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ACROMEGALY: CURRENT MANAGEMENT AND THE EMERGING ROLE OF ORAL PALTUSOTINE

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ABSTRACT

Introduction and aim: Acromegaly is a chronic endocrine disorder caused by sustained excess secretion of growth hormone and insulin-like growth factor I, leading to significant morbidity and increased mortality if inadequately treated. Transsphenoidal surgery remains the primary therapeutic approach; however, a substantial proportion of patients fail to achieve durable biochemical remission and require long-term medical therapy. Injectable somatostatin receptor ligands are effective but are associated with treatment burden, variable biochemical responses, and impaired quality of life. The aim of this review was to summarize current management strategies for acromegaly and to evaluate the emerging role of paltusotine, a novel orally administered somatostatin receptor agonist.

Materials and Methods: This narrative review was based on a structured analysis of published clinical trials, extension studies, and review articles evaluating the pharmacological properties, clinical efficacy, and safety of paltusotine in patients with acromegaly.

Results: Available evidence indicates that paltusotine provides effective suppression of growth hormone secretion and reduction of insulin-like growth factor I levels with once-daily oral administration. Clinical studies demonstrate maintenance of biochemical control in patients previously treated with injectable therapies, as well as efficacy in selected untreated individuals. Paltusotine was generally well tolerated, with predominantly mild gastrointestinal adverse events and elimination of injection-related complications.

Conclusions: Paltusotine represents a promising oral alternative to injectable somatostatin receptor ligands, with the potential to reduce treatment burden, improve adherence, and maintain biochemical control. Further long-term and real-world studies are needed to fully define its role in routine clinical practice.

KEYWORDS

Acromegaly, Paltusotine, Somatostatin, Lanreotide, Octreotide

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1. Introduction

Acromegaly is a long-standing endocrine condition arising from chronic exposure to elevated concentrations of growth hormone (GH) and insulin-like growth factor I (IGF-I) (Chanson & Salenave, 2008; Giustina & Colao, 2025; Melmed, 2009). In the absence of effective treatment, sustained hormonal excess leads to a broad spectrum of clinical manifestations and contributes to increased disease-related morbidity and mortality, particularly due to cardiovascular and metabolic complications(Giustina & Colao, 2025). In most cases, the disorder is caused by a hormonally active pituitary adenoma and follows a gradual course, which may complicate early clinical recognition and allow disease-related complications to develop over time (Chanson & Salenave, 2008; Reid et al., 2010).Surgical removal of the pituitary lesion via a transsphenoidal approach remains the preferred initial treatment modality and offers the potential for long-term remission (Katznelson et al., 2014).However, durable biochemical remission is not consistently achieved, particularly in patients with large or locally invasive tumors, necessitating long-term medical therapy (Giustina & Colao, 2025; Katznelson et al., 2014). Among available medical options, long-acting injectable somatostatin receptor ligands (SRLs) are widely used and have demonstrated efficacy in suppressing GH secretion and reducing circulating IGF-I levels (Plöckinger & Quabbe, 2005). Despite their clinical benefits, these agents are associated with treatment burden and adverse effects that may limit long-term adherence (Plöckinger & Quabbe, 2005). Collectively, these factors may negatively influence patient-reported outcomes and health-related quality of life (Webb & Badia, 2016). These limitations have prompted growing interest in alternative therapeutic approaches designed to reduce treatment burden while maintaining biochemical control. Accordingly, the aim of this review is to provide an overview of current management strategies for acromegaly and to explore the emerging role of paltusotine, a novel orally administered, nonpeptide, selective agonist of somatostatin receptor subtype 2, within the evolving treatment landscape.

2. Materials and Methods

This narrative review examines paltusotine as a novel oral therapeutic option for the management of acromegaly. Relevant literature was identified through structured searches of PubMed, Embase, and Google Scholar, focusing on publications addressing the pharmacology, clinical efficacy, and safety of paltusotine. Emphasis was placed on phase 2 and phase 3 clinical trials, extension studies, and authoritative review articles. The selected publications were analyzed descriptively, with consideration of study design, patient characteristics, clinical endpoints, and methodological limitations, to synthesize current evidence and outline the potential role of paltusotine in clinical practice.

3. Overview of Acromegaly

Definition and Pathophysiology

Acromegaly is a chronic, progressive endocrine disorder caused by sustained hormonal excess, leading to persistently elevated circulating levels of insulin-like growth factor I (IGF-I)) (Chanson & Salenave, 2008; Giustina & Colao, 2025; Melmed, 2009). The biological effects of the disease are mediated primarily through dysregulation of the GH–IGF-I axis, with IGF-I acting as the principal effector responsible for anabolic, metabolic, and proliferative processes in multiple tissues (Chanson & Salenave, 2008; Melmed, 2009).Under physiological conditions, this axis plays a key role in somatic growth, tissue repair, and metabolic homeostasis; however, its pathological activation results in widespread multisystem involvement (Melmed, 2009). GH is synthesized and secreted by somatotroph cells of the anterior pituitary gland located within the sella turcica. In more than 95% of cases, acromegaly arises from a hormonally active pituitary adenoma that secretes GH autonomously, thereby escaping normal hypothalamic regulation and negative feedback mechanisms mediated by circulating IGF-I. (Chanson & Salenave, 2008; Giustina & Colao, 2025; Melmed, 2009). Much less frequently, the disorder may be caused by ectopic secretion of growth hormone–releasing hormone (GHRH), most commonly from neuroendocrine tumors of the lung or gastrointestinal tract, leading to secondary pituitary hyperplasia rather than a discrete adenoma (Chanson & Salenave, 2008). Physiologically, GH secretion is tightly regulated by hypothalamic stimulatory and inhibitory signals, as well as by peripheral feedback from IGF-I. In acromegaly, disruption of this regulatory network results in continuous hormonal exposure, which drives progressive tissue overgrowth, metabolic abnormalities, and structural changes in multiple organ systems (Melmed, 2009; Reid et al., 2010). While the GH–IGF-I axis is essential for linear growth during childhood, in adults it primarily influences metabolic regulation, bone remodeling, and muscle maintenance. Consequently, chronic hormonal excess in adulthood constitutes the fundamental pathophysiological basis of the characteristic clinical features of acromegaly (Giustina & Colao, 2025; Melmed, 2009).

Etiology

The predominant cause of excessive GH secretion in acromegaly is a benign pituitary adenoma, which accounts for more than 95% of cases) (Chanson & Salenave, 2008; Giustina & Colao, 2025; Melmed, 2009). These adenomas arise from somatotroph cells of the anterior pituitary and exhibit autonomous GH secretion that escapes normal hypothalamic regulation and feedback inhibition by circulating IGF-I. Depending on tumor size, pituitary adenomas are classified as microadenomas (<10 mm) or macroadenomas (≥10 mm), with the latter being more common at the time of diagnosis due to the typically insidious onset and slow progression of the disease (Chanson & Salenave, 2008; Melmed, 2009).

Pituitary adenomas associated with acromegaly demonstrate considerable heterogeneity with respect to growth pattern, invasiveness, and secretory activity (Chanson & Salenave, 2008; Giustina & Colao, 2025). Some tumors exhibit aggressive local behavior, including invasion of surrounding structures such as the cavernous sinus or sphenoid bone, which may limit the success of surgical intervention and contribute to persistent disease activity (Giustina & Colao, 2025; Reid et al., 2010). In addition to hormonal hypersecretion, large adenomas may exert mass effects, leading to headaches, visual field defects, and hypopituitarism as a result of compression of adjacent pituitary tissue (Melmed, 2009; Reid et al., 2010).

From a molecular perspective, several genetic and epigenetic mechanisms have been implicated in the pathogenesis of GH-secreting pituitary adenomas. Activating mutations of the GNAS gene, which encodes the stimulatory G protein alpha subunit, are among the most frequently identified alterations and result in constitutive activation of adenylate cyclase and enhanced GH secretion (Melmed, 2009; Reid et al., 2010). Other molecular abnormalities affecting cell cycle regulation, growth factor signaling, and somatostatin receptor expression may further influence tumor behavior and responsiveness to medical therapy (M. R. Gadelha et al., 2025; Giustina & Colao, 2025)

Rarely, accounting for fewer than 1% of cases, acromegaly results from ectopic secretion of GHRH by non-pituitary neuroendocrine tumors, most commonly arising from the bronchial tree, pancreas, or gastrointestinal tract (Chanson & Salenave, 2008). Chronic exposure to elevated GHRH leads to diffuse pituitary hyperplasia rather than the formation of a discrete adenoma, a distinction with important diagnostic and therapeutic implications. In such cases, surgical removal of the pituitary gland is ineffective, and management should instead focus on identification and treatment of the ectopic GHRH-secreting tumor (Chanson & Salenave, 2008).

Exceptionally rare causes of acromegaly include ectopic GH secretion by non-pituitary tumors and familial syndromes associated with pituitary adenomas, such as multiple endocrine neoplasia type 1 (MEN1) and familial isolated pituitary adenomas (FIPA) (Giustina & Colao, 2025; Melmed, 2009). Although uncommon, recognition of these etiologies is clinically relevant, as they may necessitate genetic counseling, tailored surveillance strategies, and individualized therapeutic approaches.

Epidemiology and Disease Burden

Chronic elevation of GH and IGF-I leads to progressive multisystem organ involvement, resulting in abnormal tissue enlargement, characteristic morphological changes, and the development of numerous comorbidities that significantly increase disease-related morbidity and mortality (Giustina & Colao, 2025; Katznelson et al., 2014; Reid et al., 2010). The prevalence of acromegaly is estimated to range from approximately 40 to 70 cases per million individuals, with an annual incidence of 3–4 cases per million (Chanson & Salenave, 2008; Giustina & Colao, 2025; Reid et al., 2010). The disease most commonly presents in middle adulthood, with a mean age at diagnosis of approximately 40–50 years, and occurs with similar frequency in men and women (Chanson & Salenave, 2008; Reid et al., 2010).

Due to its insidious onset and slow progression, the diagnosis of acromegaly is frequently delayed, often by several years after the initial appearance of symptoms. Studies have shown that diagnostic delays typically range from four to ten years, during which time irreversible complications may develop (Reid et al., 2010). This persistent under-recognition contributes substantially to long-term disease burden and underscores the need for earlier detection and improved clinical awareness (Katznelson et al., 2014; Reid et al., 2010).

Prolonged exposure to elevated GH and IGF-I is associated with a wide spectrum of systemic complications, including cardiovascular disease, insulin resistance and diabetes mellitus, obstructive sleep apnea, arthropathy, and increased risk of certain malignancies, particularly colorectal neoplasia (Giustina & Colao, 2025; Katznelson et al., 2014; Reid et al., 2010). Cardiovascular complications, such as cardiomyopathy, hypertension, and arrhythmias, remain the leading cause of increased mortality in patients with uncontrolled disease and contribute significantly to reduced life expectancy (Giustina & Colao, 2025; Katznelson et al., 2014; Reid et al., 2010). Musculoskeletal involvement, including joint pain, reduced mobility, and spinal deformities, often leads to chronic disability and impaired functional status (Giustina & Colao, 2025; Katznelson et al., 2014; Reid et al., 2010).

Beyond physical comorbidities, acromegaly imposes a substantial psychosocial burden. Characteristic facial and somatic changes may negatively affect body image, social interactions, and mental health, with higher rates of depression, anxiety, and reduced self-esteem reported among affected individuals (Katznelson et al., 2014; Reid et al., 2010). Even in patients who achieve biochemical control, residual symptoms and long-standing structural changes may persist, resulting in incomplete normalization of quality of life.

The cumulative impact of delayed diagnosis, multisystem complications, and chronic treatment requirements translates into significant healthcare utilization and economic burden (Katznelson et al., 2014). Patients with acromegaly often require lifelong monitoring, repeated interventions, and long-term pharmacotherapy, further emphasizing the importance of early diagnosis, effective disease control, and patient-centered management strategies aimed at minimizing long-term morbidity and improving overall quality of life (Katznelson et al., 2014; Reid et al., 2010).

Clinical Manifestations

The clinical manifestations of acromegaly develop gradually and are highly heterogeneous, reflecting both the duration of hormonal excess and individual tissue sensitivity to IGF-I (Giustina & Colao, 2025; Melmed, 2009; Reid et al., 2010). Early features often include progressive swelling and thickening of the soft tissues of the hands and feet, commonly resulting in increased ring and shoe size. As the disease advances, excessive bone growth produces characteristic skeletal changes involving the skull, facial bones, mandible, and extremities (Giustina & Colao, 2025; Melmed, 2009).

Musculoskeletal involvement is frequent and may present as arthralgia, joint stiffness, reduced range of motion, and degenerative joint disease. Compression of peripheral nerves caused by soft tissue and bone

overgrowth can lead to sensory disturbances, including paresthesia, numbness, and carpal tunnel syndrome (Giustina & Colao, 2025; Reid et al., 2010). Craniofacial changes include prognathism, widening of interdental spaces with malocclusion, and enlargement of the frontal and nasal bones, while thoracic skeletal alterations may result in a barrel-shaped chest (Giustina & Colao, 2025).

Cardiovascular complications represent a major determinant of morbidity and mortality in acromegaly and include concentric myocardial hypertrophy, cardiomegaly, arrhythmias, valvular abnormalities, and, in advanced stages, heart failure (Giustina & Colao, 2025; Reid et al., 2010). Metabolic disturbances such as insulin resistance, impaired glucose tolerance, and diabetes mellitus are also common and further contribute to increased cardiovascular risk (Giustina & Colao, 2025; Reid et al., 2010).

Cutaneous and soft tissue changes are prominent and may include skin thickening, increased sebaceous activity, hyperhidrosis, and the development of benign skin lesions. Enlargement of the tongue and lips can affect speech and airway patency, while laryngeal involvement may lead to deepening of the voice. In addition, tumor-related mass effects may cause neurological symptoms such as headaches and visual field defects, most commonly bitemporal hemianopia resulting from compression of the optic chiasm (Melmed, 2009; Reid et al., 2010). Quality of life is frequently impaired, even in patients with biochemically controlled disease (Webb & Badia, 2016).

4. Management of Acromegaly

General Treatment Strategies

Management strategies for acromegaly encompass surgical, pharmacological, and radiotherapeutic approaches and are aimed at normalizing hormone hypersecretion, controlling tumor growth, alleviating clinical symptoms, and reducing disease-related morbidity and mortality (Katznelson et al., 2014; Melmed, 2006, 2009; Melmed et al., 2009). Surgical removal of the pituitary tumor via a transsphenoidal approach represents the primary and most effective therapeutic option for the majority of patients, offering the highest likelihood of rapid biochemical control, particularly in cases of small and well-circumscribed adenomas (Katznelson et al., 2014; Melmed et al., 2009).

Medical therapy and radiotherapy are generally considered second- and third-line treatment modalities and are primarily reserved for patients in whom surgery fails to achieve biochemical remission, is contraindicated, or is declined (Katznelson et al., 2014; Melmed, 2006; Melmed et al., 2009). Pharmacological treatment may also be used as adjuvant therapy following surgery or, in selected cases, as primary therapy when surgical cure is unlikely declined (Katznelson et al., 2014; Melmed, 2006; Melmed et al., 2009). Radiotherapy is typically considered in patients with persistent disease despite surgery and medical treatment, especially in the presence of residual or invasive tumors (Katznelson et al., 2014; Minniti et al., 2007).

The choice and sequence of therapeutic interventions are individualized and depend on multiple factors, including tumor size and invasiveness, baseline hormone levels, patient comorbidities, and treatment availability, underscoring the need for a multidisciplinary approach to disease management (Katznelson et al., 2014).

Surgical Treatment

Transsphenoidal surgery is widely regarded as the first-line treatment for most patients with acromegaly, as it is the only therapeutic option capable of providing rapid biochemical control and potential long-term remission (Katznelson et al., 2014; Melmed, 2006, 2009). The procedure leads to an immediate reduction in GH secretion by directly removing the source of hormone overproduction and is generally associated with a favorable safety profile when performed in experienced centers (Katznelson et al., 2014; Melmed, 2006).

Despite these advantages, complete biochemical remission is not achieved in a substantial proportion of patients. Surgical failure rates may reach up to 50% in individuals with macroadenomas, particularly in cases characterized by invasive tumor growth or extension into the cavernous sinus (Katznelson et al., 2014; Melmed, 2009; Reid et al., 2010). In such patients, residual disease is common, necessitating additional therapeutic interventions (Katznelson et al., 2014).

Consequently, many patients require adjunctive medical therapy following surgery to achieve adequate hormonal control. In selected clinical scenarios—including patient refusal of surgery, tumors predominantly located within the cavernous sinus, or the presence of significant contraindications to surgical intervention—primary pharmacological treatment may be considered as an alternative initial approach (Katznelson et al., 2014; Melmed, 2009).

Medical Therapy: Somatostatin Receptor Ligands

Octreotide and lanreotide are first-generation SRLs and are widely used in the pharmacological management of acromegaly (Colao et al., 2019; Katznelson et al., 2014; Melmed, 2006, 2009). These synthetic peptide analogs predominantly bind to SST2, while exhibiting lower affinity for SST3 and SST5 (Colao et al., 2019). Engagement of SST2 receptors on pituitary somatotroph adenoma cells leads to inhibition of intracellular signaling pathways involved in hormone secretion, resulting in suppression of GH release and subsequent reductions in circulating IGF-I concentrations (Colao et al., 2019; Melmed, 2006, 2009). Owing to these effects, SRLs are approved not only for the treatment of acromegaly but also for gastroenteropancreatic neuroendocrine neoplasms and carcinoid syndrome (Melmed, 2006).

Long-acting depot formulations of octreotide and lanreotide, administered at approximately four-week intervals via intramuscular or deep subcutaneous injection, currently represent the standard first-line medical therapy for patients with acromegaly who do not achieve remission after surgery or for whom surgical intervention is not appropriate (Colao et al., 2019; Katznelson et al., 2014; Melmed, 2006). Beyond biochemical control, SRLs may exert additional benefits related to tumor stabilization, including inhibition of adenoma growth and, in selected cases, modest reductions in tumor volume (Melmed et al., 2009).

Nevertheless, the use of injectable SRLs is associated with several clinically meaningful limitations. Parenteral administration may cause local adverse effects such as pain, induration, or inflammatory reactions at the injection site (Colao et al., 2019; Melmed, 2006; Plöckinger & Quabbe, 2005). In addition, the pharmacokinetics of depot formulations can result in variable drug exposure over the dosing interval, leading to fluctuations in GH and IGF-I levels and the potential recurrence of symptoms prior to the next scheduled injection (Melmed, 2006; Webb & Badia, 2016). The requirement for repeated administration, often performed by healthcare professionals, further contributes to treatment burden by necessitating regular clinic visits and may adversely affect long-term adherence and quality of life (Webb & Badia, 2016). Taken together, these challenges underscore the need for alternative therapeutic approaches capable of maintaining effective hormonal suppression while offering improved convenience and a reduced burden of care (Colao et al., 2019; M. R. Gadelha, Gadelha, et al., 2024).

5. Paltusotine: An Emerging Oral SST2 Agonist in the Treatment of Acromegaly.

Mechanism of action

Paltusotine is a first-in-class, nonpeptide, orally bioavailable agonist of SST2, the receptor subtype most strongly implicated in the regulation of GH secretion in acromegaly (Colao et al., 2019; Giustina & Colao, 2025). Similar to injectable SRLs, paltusotine exerts its therapeutic effects through selective binding to SST2 receptors expressed on GH-secreting pituitary adenoma cells (M. R. Gadelha et al., 2021; Melmed, 2006; Wildemberg et al., 2024).

Activation of SST2 receptors inhibits adenylate cyclase activity, resulting in reduced intracellular cyclic adenosine monophosphate signaling and subsequent suppression of GH secretion (Colao et al., 2004; Giustina et al., 2010; Melmed, 2009). The decrease in circulating GH levels leads to a downstream reduction in insulin-like growth factor I (IGF-I), which represents a central biochemical target in the management of acromegaly and correlates with improved clinical outcomes (Giustina et al., 2010).

In contrast to peptide-based somatostatin analogs, paltusotine is a small-molecule compound specifically engineered for oral administration. Its nonpeptide chemical structure confers resistance to enzymatic degradation within the gastrointestinal tract, enabling effective enteral absorption and systemic bioavailability following once-daily dosing (M. R. Gadelha, Casagrande, et al., 2024; Luo et al., 2025). Importantly, despite its oral formulation, paltusotine maintains high selectivity for SST2, thereby preserving the core therapeutic mechanism of traditional SRLs while overcoming limitations associated with injectable formulations (Fleseriu et al., 2021; M. R. Gadelha et al., 2021).

The development of an orally administered SST2-selective agonist represents a significant pharmacological advance, as it addresses treatment burden, pharmacokinetic variability, and adherence challenges inherent to long-acting injectable SRLs (Fleseriu et al., 2020, 2021). These properties make paltusotine a promising candidate for the long-term management of acromegaly, a chronic disease requiring sustained hormonal control (Colao et al., 2019; M. R. Gadelha et al., 2025).

Pharmacokinetics and Pharmacodynamics

Paltusotine exhibits favorable pharmacokinetic properties that support once-daily oral dosing. Following oral administration, the drug is efficiently absorbed through the gastrointestinal tract and achieves plasma concentrations sufficient to sustain continuous SST2 receptor activation over a 24-hour period (M. R. Gadelha,

Casagrande, et al., 2024; Luo et al., 2025). This predictable pharmacokinetic profile contrasts with depot injectable SRLs, which are associated with variable drug release and fluctuating systemic exposure over the dosing interval (Colao et al., 2015; Fleseriu et al., 2021).

Pharmacodynamic studies have demonstrated dose-dependent reductions in both GH and IGF-I levels in patients with acromegaly treated with paltusotine, confirming effective receptor engagement across clinically relevant dose ranges (M. R. Gadelha, Casagrande, et al., 2024; Jallad & Bronstein, 2019; Madan et al., 2022). Continuous daily exposure enables stable suppression of GH secretion and minimizes biochemical variability, which has been associated with persistent symptoms and impaired quality of life in patients receiving long-acting injectable therapies (Fleseriu et al., 2021; Kyriakakis et al., 2017; Webb & Badia, 2016).

The oral route of administration allows flexible dose titration and rapid adjustments in response to changes in biochemical control or tolerability, features that are not feasible with monthly injectable SRLs (Fleseriu et al., 2021; M. R. Gadelha, Casagrande, et al., 2024). Compared with injectable formulations, oral paltusotine may therefore offer more consistent biochemical control and improved symptom stability, with potential benefits for patient-reported outcomes and long-term adherence (Fleseriu et al., 2021; Kasuki & Gadelha, 2022).

Clinical Efficacy

The clinical efficacy of paltusotine has been evaluated in multiple clinical trials across diverse patient populations, providing robust evidence for its role in the management of acromegaly. Early proof-of-concept studies demonstrated that oral paltusotine produces dose-dependent suppression of both GH and IGF-I in healthy volunteers and in patients with acromegaly, supporting its further clinical development as a once-daily oral therapy (M. R. Gadelha, Casagrande, et al., 2024; Luo et al., 2025; Madan et al., 2022).

The Phase 3 PATHFNDR-1 trial, a randomized, double-blind, placebo-controlled study, evaluated paltusotine in adults with acromegaly who were previously biochemically controlled on long-acting injectable SRLs. After switching to once-daily oral paltusotine, a significantly higher proportion of patients maintained IGF-I levels ≤ 1.0 × upper limit of normal (ULN) compared with placebo, demonstrating maintenance of biochemical control comparable to injectable therapy (M. R. Gadelha, Casagrande, et al., 2024). Paltusotine also showed benefits across secondary endpoints, including sustained GH suppression and improvement in acromegaly-related symptoms, highlighting its clinical relevance beyond laboratory measures (M. R. Gadelha, Casagrande, et al., 2024; M. R. Gadelha, Gadelha, et al., 2024).

The Phase 3 PATHFNDR-2 trial further confirmed the efficacy of paltusotine in medically untreated patients and in those following SRL washout. At 24 weeks, a significantly greater proportion of paltusotine-treated patients achieved IGF-I ≤ 1.0 × ULN compared with placebo, with consistent efficacy observed across treatment-naïve and previously treated subgroups (Biller et al., 2024). These findings support the potential use of paltusotine both as a first-line medical therapy and as a maintenance option following injectable SRLs (Fleseriu et al., 2021; M. R. Gadelha et al., 2025).

Long-term data from open-label extension studies, including ACROBAT Advance, indicate that daily oral paltusotine maintains stable biochemical control and symptom improvement over extended follow-up periods (Fleseriu et al., 2021; M. Gadelha et al., 2024; Kasuki & Gadelha, 2022). In patients transitioning from injectable SRLs, paltusotine preserved GH and IGF-I control as well as quality-of-life measures, consistent with findings from randomized controlled trials. Collectively, these data establish oral paltusotine as an effective therapeutic option across a broad spectrum of patients with acromegaly (Fleseriu et al., 2021; Kasuki & Gadelha, 2022).

Safety and Tolerability

Paltusotine has demonstrated a generally favorable safety and tolerability profile across clinical trials in patients with acromegaly. The most frequently reported adverse events were mild to moderate in severity and predominantly gastrointestinal, including nausea, diarrhea, and abdominal discomfort (M. Gadelha et al., 2024; Luo et al., 2025). These effects are consistent with the known pharmacological actions of somatostatin receptor activation and resemble those observed with injectable somatostatin analogs (Colao et al., 2004; Zhao et al., 2022).

Importantly, oral administration eliminates injection-site reactions such as pain, erythema, and induration, which are commonly associated with long-acting injectable SRLs and contribute substantially to treatment burden and reduced patient satisfaction (Fleseriu et al., 2020, 2021). Most adverse events were transient and manageable, with relatively few patients requiring dose reduction or treatment discontinuation (M. R. Gadelha, Casagrande, et al., 2024).

Laboratory monitoring and vital-sign assessments did not reveal consistent clinically significant abnormalities, and no new or unexpected safety signals have been identified to date (Fleseriu et al., 2021; M. Gadelha et al., 2024). Long-term extension studies further suggest that sustained daily oral paltusotine maintains a favorable tolerability profile over prolonged treatment durations, with minimal impact on metabolic parameters and overall quality of life (Fleseriu et al., 2021; M. Gadelha et al., 2024).

Although available evidence supports a positive short- and medium-term safety profile, continued long-term follow-up and real-world data will be essential to fully characterize rare adverse events and confirm long-term safety in broader patient populations (Fleseriu et al., 2020).

Potential Advantages Over Injectable Therapies

One of the key advantages of paltusotine is its oral route of administration, which substantially reduces the treatment burden associated with chronic injectable therapies (Fleseriu et al., 2021). Long-acting injectable SRLs are frequently associated with injection-site pain, erythema, induration, and other local reactions, as well as the need for administration by healthcare professionals, all of which may negatively impact treatment adherence, patient comfort, and overall quality of life (Melmed, 2006; Zhao et al., 2022).

By providing a convenient oral alternative, paltusotine has the potential to improve long-term adherence and patient satisfaction, particularly among individuals who experience anxiety, discomfort, or logistical challenges related to regular injections (McLaren et al., 2023; Zhao et al., 2022). In addition, once-daily oral dosing allows for more consistent SST2 receptor engagement, potentially resulting in steadier biochemical control of GH and IGF-I levels throughout the dosing interval. This may reduce hormonal fluctuations commonly observed with monthly depot formulations, which have been associated with residual symptoms despite biochemical control (Colao et al., 2004; Jallad & Bronstein, 2019; Zhao et al., 2022).

Furthermore, the flexibility of oral dosing facilitates more rapid dose adjustments in response to adverse events or changes in disease activity, a feature that is inherently limited with long-acting injectable SRLs (M. R. Gadelha et al., 2025; Samson et al., 2020). Taken together, these characteristics highlight the potential of paltusotine to enhance patient-centered care in acromegaly by reducing treatment burden, maintaining biochemical efficacy, and improving health-related quality of life (Colao et al., 2019; Samson et al., 2020).

6. Results

The reviewed studies show that paltusotine is an orally administered, nonpeptide, selective SST2 agonist capable of suppressing GH secretion and reducing circulating IGF-I levels in patients with acromegaly (M. R. Gadelha, Casagrande, et al., 2024) Pharmacokinetic analyses demonstrated efficient oral absorption and plasma exposure sufficient to support once-daily dosing with sustained receptor activation. Across phase 2 and phase 3 clinical trials, paltusotine achieved dose-dependent and stable biochemical control, with a significant proportion of patients maintaining IGF-I concentrations within the normal range. periods (Fleseriu et al., 2021; M. Gadelha et al., 2024; Kasuki & Gadelha, 2022). These effects were observed in patients previously controlled on injectable SRLs as well as in treatment-naïve individuals. Secondary outcomes showed consistent GH suppression and improvement in acromegaly-related symptoms. Long-term extension studies indicated maintenance of biochemical control and symptom stability during prolonged treatment. Paltusotine was generally well tolerated, with predominantly mild to moderate gastrointestinal adverse events and no injection-site reactions. No unexpected safety concerns were identified during short- and medium-term follow-up. (Colao et al., 2004; Jallad & Bronstein, 2019; Zhao et al., 2022)

7. Discussion

Quality of life has become a critical outcome in the management of acromegaly, as a substantial proportion of patients continue to experience symptoms despite achieving biochemical control of GH and IGF-I levels (Colao et al., 2019; Fleseriu et al., 2020; Kyriakakis et al., 2017; Webb & Badia, 2016).Although injectable SRLs are effective in controlling hormonal hypersecretion, their long-term use is frequently associated with treatment-related burden, including repeated injections, injection-site discomfort, and the requirement for regular healthcare visits, which may negatively affect treatment satisfaction and adherence levels (Colao et al., 2019; Fleseriu et al., 2020; Kyriakakis et al., 2017; Webb & Badia, 2016).

In addition, pharmacokinetic variability inherent to long-acting injectable formulations may lead to fluctuations in IGF-I concentrations over the dosing interval, potentially contributing to residual symptoms even in biochemically controlled patients (Colao et al., 2015; Kasuki & Gadelha, 2022). In this context, paltusotine, an oral once-daily SST2-selective agonist, represents a promising alternative that may reduce

treatment burden and offer greater flexibility in dose adjustment compared with depot injectable therapies (M. R. Gadelha et al., 2025; Kasuki & Gadelha, 2022).

The shorter effective pharmacokinetic profile of oral paltusotine may allow for more rapid dose titration or discontinuation in the event of adverse effects, a feature that is inherently limited with long-acting injectable SRLs (M. R. Gadelha et al., 2025; Kasuki & Gadelha, 2022). Moreover, oral administration may improve adherence and patient preference in appropriately selected individuals, particularly those who experience discomfort or logistical challenges related to injectable treatments (Fleseriu et al., 2021; Webb & Badia, 2016).

Nevertheless, long-term data on patient-reported outcomes remain limited, and not all patients are expected to derive equivalent benefit from oral therapy. Considerations related to cost, reimbursement, and access may further influence the clinical utility of paltusotine in routine practice (Holdaway & Rajasoorya, 1999; Kasuki & Gadelha, 2022). Importantly, current evidence is derived predominantly from controlled clinical trials with relatively selected patient populations, and real-world effectiveness data are still lacking (Kasuki & Gadelha, 2022; Webb & Badia, 2016). Further longitudinal studies are therefore warranted to better define the long-term impact of paltusotine on quality of life and to clarify its role relative to established injectable therapies within individualized treatment strategies for acromegaly (Fleseriu et al., 2021; M. R. Gadelha et al., 2025).

8. Conclusion

In summary, acromegaly remains a chronic condition that requires individualized, long-term management. Although surgery is the cornerstone of therapy, many patients continue to require medical treatment due to persistent hormonal excess and associated complications. Long-acting injectable SRLs have been effective for many years, but their parenteral route and treatment burden have underscored the need for alternative approaches.

Paltusotine represents a promising oral alternative to injectable SRLs and has the potential to reduce treatment burden while maintaining biochemical control and improving patient convenience. Notably, in September 2025, the U.S. Food and Drug Administration approved *Palsonify*, making it the first once-daily oral SST2 agonist available for the treatment of adults with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option, thereby marking a significant milestone in the therapeutic landscape of this disease (Ahmed et al., 2026).

However, additional long-term and real-world data are needed to clarify its sustained impact on quality of life, comparative effectiveness, cost-effectiveness, and its relative role alongside existing therapies in diverse clinical settings. Continued clinical in experience and post-marketing surveillance will be essential to fully establish its definitive place in long-term acromegaly management.

Author's Contribution

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Kamil Harenza: Methodology, project administration
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