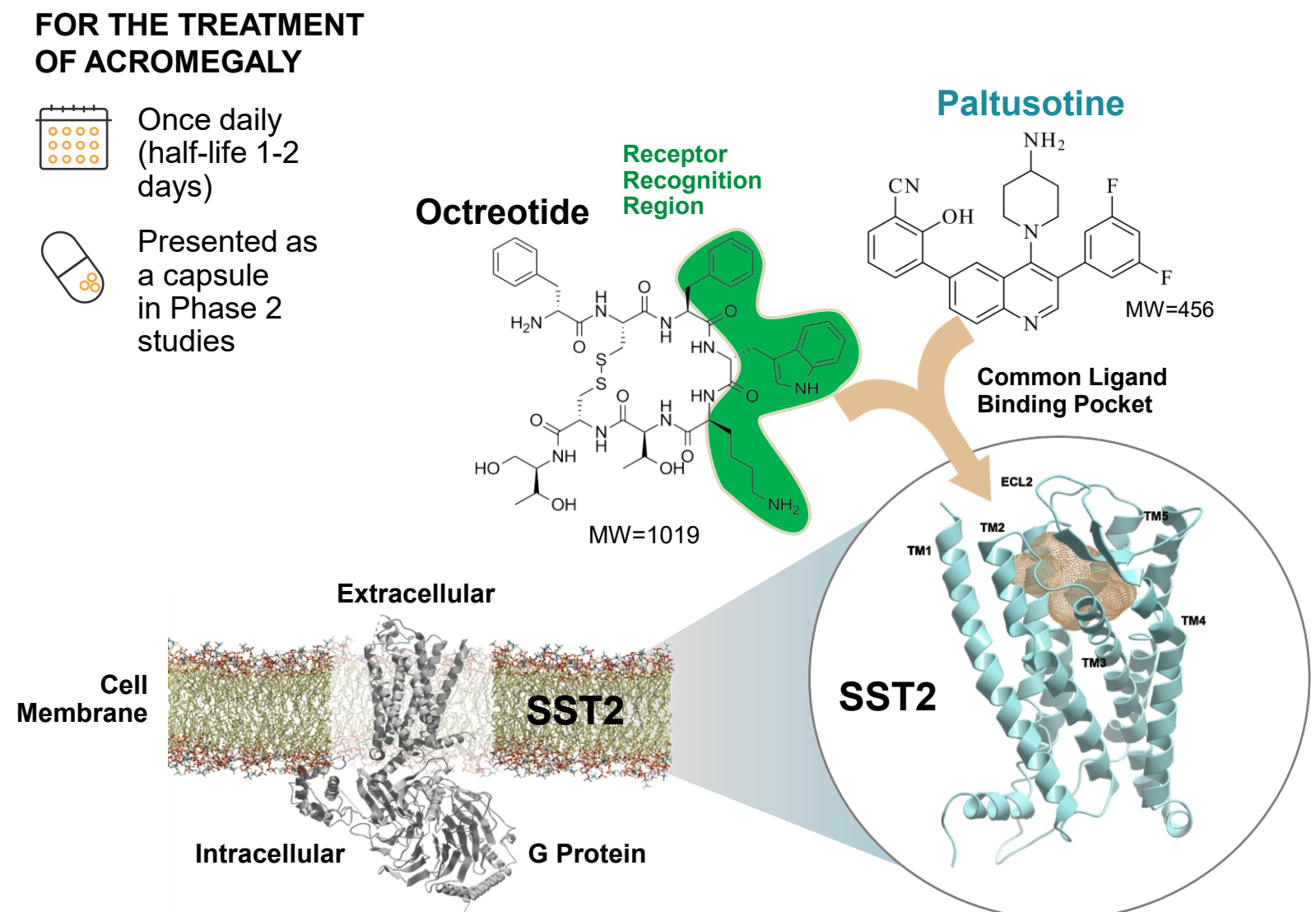
OBJECTIVE

To design a PK/PD study evaluating the use of once daily oral paltusotine to control symptoms and inhibit functional tumor markers in patients with CS.

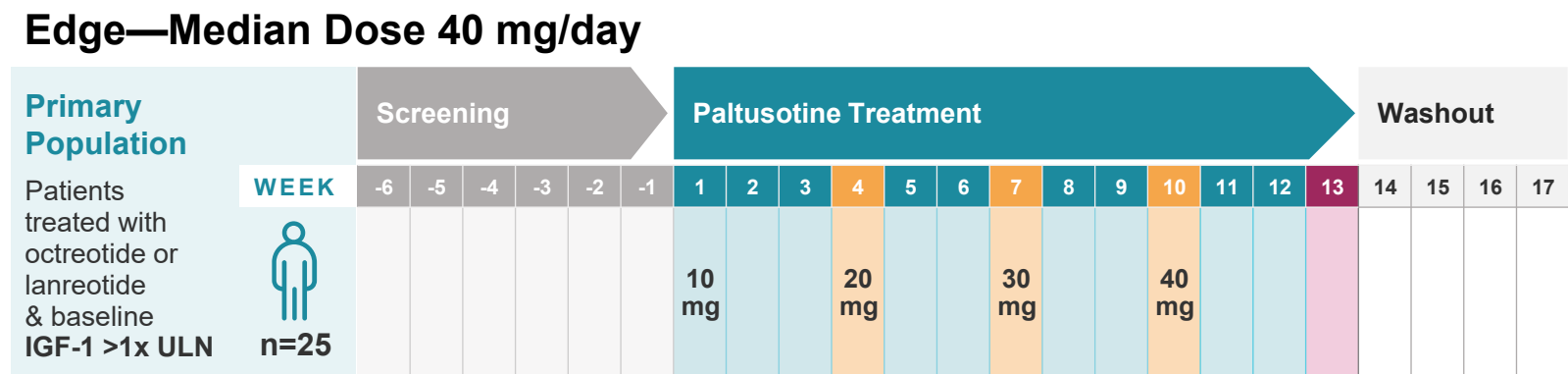
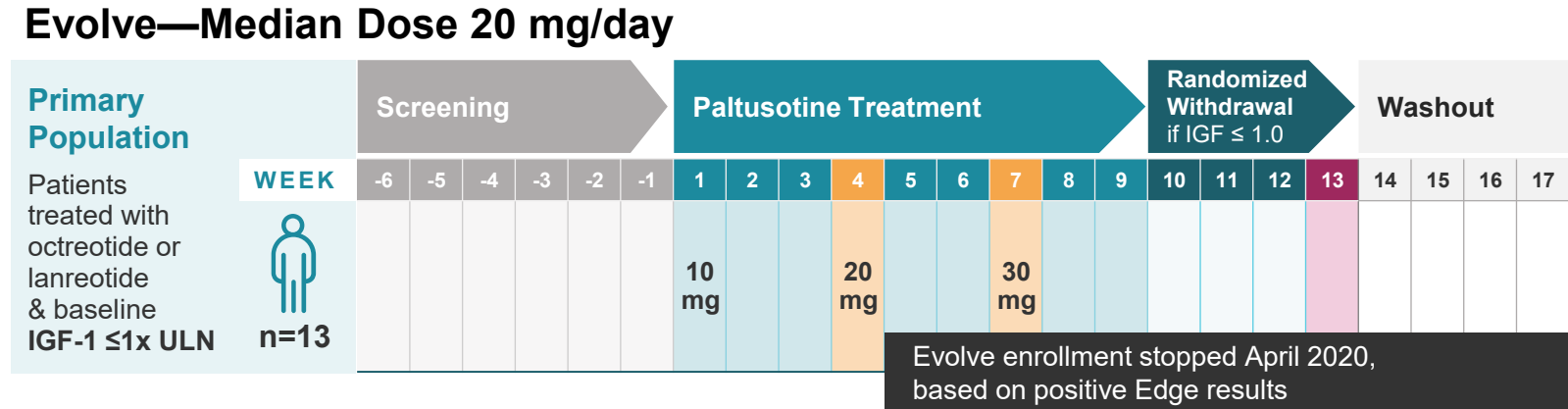
METHODS

We analyzed data from the capsule formulation used in the acromegaly patient studies to determine dose- and exposure-response and from a new tablet formulation evaluated in healthy volunteers.

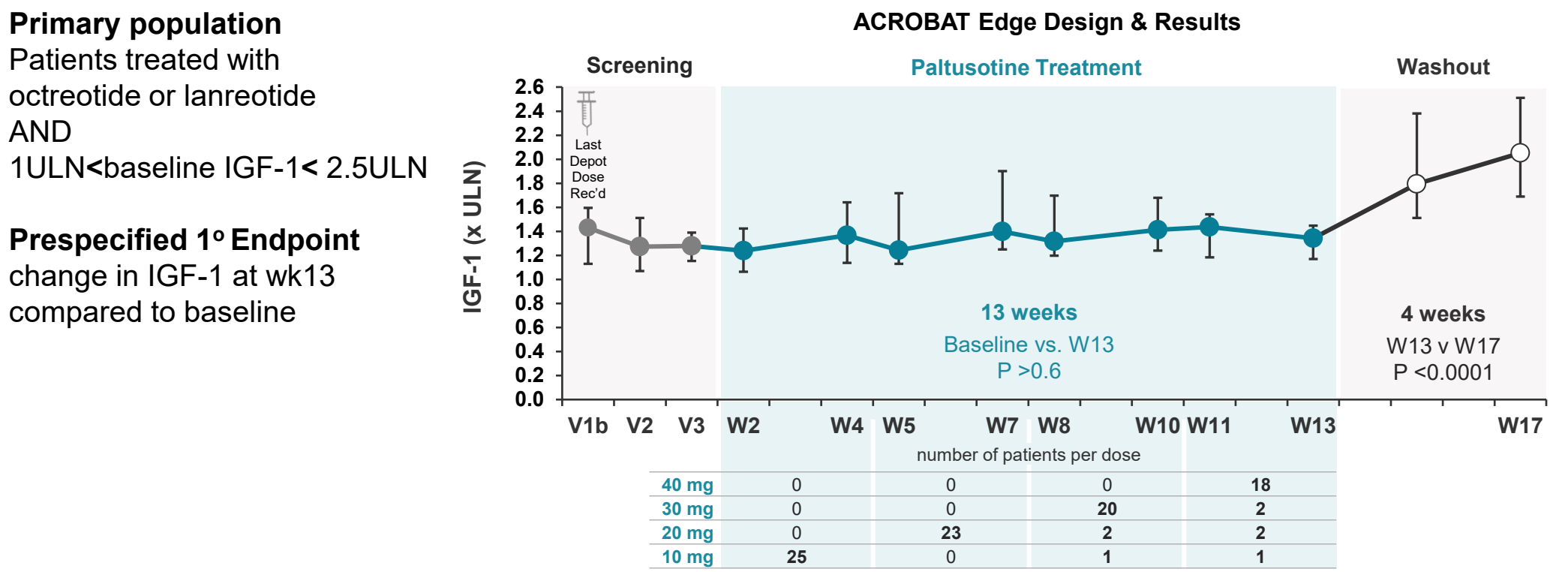
Paltusotine is a first-in-class, oral, nonpeptide, somatostatin receptor type 2 (SST2) agonist



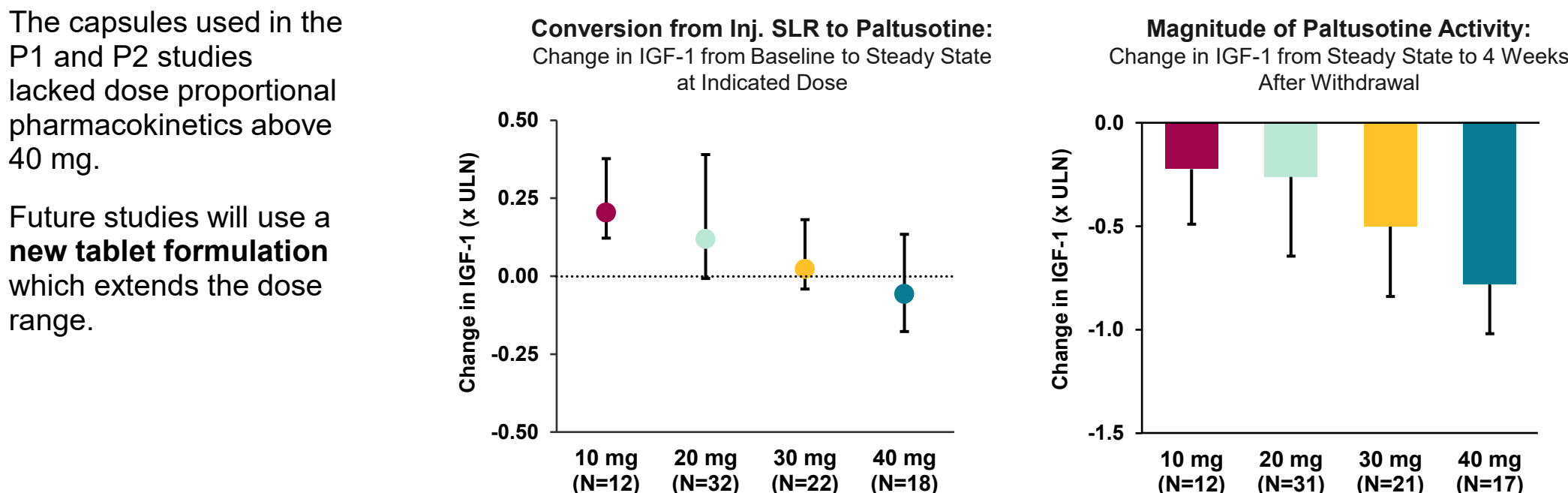
ACROBAT Edge & Evolve: Phase 2 studies in acromegaly



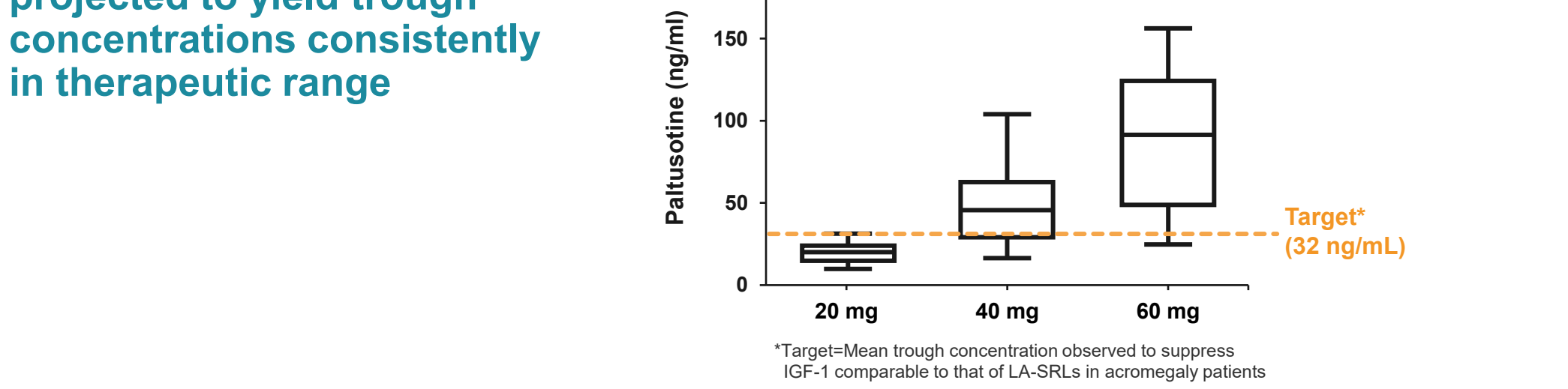
ACROBAT Edge primary analysis population—IGF-1 levels maintained after switching from SRL depots to paltusotine



Edge and Evolve provide evidence of a Dose Response



Paltusotine 40 & 60 mg/day of new tablet formulation projected to yield trough concentrations consistently in therapeutic range



RESULTS

The dose- and exposure-response data from EDGE, EVOLVE and in phase 1 with healthy volunteers suggest that a dose range of 40 to 60 mg once daily results in consistent IGF-1 suppression in patients with acromegaly.

CONCLUSIONS

- Dose-response analyses indicate that the 40 – 60 mg/day dose of paltusotine achieves IGF-1 control comparable to depot SRLs in patients with acromegaly.
- Taking into account the potential for maldigestion and/or malabsorption associated with CS, we project to investigate the 40 and 80 mg dose of the tablet formulation in the treatment of CS, with the potential for up titration to a higher dose.
- This potential for up titration is based on a multi-center retrospective chart review study, where the most common initial dose of octreotide LAR depot (40 to 60 mg every 4 weeks) was escalated subsequently up to 160 mg every 4 weeks (Strosberg, 2014).

Reference:
 Strosberg JR et al Clinical benefits of above-standard dose of octreotide LAR in patients with neuroendocrine tumors for control of carcinoid syndrome symptoms: a multicenter retrospective chart review study. The oncologist. 2014;19:930-936

Disclosures:
 Employee and stockholder of Crinetics Pharmaceuticals