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Paltusotine: The first selective nonpeptide agonist of somatostatin receptor 2 (SSTR2) for the treatment of acromegaly

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SUMMARY: Acromegaly is an endocrine disorder characterized by abnormal enlargement of the extremities and internal organs resulting from excessive secretion of growth hormone (GH) by the pituitary gland, which in turn leads to elevated levels of insulin-like growth factor 1 (IGF-1). Approximately 45% of patients remain biochemically uncontrolled after surgery and require long-term treatment with injectable somatostatin analogs such as octreotide or lanreotide. These polypeptide drugs generally require monthly administration to maintain disease control; however, many patients experience recurrence of symptoms towards the end of the dosing interval. Moreover, injection-site pain and local reactions are common, significantly impacting patients' quality of life. On September 25, 2025, the U.S. Food and Drug Administration (FDA) approved paltusotine, the first once-daily oral, nonpeptide somatostatin receptor 2 (SSTR2) agonist for the treatment of acromegaly. By enabling oral rather than injectable therapy, paltusotine reduces the treatment burden and enhances patient adherence. With its rapid onset and durable biochemical control, this novel agent has the potential to reshape the current paradigm of acromegaly pharmacotherapy and offer patients a more convenient and effective treatment option. Nevertheless, its long-term safety and efficacy warrant further evaluation in real-world clinical settings.

Keywords: acromegaly, GH, IGF-1, SRLs

Acromegaly is a rare, chronic endocrine disorder primarily caused by excessive secretion of growth hormone (GH) from pituitary adenomas, which in turn stimulates hepatic overproduction of insulin-like growth factor 1 (IGF-1) (*1*). Sustained exposure to elevated levels of GH and IGF-1 leads to a wide range of systemic complications — including cardiovascular, musculoskeletal, respiratory, and endocrine abnormalities, as well as an increased risk of malignancies — thereby imposing a substantial clinical burden, impairing quality of life, and reducing overall survival (*2,3*).

The primary treatment modalities for acromegaly include pituitary surgery, pharmacotherapy, and radiotherapy (*4*). Transsphenoidal resection of the GH-secreting pituitary adenoma remains the first-line approach (*5*); however, adequate disease control is not achieved in approximately 45% of patients following surgery (*6*). These patients receive medical therapies such as somatostatin receptor ligands (SRLs), dopamine agonists (DAs), and growth hormone receptor antagonists (GHRAs) (*7*). SRLs — including octreotide and lanreotide — are currently the first-line pharmacological options targeting somatostatin receptors (SSTRs). Nevertheless, the requirement for regular monthly injections places a considerable burden on patients (*8*). Consequently, developing a convenient, non-injectable formulation is essential to enhancing treatment adherence and improving quality of life.

On September 25, 2025, the U.S. Food and Drug Administration (FDA) approved paltusotine, the first once-daily oral nonpeptide SSTR2 agonist for the treatment of acromegaly (*9,10*). Its mechanism of action resembles that of the natural hormone somatostatin but the medication exhibits higher selectivity for SSTR2 with little or no affinity for other SSTR subtypes. Paltusotine activates human SSTR2 to suppress cyclic AMP accumulation, with a mean half-maximal effective concentration (EC_{50}) of 0.25 nM (*11*). Paltusotine's advantage lies in its ability to meet patients' expectations for a convenient, once-daily oral therapy, thereby filling an unmet need in the current treatment landscape. It not only eliminates the inconvenience and injection-related complications associated with parenteral administration but also alleviates the negative impact on patients' quality of life. Moreover, the oral formulation allows for more flexible dose adjustments, as paltusotine reaches steady-state concentrations within 3-5 days. In contrast, long-acting somatostatin receptor ligands administered by monthly injection typically require at least three doses before dose optimization can be evaluated and steady-state levels achieved (*12*).

The approval was based on two randomized, double-

blind, parallel-group, placebo-controlled clinical studies: PATHFNDR-1 (NCT05192382) and PATHFNDR-2 (NCT04837040), which assessed the safety and efficacy of paltusotine in adults with acromegaly whose biochemical parameters were either uncontrolled or controlled at the baseline. Results indicated that paltusotine rapidly, durably, and effectively controlled biochemical markers of acromegaly (*11*).

PATHFNDR-1 enrolled 111 adults with biochemically uncontrolled acromegaly; 95% had undergone pituitary surgery before enrollment. Of those patients, 86 (78%) had macroadenomas (> 10 mm), 9 (8%) had microadenomas (≤ 10 mm), and 16 (14%) had tumors of unknown size (*11*). Participants were randomized to receive either paltusotine (n = 54) or a placebo (n = 57) for 24 weeks. The primary endpoint was the proportion of participants in whom biochemical control (IGF-1 ≤ 1.0 × ULN) was achieved compared to the placebo. At week 24, biochemical control was achieved in 56% of the paltusotine group versus achievement of control in only 5% in the placebo group (p-value < 0.0001) (*11*). IGF-1 normalization was achieved in most patients within 2-4 weeks of their starting treatment and control was maintained until the end of the study. Participants receiving paltusotine also reported alleviation of acromegaly-related symptoms such as headaches, joint pain, sweating, fatigue, weakness, swelling, and/or numbness/tingling compared to those receiving a placebo (*11*).

PATHFNDR-2 enrolled 58 adults with controlled biochemical parameters who had previously been treated with SRLs (octreotide or lanreotide); 86% had prior pituitary surgery. Of the patients, 33 (57%) had macroadenomas (> 10 mm), 11 (19%) had microadenomas (≤ 10 mm), and 14 (24%) had tumors of unknown size (*11*). Participants were randomized to receive either paltusotine (n = 30) or a placebo (n = 28) for 36 weeks. The primary endpoint was the proportion of participants in whom biochemical control (IGF-1 ≤ 1.0 × ULN) was maintaining compared to a placebo. At week 36, biochemical control was maintained in 83% of the paltusotine group versus 4% of the placebo group (p-value < 0.0001) (*11*). Symptom relief in the paltusotine group was also superior to that in the placebo group (*11*).

In terms of safety, the most common adverse events (≥ 5%) are diarrhea, abdominal pain, nausea, decreased appetite, sinus bradycardia, hyperglycemia, palpitations, and gastroenteritis (*11*).

As the first once-daily oral nonpeptide SSTR2 agonist approved by the FDA for acromegaly, paltusotine shifts therapy from injectable to oral administration, reducing the treatment burden and improving adherence. With its rapid onset, durable biochemical control, paltusotine has the potential to transform the current paradigm of acromegaly pharmacotherapy and provide a novel treatment option for patients. Nevertheless, its long-term safety and efficacy warrant further evaluation in real-world clinical settings.

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References

1. Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM, Pivonello R. Acromegaly. Nat Rev Dis Primers. 2019; 5:20.
2. Ershadinia N, Tritos NA. Diagnosis and treatment of acromegaly: An update. Mayo Clin Proc. 2022; 97:333-346.
3. Giustina A, Barkan A, Beckers A, *et al*. A consensus on the diagnosis and treatment of acromegaly comorbidities: An update. J Clin Endocrinol Metab. 2020; 105:dgz096.
4. Giustina A, Barkhoudarian G, Beckers A, *et al*. Multidisciplinary management of acromegaly: A consensus. Rev Endocr Metab Disord. 2020; 21:667-678.
5. Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, Molitch ME, Samson SL, Strasburger CJ, van der Lely AJ, Melmed S. A Pituitary Society update to acromegaly management guidelines. Pituitary. 2021; 24:1-13.
6. Starnoni D, Daniel RT, Marino L, Pitteloud N, Levivier M, Messerer M. Surgical treatment of acromegaly according to the 2010 remission criteria: Systematic review and meta-analysis. Acta Neurochir (Wien). 2016 ; 158:2109-2121.
7. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, Strasburger CJ, Luger A, Clemmons DR, Giustina A. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018; 14:552-561.
8. Geer EB, Sisco J, Adelman DT, Ludlam WH, Haviv A, Liu S, Mathias SD, Gelbaum D, Shi L. Patient reported outcome data from acromegaly patients treated with injectable somatostatin receptor ligands (SRLs) in routine clinical practice. BMC Endocr Disord. 2020; 20:117.
9. FDA approves new treatment for acromegaly, a rare endocrine disorder. *https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-treatment-acromegaly-rare-endocrine-disorder* (Accessed October 4, 2025).
10. Crinetics Announces FDA Approval of PALSONIFY™ (paltusotine) for the Treatment of Acromegaly in Adults. *https://crinetics.com/crinetics-announces-fda-approval-of-palsonify-paltusotine-for-the-treatment-of-acromegaly-in-adults* (Accessed October 4, 2025).
11. PALSONIFY (paltusotine) tablets, for oral use. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219070s000lbl.pdf* (Accessed October 4, 2025).
12. Melmed S, di Filippo L, Fleseriu M, *et al*. Consensus on acromegaly therapeutic outcomes: An update. Nat Rev Endocrinol. 2025; 21:718-737.

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