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Paltusotine as a therapeutic intervention for acromegaly: A systematic review of clinical efficacy, patient-reported outcomes, and safety profile

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 November 2025 and was last updated on 25 November 2025.

INTRODUCTION

Review question / Objective To systematically evaluate the efficacy, safety, and patient-reported outcomes of paltusotine as a monotherapy or adjunctive treatment for acromegaly compared to standard-of-care interventions.

Rationale Acromegaly is a rare but serious endocrine disorder characterized by excessive growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion, typically resulting from a pituitary adenoma. Current standard treatment includes surgical intervention, radiation therapy, and medical management with somatostatin receptor ligands (SRLs), dopamine agonists, and pegvisomant. Despite these options, a significant proportion of patients experience inadequate biochemical control or intolerance to existing therapies. Paltusotine represents a novel therapeutic approach as an oral GH receptor antagonist, offering potential advantages in efficacy, convenience, and patient tolerability. A comprehensive systematic review of paltusotine's clinical efficacy and safety profile is warranted to inform clinical decision-making and establish its role in the acromegaly treatment algorithm..

Condition being studied Acromegaly is a chronic, progressive disorder caused by excessive GH secretion, most commonly due to pituitary adenoma. The disease results in characterized features including acral enlargement (hands, feet, nose), coarsening of facial features, organomegaly, metabolic disturbances, and systemic complications including diabetes mellitus, hypertension, cardiovascular disease, and sleep apnea. The clinical burden of acromegaly extends beyond morphological changes to include significant morbidity and premature mortality if untreated or inadequately controlled. Treatment goals focus on achieving GH suppression to <1.0 ng/mL and IGF-1 normalization to restore normal life expectancy. Acromegaly treatment typically involves multimodal therapy, and many patients remain inadequately controlled on conventional

medical management, highlighting the clinical need for novel therapeutic options such as paltusotine.

METHODS

Search strategy An initial search was performed on November 6th, 2025, using five electronic databases: EBSCOhost, CINAHL Ultimate, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews. Boolean search operators included ("paltusotine" OR "palsonify" OR "CRN00808") AND ("acromegaly"). Filters were applied to limit results to articles published in English with human subjects only. No publication date filters were applied to capture all available evidence from the inception of paltusotine clinical development. Gray literature searches were conducted using ClinicalTrials.gov and MedRxiv to identify unpublished or preprint studies relevant to paltusotine/palsonify in acromegaly treatment. The final comprehensive search will be conducted on November 25th, 2025. Search strategies will be adapted for each database interface to optimize retrieval sensitivity and specificity.

Participant or population Studies will include adult participants aged ≥18 years with a confirmed diagnosis of acromegaly. Participants may be either uncontrolled (not achieving GH <1.0 ng/mL and/or IGF-1 normalization) on standard somatostatin receptor ligands/analogues or previously controlled on these agents. There will be no restrictions based on sex, ethnicity, or comorbid conditions. Studies involving pediatric patients (<18 years) will be excluded. Animal models and in vitro studies will be excluded.

Intervention The intervention of interest is paltusotine (brand name Palsonify; pharmaceutical identifier CRN00808), an oral selective GH receptor antagonist. Paltusotine will be evaluated as a therapeutic monotherapy or as part of a treatment regimen in patients with acromegaly. Any dose, frequency, or duration of paltusotine treatment will be included if reported in the primary literature.

Comparator Comparator interventions include standard-of-care pharmacologic treatments for acromegaly, including somatostatin receptor ligands (octreotide, lanreotide, pasireotide), dopamine agonists (cabergoline), GH receptor antagonists (pegvisomant), or placebo. Studies with no comparator but reporting efficacy data in a single-arm design will also be included to assess paltusotine's observed clinical benefit.

Study designs to be included Eligible study designs include randomized controlled trials (RCTs), non-randomized interventional studies, clinical trials (Phases 1-4), and preprints published in English. Studies must have full-text articles available electronically and must report relevant patient outcome data or adverse event information.

Eligibility criteria Inclusion Criteria: Adults aged ≥18 years with confirmed acromegaly diagnosis, Paltusotine intervention (monotherapy or combination therapy), Comparator as defined above or single-arm design with outcome data, Published in English with available full-text, Human subjects only, Reported outcomes: biochemical markers (IGF-1, GH), symptom improvement, or adverse events Exclusion Criteria: Pediatric patients (<18 years), Animal studies or in vitro models, Studies lacking relevant patient outcome or adverse event data, Non-English language publications without translation, Studies examining paltusotine for conditions other than acromegaly, Letters, editorials, or opinion pieces without original data, Duplicate publications (the most complete or recent version will be retained).

Information sources Electronic databases: EBSCOhost, CINAHL Ultimate, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews. Gray literature sources include ClinicalTrials.gov for registered clinical trials and MedRxiv for preprints. Manual screening of reference lists from included studies and relevant review articles will be conducted. Authors of potentially eligible studies will be contacted to clarify eligibility or obtain unreported outcomes if necessary.

Main outcome(s) Primary Outcomes:
1. Biochemical control of IGF-1: Proportion of patients achieving IGF-1 normalization (≤1.0 × upper limit of normal) at study endpoint
2. Biochemical control of GH: Proportion of patients achieving GH suppression (<1.0 ng/mL) and mean change in GH from baseline
Secondary Outcomes:
1. Sustained efficacy: Maintenance of IGF-1/GH control over the duration of follow-up
2. Patient-reported symptom improvement: Change in acromegaly symptom burden measured by validated instruments or clinician-assessed improvement.

Additional outcome(s) Tertiary Outcomes:
1. Adverse event profile: Type, frequency, severity, and withdrawal due to adverse events

2. Quality of life outcomes: Patient-reported quality of life measures or functional assessments
3. Pharmacokinetic parameters: Drug concentration, half-life, and bioavailability, where reported
4. Subgroup responses: Efficacy stratified by prior treatment status (SRL-naive vs. SRL-experienced) or baseline disease severity.

Data management Data extraction will be conducted using standardized electronic forms (Google Sheets) to ensure consistency across sources. Extracted variables include: population characteristics (age, sex, prior intervention, prior surgical history, sample size), intervention details (dose, frequency, duration), comparator information, outcome measures (IGF-1, GH, adverse events, quality of life), and follow-up duration. Two independent reviewers will extract each variable and compare entries; disagreements will be resolved through discussion and consultation with the original articles. Data will be managed and stored securely with access restricted to the research team.

Quality assessment / Risk of bias analysis Randomized controlled trials will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating bias arising from randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting. Non-randomized interventional studies will be assessed using the ROBINS-I tool (Risk of Bias in Non-randomized Studies–Intervention), which evaluates bias due to confounding, participant selection, intervention classification, departures from intended intervention, missing data, outcome measurement, and selective reporting. Clinical trials and preprints will be assigned to appropriate tools (RoB 2 vs. ROBINS-I) based on their individual study designs. Risk of bias assessments will be conducted independently by two reviewers, with discrepancies resolved through discussion or arbitration with a senior author.

Strategy of data synthesis Given the heterogeneity in study designs, populations, intervention protocols, and outcome reporting, this systematic review will employ primarily narrative synthesis with structured tabulation of results.

Descriptive synthesis will systematically summarize study characteristics, populations, interventions, and outcomes, organized by study design and acromegaly disease status (SRL-responders vs. treatment-naive/uncontrolled). Individual study results will be presented narratively with corresponding effect measures (proportions, odds ratios, means with 95% confidence intervals) as reported in primary publications. Findings will be synthesized qualitatively to highlight: (1) consistency of efficacy signals across trials; (2) magnitude of treatment effects; (3) differences in efficacy by patient population or prior treatment status; (4) adverse event profiles and tolerability; and (5) gaps in evidence or methodological limitations affecting interpretation.
Where sufficient clinical similarity permits, descriptive comparison of effect estimates across studies will be conducted without pooling. Visual presentation will include summary tables of study characteristics, risk of bias assessments, and outcome data to facilitate transparent interpretation. This approach preserves the distinct clinical insights offered by each study design while maintaining transparency regarding data heterogeneity and limitations that preclude meta-analysis. The narrative synthesis will be conducted in compliance with PRISMA 2020 guidelines for systematic reviews.

Subgroup analysis Planned subgroup analyses include: (1) stratification by acromegaly disease status (SRL-responders vs. treatment-naive or SRL-uncontrolled); (2) stratification by study phase (Phase 2 vs. Phase 3); (3) stratification by study design (RCT vs. non-randomized); (4) baseline disease severity (well-controlled vs. uncontrolled at baseline); (5) prior treatment history (treatment-naive vs. previously treated); (6) patient age groups if data permit (e.g., <50 years vs. ≥50 years).

Sensitivity analysis Sensitivity analyses will examine the robustness of main findings by: (1) excluding studies with critical or high risk of bias; (2) excluding single-arm, non-comparative studies; (3) sequentially removing each study to assess influence on pooled estimates; (4) alternative meta-analytic models (fixed-effects vs. random-effects); (5) using different effect measure definitions or cutoff values for outcome definitions (e.g., alternative IGF-1 or GH targets). Additional sensitivity analyses will examine the impact of including preprints and gray literature sources versus peer-reviewed publications only.

Language restriction Studies will be limited to those published in English with available full-text translations. This restriction reflects feasibility and available resources for translation.

Country(ies) involved United States.

Other relevant information This systematic review contributes to the evidence base for paltusotine as an emerging therapeutic option for acromegaly. Findings will inform clinical decision-making regarding acromegaly treatment sequencing and the comparative effectiveness of novel agents versus established therapies. The review adheres to PRISMA 2020 guidelines and will be reported transparently to facilitate interpretation and future research.

Keywords Paltusotine; acromegaly; GH receptor antagonist; systematic review; IGF-1; growth hormone; pharmacotherapy.

Dissemination plans Findings will be disseminated through peer-reviewed journal publication, presentation at endocrinology and internal medicine conferences, and stakeholder engagement with patient advocacy groups focused on acromegaly. The registered protocol will be made publicly available through INPLASY to promote transparency and reduce the risk of duplicate systematic reviews.

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