5 March 2026
EMA/OD/0000302963
EMADOC-1700519818-2973073
Committee for Orphan Medicinal Products

EMA/COMP position on review of criteria for orphan designation

of an orphan medicinal product submitted for marketing authorisation application

Palsonify (paltusotine)
Treatment of acromegaly
EU/3/25/3035

Sponsor: Crinetics Pharmaceuticals Europe GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance	Paltusotine
Other name(s)	--
International Non-Proprietary Name	Paltusotine
Tradename	Palsonify
Orphan condition	Treatment of acromegaly
Sponsor's details:	Crinetics Pharmaceuticals Europe GmbH Barbara Strozzilaan 201 1083 HN Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Voisin Consulting Life Sciences
COMP opinion	23 January 2025
EC decision	26 February 2025
EC registration number	EU/3/25/3035
Post-designation procedural history	
Transfer of sponsorship	Transfer from Voisin Consulting Life Sciences to Crinetics Pharmaceuticals Europe GmbH – EC decision of 24 September 2025
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Nicolas Beix / Paolo Gasparini
Applicant	Crinetics Pharmaceuticals Europe GmbH
Application submission	4 March 2025
Procedure start	27 March 2025
Procedure number	EMA/H/C/006636
Invented name	Palsonify
Proposed therapeutic indication	Palsonify is indicated for the medical treatment of adult patients with acromegaly. Further information on Palsonify can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/palsonify
CHMP opinion	26 February 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cécile Dop / Vallo Tillmann
Sponsor's report submission	7 October 2025
COMP discussion	17-19 February 2026
COMP opinion (adoption via written procedure)	5 March 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in designation in 2025 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing paltusotine was considered justified based on preliminary assessment of clinical data showing normalisation of Growth hormone and IGH-1 serum levels;
- the condition is life-threatening and chronically debilitating due to disproportionate skeletal, tissue, and organ growth, leading to multisystem morbidities and terminal cardiovascular, cerebrovascular, and respiratory disease;
- the condition was estimated to be affecting approximately 1.1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing paltusotine will be of significant benefit to those affected by the condition. Preliminary assessment of the clinical data provided by the sponsor has indicated improved efficacy to current authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing paltusotine as an orphan medicinal product for the orphan condition: treatment of acromegaly.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Acromegaly is a rare, chronic, progressive growth disorder characterised by excessive secretion of growth hormone (GH) and its effector hormone, insulin-like growth factor (IGF)-1. The disorder is usually the result of a benign GH-producing pituitary gland tumour or adenoma.

Acromegaly most commonly affects middle-aged adults and can result in serious illness and premature death. Patients have disproportionate skeletal, tissue, and organ growth. Once recognised, acromegaly is treatable in most patients. If left uncontrolled, acromegaly is associated with multisystem

morbidities and increased mortality, predominantly from cardiovascular, cerebrovascular, and respiratory disease.

The pathophysiology starts with hyper-production of GH. GH (also known as somatotropin) is a peptide hormone synthesised, stored and secreted by the somatotroph cells of the pituitary gland. GH is secreted from the anterior pituitary gland in a pulsatile manner throughout the day. GH exerts its effects by binding to the Growth Hormone Receptor (GHR) on target cells. The GHR is a transmembrane glycoprotein that binds GH in its extracellular domain and induces downstream signalling leading to receptor dimerization and activation of intra- and intercellular signal transduction pathways, which trigger production and subsequent release of its effector insulin-like growth factor-1 (IGF-1) (either paracellularly or into the bloodstream) (Parkinson and Trainer 1999, Rosenfeld and Hwa 2009). GHR is expressed in many tissues, the most abundant being the liver (primarily hepatocytes) and adipose tissue. The liver is the major site of IGF-1 production. IGF-1, also known as somatomedin C, has growth-stimulating effects on a wide variety of tissues including activity on osteoblasts and chondrocytes to promote bone growth (Rosenfeld and Hwa 2009).

The condition has not changed in terms of classification or description since the initial designation.

The approved therapeutic indication "Palsonify is indicated for the medical treatment of adult patients with acromegaly." falls within the scope of the designated orphan condition "Treatment of acromegaly".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Acromegaly is a chronic, debilitating disease associated with increased morbidity and mortality as well as compromised quality of life. The burden associated with acromegaly are described in detail in the consensus statement on acromegaly therapeutic outcomes from 2018 (Melmed 2018).

Coexisting illnesses are determined by the level of growth hormone before and after treatment, IGF-1 levels, patients' age, size of the tumour, degree of tumour invasion, and duration of symptoms before diagnosis. Skeletal disorders account for the most significant functional disability and contribute to a compromised quality of life. Up to 70% of acromegaly patients have large-joint and axial arthropathy that includes thickened articular cartilage, periarticular calcifications, osteophyte overgrowth, and synovitis. Degenerative osteoarthritis, scoliosis, kyphosis, and vertebral fractures can occur. Such fractures have been observed in up to 60% of patients with acromegaly. These fractures can be present despite disease control and are frequently asymptomatic. Normal BMD on dual X- ray absorptiometry might offer false reassurance, as BMD does not predict fracture risk in patients with acromegaly.

Excessive levels of GH and IGF-1 can also cause major structural and functional cardiac changes. By the time of diagnosis, arrhythmias, hypertension, and valvular heart disease are present in up to 60% of patients. Myocardial hypertrophy develops and diastolic heart failure occurs with untreated prolonged disease. Unlike diastolic heart failure, aortic and mitral valve regurgitation.

According to a series published in the 1980-1990s about 60% of the patients die from cardiovascular disease, 25% from respiratory complications (Colao 2004). Untreated acromegaly patients would be expected to die 10 years earlier than healthy subjects.

Based on this clinical picture, acromegaly disease is regarded a life-threatening and chronically debilitating condition. There have been no changes in the chronically debilitating or life-threatening nature of the condition since the designation stage.

Number of people affected or at risk

The sponsor's strategy to estimate the prevalence of acromegaly in the European Union (EU) and European Economic Area (EEA) was developed in accordance with the Committee for Orphan Medicinal Products (COMP) guidance document COMP/436/01 Rev. 1 ("Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation"). The approach aimed to provide a comprehensive and conservative estimate of complete (point) prevalence to support orphan maintenance.

The COMP had previously accepted a prevalence of approximately 1.1 per 10,000 persons in the EU at the time of initial orphan designation in 2024. The current analysis was undertaken to reassess this estimate using updated population data and an expanded evidence base.

The sponsor performed a structured review of available epidemiological data. Primary sources included national acromegaly registries and healthcare databases. Registries were identified in Belgium, Bulgaria, and Spain and prevalence data were extracted from peer-reviewed publications reporting analyses derived from these registries. In addition, a systematic literature search was conducted. Studies conducted in large or nationally representative populations were prioritized. Relevant data were identified for multiple European countries, including Denmark, France, Iceland, Italy, Malta, Spain, and others. Where studies were regional rather than national in scope, this was explicitly noted. This is displayed in Table 1.

Table 1. Prevalence of Acromegaly in Europe.

Country (Data source)	**Prevalence per 10,000**	**Population**	**Reference**
Belgium and Luxembourg (AcroBel)	0.4	37 Hospitals	(Bex et al., 2007)
Belgium (Healthcare databases)	1.25	Province of Liege	(Daly et al., 2006)
Bulgaria (National Acromegaly Database)	0.4838	National scope	(Vandeva et al., 2010)
Croatia (Literature)	0.85	National Scope	(Bolanowski et al., 2022)
Denmark (National Acromegaly Cohort)	1.08	National Scope	(Rosendal et al., 2024)
Denmark (National healthcare records)	1.22	North Denmark Region	(Aagaard et al., 2022)
Denmark (Healthcare databases)	0.85	National Scope	(Dal et al., 2016)
Finland (Statistical registries)	0.90	National Scope	(Raappana et al., 2010)
France (National hospital discharge databases)	1.04	National Scope	(Fauchier et al., 2024)
Hungary (Literature)	0.62	National Scope	(Bolanowski et al., 2022)

Country (Data source)	Prevalence per 10,000	Population	Reference
Iceland (National Healthcare records)	1.367	National Scope	(Agustsson et al., 2015)
Iceland (University Hospital)	1.33	1 University Hospital	(Hoskuldsdottir, Fjalldal & Sigurjonsdottir, 2015)
Italy (Healthcare records)	0.98	Province of Messina, Sicily	(Cannavò et al., 2010)
Italy (Healthcare databases)	0.83	Administrative health databases in Piedmont Region	(Caputo et al., 2019)
Italy (Health Search database)	0.69	Health Search Database, 1 million patients nationwide	(Gatto et al., 2018)
Malta (National Healthcare database)	1.14	National Scope	(Mercieca, Gruppetta & Vassallo, 2012)
Malta (Healthcare databases)	1.24	National Scope	(Gruppetta, Mercieca & Vassallo, 2013)
Poland (Literature)	0.7	National Scope	(Bolanowski et al., 2022)
Slovenia (Literature)	0.6	National Scope	(Bolanowski et al., 2022)
Spain (Spanish Acromegaly Registry)	0.337	National Scope	(Mestron et al., 2004)
Spain (Literature)	0.6	Province of Vizcaya	(Etxabe et al., 1993)
Sweden (Healthcare records)	0.69	Western region of Sweden	(Bengtsson et al., 1988)
Sweden (SPR and Healthcare databases)	0.33	National Scope	(Tjörnstrand et al., 2014)

All identified studies reporting prevalence per 10,000 population were compiled. Reported prevalence estimates ranged from 0.33 to 1.367 per 10,000 persons. Variability across countries is attributed, by the sponsor, to differences in data sources (e.g., hospital registries, administrative healthcare databases, national statistical registries), study periods, case ascertainment methodologies, and geographic coverage. For several countries, more than one prevalence estimate was available; in such cases, the higher estimate was selected for subsequent calculations in order to provide a conservative (upper-bound) estimate of disease burden.

A prevalence estimate derived indirectly from incidence was not calculated. The sponsor justified this decision by noting that acromegaly is a chronic condition with complex and variable disease duration, making incidence-based extrapolation less reliable. Given the substantial population coverage of the identified prevalence studies, direct extrapolation of observed prevalence values to other EU Member States was considered methodologically more appropriate by the sponsor.

For the estimation of total cases, country-specific prevalence values (per 10,000 persons) were applied to Eurostat 2024 population data for each of the 27 EU Member States plus three EEA countries (Iceland, Liechtenstein, and Norway). Where no country-specific prevalence data were available, the highest reported European prevalence (1.367 per 10,000, derived from Icelandic national data) was used to ensure a maximum-case scenario. With a total population of 455,279,983, the number of

cases resulted in an estimated 48,052 cases of acromegaly across the EU+3EEA. This corresponds to an overall prevalence of approximately 1.1 per 10,000 persons (upper estimate).

This estimate is consistent with the prevalence previously acknowledged by the COMP, and no change in EU prevalence is identified since the initial orphan designation assessment. The methodology and proposal were considered acceptable by the Committee.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are several medicinal products authorised in the European Community for treatment of acromegaly. According to the Endocrine Society Clinical Practice Guideline (co-sponsored by the Endocrine Society and the European Society of Endocrinology), the clinical aims in the management of acromegaly include the following: (1) to control biochemical indices of activity (principally GH and IGF-I), (2) to control tumour size and prevent local mass effects, (3) to reduce the signs and symptoms of disease, (4) to prevent or improve comorbidities, and (5) to prevent early mortality (Katznelson et al 2014).

A stepwise therapeutic strategy using surgery to remove or debulk the pituitary tumour, and/or radiotherapy to ablate the tumour, and/or pharmacological intervention to achieve GH and IGF-1 control, is used to achieve the goals (Katznelson et al 2014). The treatment strategy depends on the details of the condition, such as presence of micro-/ macroadenoma, responsiveness to treatment, and GH or IGF-1 levels. Transsphenoidal surgery has been recommended as the primary therapy in most patients. Use of a somatostatin receptor ligand (SRL) as primary therapy has been recommended for patients who cannot be cured by surgery, have extensive cavernous sinus invasion, do not have chiasmal compression, or are poor surgical candidates.

The following classes of pharmacological agents are used for the treatment of acromegaly: somatostatin analogues or somatostatin receptor ligands (SRLs) (octreotide, lanreotide, pasireotide), dopamine agonists (bromocriptine and cabergoline), GH receptor antagonists (pegvisomant), and prolactin inhibitors (lisuride, if tumour also secretes prolactin).

As per the latest European treatment guidance (Melmet 2018) acromegaly patients should be treated as follows :

First line: Surgical resection of the pituitary adenoma is recommended where possible and represents the optimal opportunity for cure. Primary medical therapy with an SRL might be considered if surgery is contraindicated or if a poor likelihood of success is expected owing to patient-specific and/or tumour-specific factors.

For patients with persistent disease after surgery, a first-generation long-acting SRL is recommended as first-line medical therapy. The choice between octreotide LAR and lanreotide autogel is determined by availability, convenience of administration and patient preference. Cabergoline can be attempted as a first line medical therapy in patients with acromegaly and mildly elevated levels of IGF1 of <2.5 times the upper limit of normal.

Second line: Additional therapies are necessary when first-line medical therapy is not successful in normalizing levels of IGF1. For patients who achieve partial response (a decrease in GH and/or IGF1 ≥50%) after using a long-acting first-generation SRL as first-line medical therapy, increasing the dose of the SRL and/or increasing the dose frequency of lanreotide autogel should be attempted. Addition of cabergoline to continued SRL treatment when levels of IGF1 remain modestly elevated during SRL administration is recommended. If a tumoral remnant is surgically resectable, which would enable a considerable decrease in tumour mass, a second surgical intervention might be proposed before re-initiating SRL treatment.

If biochemical control is not achieved after administering the maximal dose of first-generation SRL, treatment should be individualized on the basis of the presence or absence of clinically relevant residual tumour and impaired glucose tolerance.

Additional consideration: If biochemical control is not achieved after second-line therapy, stereotactic radiosurgery or surgical intervention or reintervention should be reconsidered, as appropriate. Use of temozolomide should be limited to patients with unusually aggressive or proven malignant pituitary tumours.

The medicinal products approved in the EU for the treatment of acromegaly are shown in Table 2.

Table 2. Medicinal products approved in the EU for the treatment of acromegaly.

Product	**Approved indication**	**Satisfactory**
Sandostatine (octreotide)	Symptomatic control and reduction of growth hormone (GH) and IGF-1 plasma levels in patients with acromegaly who are inadequately controlled by surgery or radiotherapy. Sandostatin is also indicated for acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective.	Yes
Somatuline (lanreotide)	The treatment of individuals with acromegaly when the circulating levels of Growth Hormone (GH) and/or Insulin-like Growth Factor-1 (IGF-1) remain abnormal after surgery and/or radiotherapy, or in patients who otherwise require medical treatment. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalise these values.	Yes
Signifor (Pasireotide)	Treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.	No, due to differences in patient population
Bromocriptine	As an adjunct to surgery and/or radiotherapy to reduce circulating growth hormone levels in the management of acromegalic patients.	No, due to differences in patient population
Somavert (Pegvisomant)	Treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.	No, due to differences in patient population

Product	Approved indication	Satisfactory
Oczyesa (octreotide)	Indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues	No, due to differences in patient population

Mycapssa was granted marketing authorisation in the EU on 2 December 2022 for the maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues. The marketing authorisation was initially valid for a 5-year period. On 26 February 2025, the European Commission withdrew the marketing authorisation for Mycapssa (octreotide) in the European Union (EU). The withdrawal was done at the request of the marketing authorisation holder.

Palsonify is indicated for the medical treatment and maintenance therapy of adult patients with acromegaly. In this specific therapeutic area, Sandostatine (octreotide) and Somatuline (lanreotide) are considered satisfactory methods, as these medicines are approved for treatment of acromegaly and have complete overlap with Palsonify in their indications. The medicines Signifor (pasireotide), Bromocriptine, Somavert, Oczyesa are not considered satisfactory methods as they do not address the totality of the patient population addressed by Palsonify.

Significant benefit

Paltusotine is an orally bioavailable somatostatin receptor subtype 2 (SST2) agonist developed for the medical treatment and long-term maintenance therapy of acromegaly in both treatment-naïve patients and those switching from current standard of care. The pharmacokinetic profile is reported to support once-daily oral administration, with consistent systemic exposure achieved within approximately one week. The sponsor therefore considers that paltusotine may offer rapid, consistent, and durable biochemical and clinical control while avoiding the burden of injectable therapy and potentially reducing treatment-limiting adverse events associated with some approved therapies.

The sponsor’s claims of significant benefit over currently approved therapies - Oczyesa (octreotide hydrochloride), octreotide acetate injection depot, and lanreotide acetate injection depot - are based on arguments of improved efficacy and major contribution to patient care.

Since Oczyesa (octreotide hydrochloride) is not considered a satisfactory method given the authorised indication, a discussion versus this product is not considered needed, and the claims were not assessed.

Clinical programme of paltusotine

Across the development programme, paltusotine is reported to have demonstrated rapid and sustained reductions in insulin-like growth factor 1 (IGF-1) and growth hormone (GH) levels, improvements in acromegaly-related symptoms, and an overall tolerability profile considered acceptable by the sponsor. Efficacy for both medical treatment and long-term maintenance therapy was evaluated in two pivotal global, randomised, double-blind, placebo-controlled Phase 3 studies (CRN00808-08 and CRN00808-09). These studies are reported to have met their primary and all predefined secondary endpoints, demonstrating statistically significant and clinically meaningful treatment effects.

Study CRN00808-08 enrolled participants with confirmed, uncontrolled acromegaly at baseline, including medically naïve patients, previously treated patients (not within the prior 4 months), and patients washed out from prior short- or long-acting somatostatin receptor ligands (SRLs). Study

CRN00808-09 enrolled participants with confirmed, biochemically controlled disease while receiving stable long-acting octreotide acetate or lanreotide acetate prior to switching to paltusotine. According to the sponsor, once-daily oral paltusotine at 40 mg or 60 mg resulted in maintenance of IGF-1 and GH normalisation in both settings and allowed a transition from injectable SRLs to oral monotherapy in controlled patients. Treatment effects were reported to be consistent across subgroups, including age, sex, race/ethnicity, region, baseline IGF-1 level, and disease status.

For the primary endpoint of biochemical control (IGF-1 ≤1.0× upper limit of normal [ULN]), a significantly higher proportion of participants receiving paltusotine achieved control at end of randomised treatment (EOR) in Study CRN00808-08 (55.6% vs 5.3% with placebo; p<0.0001). In Study CRN00808-09, a higher proportion of participants maintained biochemical control at EOR with paltusotine compared with placebo (83.3% [25/30] vs 3.6% [1/28]; p<0.0001). Sensitivity analyses were reported to confirm these findings.

For the secondary endpoint assessing change from baseline to EOR in IGF-1×ULN, statistically significant differences in favour of paltusotine were observed in both studies (p<0.0001). In CRN00808-08, least squares mean (±SE) changes were -0.819 (±0.0789) for paltusotine and 0.087 (±0.0751) for placebo, with a treatment difference of -0.906 (95% CI: -1.106 to -0.706). Mean IGF-1 levels in the paltusotine group decreased by Week 2 and remained stable from Week 4 to Week 24, whereas placebo-treated participants showed no reduction and some required rescue therapy. In CRN00808-09, least squares mean (±SE) changes were -0.042 (±0.0932) for paltusotine and 0.833 (±0.0962) for placebo, with a treatment difference of -0.791 (95% CI: -1.057 to -0.525). IGF-1 levels remained stable with paltusotine and increased in the placebo group, with multiple participants requiring rescue therapy.

Symptom burden was assessed using the Acromegaly Symptom Diary (ASD), a sponsor-developed a patient-reported outcome instrument. Both Phase 3 studies showed reductions and stabilisation in ASD total scores with paltusotine, indicating improvement in patient-reported symptoms such as headache, joint pain, sweating, fatigue, weakness, swelling, and paraesthesia.

The sponsor further notes that rescue therapy was rarely required in participants receiving paltusotine, irrespective of prior treatment status. In open-label extension (OLE) phases, including Study CRN00808-05, participants reportedly maintained disease control and long-term treatment benefits for up to four years, with no evidence of tachyphylaxis and limited need for additional therapy.

Pituitary tumour volume was assessed by magnetic resonance imaging (MRI) and evaluated by investigators for clinically significant findings and by a central radiologist for volumetric measurement. In Study CRN00808-08, a tumour volume reduction >20% was observed in 11.8% of participants receiving paltusotine and in none receiving placebo. In Study CRN00808-09, no clinically significant (>25%) increases or decreases in residual tumour volume were observed from baseline to EOR.

Treatment preference was evaluated at end of treatment in both Phase 3 studies. In CRN00808-08, 77.8% of participants in the paltusotine group and 63.2% in the placebo group indicated a preference for oral medication over injections. In CRN00808-09, 60.0% of participants in the paltusotine group and 60.7% in the placebo group expressed a preference for oral therapy. The sponsor suggests that this preference may support improved adherence and, potentially, improved long-term disease control.

Regarding safety, adverse reactions associated with paltusotine included gastrointestinal events (diarrhoea, abdominal pain, nausea, abdominal discomfort), sinus bradycardia, and cholelithiasis, consistent with the class effects of SRLs. Gastrointestinal events were reported to occur primarily within the first three months, were generally non-serious, and infrequently led to discontinuation. Sinus bradycardia events were non-serious and asymptomatic, without associated adverse

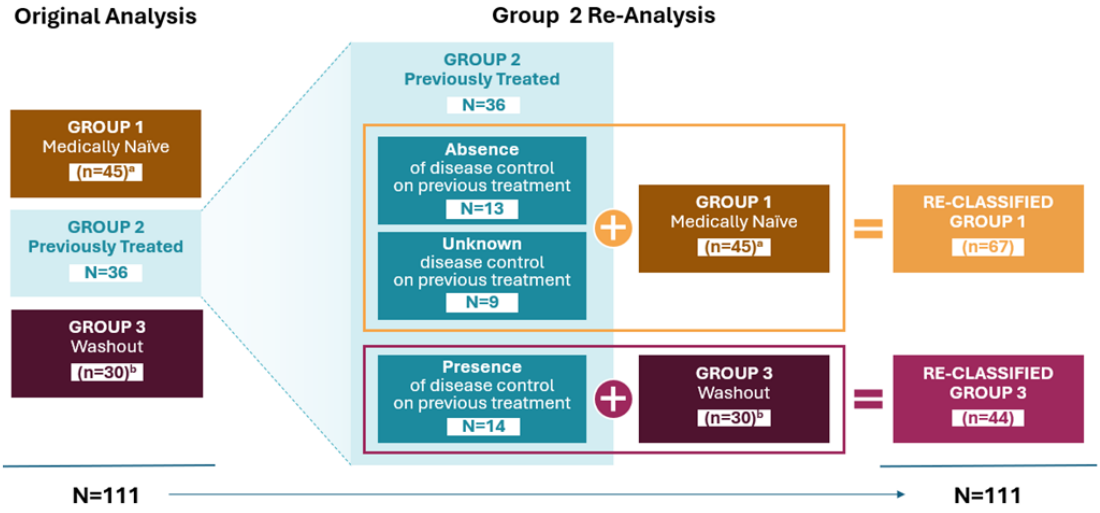
cardiovascular outcomes. Cholelithiasis events occurred after more than six months of exposure and did not result in treatment discontinuation.

Claim based on improved efficacy versus standard-of-care injected SRLs (octreotide acetate and lanreotide acetate)

For the claim of improved efficacy versus standard-of-care injected first-generation somatostatin receptor ligands (SRLs), the sponsor contextualises the efficacy of octreotide acetate and lanreotide acetate by noting that reported biochemical control rates across published studies are highly variable and depend on study design features (e.g., eligibility criteria, prior surgical debulking, the IGF-1 assay used, and whether endpoints are defined using IGF-1, GH, or a composite measure) (Zahr & Fleseriu, 2018). In support of this variability, the sponsor cites a clinical review reporting IGF-1 normalisation rates of 41-75% for octreotide acetate LAR and 30-63% for lanreotide acetate slow release (SR), with GH control rates ranging from 47-75% and 14-78%, respectively (Freda et al., 2002). The sponsor further refers to a meta-analysis examining how trial design influences reported SRL efficacy, which reported mean response rates of 56% (±SD 19.7) for GH control and 55% (±SD 17.3) for IGF-1 normalisation, and concluded that later year of publication, study duration, and prior SRL use were determinants of outcomes (Carmichael et al., 2014). Against this background, the sponsor argues that the primary endpoint results from paltusotine Phase 3 studies — maintenance of IGF-1 ≤1.0× ULN in PATHFNDR-1 (83.3%) and achievement of IGF-1 ≤1.0× ULN in PATHFNDR-2 (55%) — are consistent with, and in the case of PATHFNDR-1 exceed, the ranges reported for injected SRLs.

To support a further efficacy argument in patients not responding to available therapies, the sponsor describes a US FDA–informed post hoc analysis undertaken to better characterise previously treated participants (original Group 2) in Study CRN00808-08 (PATHFNDR-2). This analysis involved supplemental collection of historical data and a retrospective reclassification based on documented presence or absence of biochemical disease control on prior acromegaly therapies, including dopamine agonists, GH receptor antagonists, and somatostatin analogues. Following reclassification, the sponsor reports two reconfigured groups: a redefined Group 1 comprising medically naïve participants, prior non-responders, and those with unknown prior response status (total n=67; 32 paltusotine, 35 placebo), and a redefined Group 3 comprising participants who washed out from standard of care immediately prior to randomisation plus participants with evidence of prior disease control on standard of care (total n=44; 22 paltusotine, 22 placebo) (Figure 2).

Figure 1. Disposition of PATHFNDR-2 Participants in Group 2 Based on Presence or Absence off Disease Control with Prior Acromegaly Therapy and Resulting Study Group Reclassification



[a] Participant BR014-0815 was incorrectly assigned to the medically naive group (Group 1) but was previously treated. This participant had presence of disease control after previous treatment and was reassigned to the previously treated group (Group 3).

[b] Participant US031-08001 was incorrectly assigned to the previously treated group (Group 2) but was washed out of previous SRL treatment. This participant is now included in the reclassified Group 3.

On the primary endpoint (IGF-1 ≤1.0× ULN at end of the randomised controlled phase [EOR]), the sponsor reports that 34.4% (11/32) of participants in the redefined Group 1 receiving paltusotine achieved biochemical control compared with 2.9% (1/35) receiving placebo (nominal p=0.0016). Within the subset characterised as having absence of disease control on any previous therapy, the sponsor reports biochemical control in 57.1% (4/7) with paltusotine versus 0% (0/6) with placebo (nominal p=0.049), and among those with unknown prior response status, biochemical control in 66.7% (2/3) with paltusotine versus 0% (0/6) with placebo (nominal p=0.0833) (Table 3). The sponsor further reports that among participants who had not achieved disease control on prior injected SRLs specifically (octreotide acetate or lanreotide acetate), 50.0% (2/4) in the paltusotine group achieved biochemical control compared with 0% (0/4) in the placebo group (Table 4), and that secondary endpoints related to IGF-1 and GH also favoured paltusotine in these reanalyses.

Table 3. Primary Efficacy Analysis for Group 1 and Group 3: IGF-1 ≤1.0x ULN at EOR Based on Re classification of Group 2 (Any Prior Treatment)

	Paltusotine (N=54) n/N (%)	**Placebo (N=57) n/N (%)**	**p-Value**
Group 1 Re-analysis			
Medically Naïve + Absence of disease control + Unknown	34.4% (11/32)	2.9% (1/35)	0.0016
Absence disease control on any Tx	57.1% (4/7)	0% (0/6)	0.049
Unknown	66.7% (2/3)	0% (0/6)	0.0833
Group 3 Re-analysis			
Washout + Presence of disease control	86.4% (19/22)	9.1% (2/22)	<0.0001
Presence of disease control on any Tx	75% (6/8)	0% (0/6)	0.0093

EOR=End of RC phase, IGF-1=Insulin-like Growth Factor-1, ULN=Upper Limit of Normal
Source: ISE Table 14.101.2.1.5.1

Table 4. Primary Efficacy Analysis for Group 1 and Group 3: IGF-1 ≤1.0x ULN at EOR Based on Re-classification of Group 2 (Prior SRL Treatment)

	Paltusotine (N=54) n/N (%)	**Placebo (N=57) n/N (%)**	**P Value**
Group 1 Re-analysis			
Medically Naïve + Absence of disease control + Unknown	28.6 (8/28)	2.9% (1/35)	0.0098
Absence of disease control on prior SRL	50.0% (2/4)	0% (0/4)	0.2143
Unknown	50.0% (1/2)	0% (0/8)	0.2000
Group 3 Re-analysis			
Washout + Presence of disease control	86.4% (19/22)	9.1% (2/22)	<0.0001
Presence of disease control on prior SRL	77.8% (7/9)	0% (0/6)	0.0056

EOR=End of RC phase, IGF-1=Insulin-like Growth Factor-1, SRL=somatostatin receptor ligand, ULN=Upper Limit of Normal
Source: ISE Table 14.101.2.1.5.2

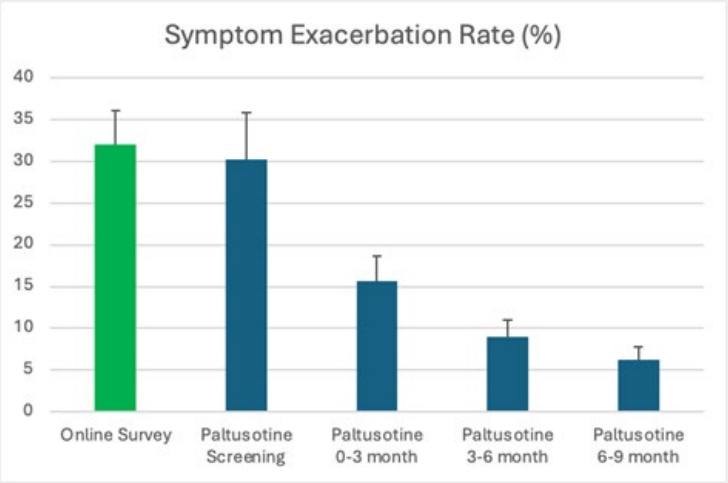
For the redefined Group 3, which the sponsor characterises as a more homogeneous population of prior responders and washout participants, the sponsor reports that 86.4% (19/22) receiving paltusotine achieved IGF-1 ≤1.0× ULN at EOR compared with 9.1% (2/22) receiving placebo (nominal p<0.0001) (Table 3 and Table 4). In the subset with documented presence of disease control on any prior therapy, the sponsor reports biochemical control in 75% (6/8) with paltusotine versus 0% (0/6) with placebo (nominal p=0.0093), and for those with documented disease control on prior SRL therapy, 77.8% (7/9) versus 0% (0/6) (nominal p=0.0056). The sponsor interprets these findings as indicating that lack of disease control or resistance to prior somatostatin analogue therapy does not preclude achieving biochemical control with paltusotine, and highlights in particular the approximately 60% control rate among participants considered non-responders to previous medical therapies, including the reported 50% control rate in the small subgroup previously not controlled on octreotide acetate or lanreotide acetate depot injections.

In addition to biochemical endpoints, the sponsor argues that paltusotine may provide improved stability of symptom control compared with injected long-acting SRLs, addressing symptom variability that would be associated with depot injection cycles. To characterise symptom instability with injected SRLs, the sponsor cites a survey of 195 patients treated in nine pituitary centres across Germany, the United Kingdom, and the Netherlands, in which most patients receiving depot octreotide acetate or lanreotide acetate reported ongoing symptoms, including within-cycle symptom worsening and variability (Strasburger et al., 2016). The sponsor also references a web-based survey in 58 medically treated patients (including 31 on injected depot SRLs as mono- or combination therapy) that collected daily symptom burden for three months using symptom items aligned with the Acromegaly Symptom Diary (ASD) used in the paltusotine programme (Martin et al., 2023). In that survey, 67% (12/18) of patients on monthly long-acting SRL injection monotherapy reported at least one breakthrough symptom before the next injection, and breakthrough symptom exacerbations - defined as a 2-point increase in any individual symptom score comparing successive 2-day averages - occurred on an average of 32.1% of days.

The sponsor then describes a retrospective intra-subject (cross-over) analysis within PATHFNDR-1, comparing daily ASD data collected during screening while participants were receiving their last injected SRL dose (during at least the final two weeks before randomisation) with ASD data collected

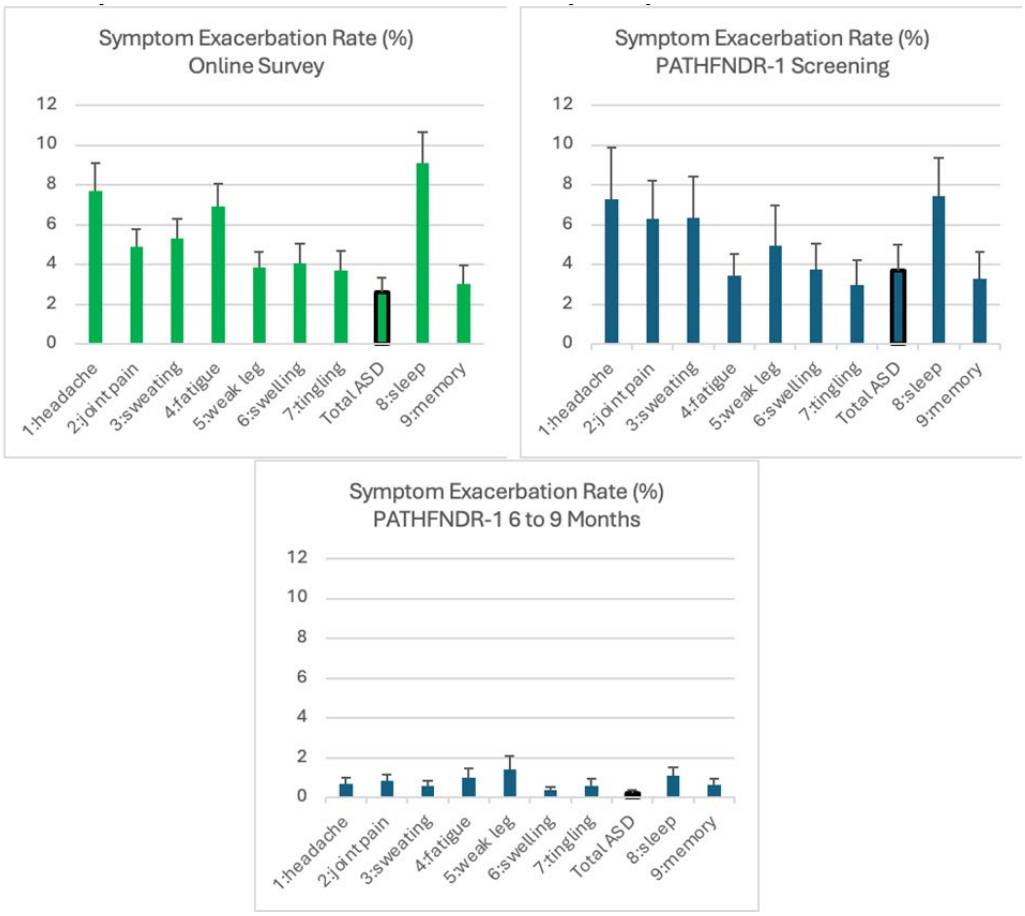
during the subsequent randomised treatment period. Using the same definition of breakthrough symptom exacerbation as the online survey, the sponsor reports that biochemically normalised participants (n=22) had a frequency of breakthrough symptoms during injected SRL treatment comparable to that observed in the clinical practice online survey (30.2% ± 5.63 vs 32.1% ± 4.06), whereas during paltusotine treatment the daily frequency of breakthrough symptoms progressively declined to a nadir of 6.2% ± 1.56 (Figure 2, and Figure 3). The sponsor further indicates that reductions in breakthrough symptom exacerbation were observed across individual symptoms and for the composite ASD score.

Figure 2. Frequency of breakthrough acromegaly symptom exacerbations: Online survey of LA-SRL injection treated patients and PATHFNDR-1 clinical trial participants



LA=Long Acting, SRL= somatostatin receptor ligand
Note: Error bars represent SE. Breakthrough acromegaly symptom exacerbation defined as a 2-point increase for any individual symptom score comparing a 2-day average to the previous 2-day average.

Figure 3. Frequency of breakthrough acromegaly symptom exacerbations: Individual Symptoms and Total ASD Score from Online survey of injected LA-SRL treated patients and PATHFNDR-1 clinical trial participants



Note: Error bars represent SE. Breakthrough acromegaly symptom exacerbation defined as a 2-point increase for any individual item score comparing a 2-day average to the previous 2-day average. Total ASD score was pre-defined as the sum of core symptom item (1 to 7) scores. Exacerbation of total ASD score is defined by 8-point increase in symptom items 1 to 7.

Claim based on a major contribution to patient care versus standard-of-care injected SRLs (octreotide acetate and lanreotide acetate)

For the claim of major contribution to patient care compared with injected SRLs, the sponsor notes that, within the CHMP early dialogue methodology involving patient and healthcare professional organisations, consultation with the European Society of Endocrinology and the Dutch Pituitary Foundation highlighted the burden of standard-of-care injections and the need for an oral acromegaly therapy. The sponsor argues that the tablet formulation of paltusotine would avoid burdens inherent to long-term parenteral administration of octreotide acetate and lanreotide acetate. As supporting evidence for injection burden, the sponsor cites the Strasburger et al. (2016) survey, in which most participants reported persistent symptoms despite therapy and 52% reported symptom worsening toward the end of the dosing interval; injection-site pain lasting up to a week was reported by 70% of patients, with additional local reactions such as nodules (38%), swelling (28%), bruising (16%), scar tissue (8%), and inflammation (7%), and limited uptake of home administration (17%) and self-injection (5%). The sponsor further reports that more than one-third of respondents indicated loss of independence due to injections and 16% reported repeated work-loss days, while also noting that despite overall satisfaction with treatment, respondents identified "avoiding injections" and "better symptom control" as changes that would represent major improvements in care (Strasburger et al.,

2016). On this basis, the sponsor concludes that the long-term injection requirement for currently used SRLs imposes substantial functional, emotional, and daily-life burden, and that an effective oral alternative such as paltusotine would be expected to mitigate this burden.

Taken together, the sponsor summarises the significant benefit rationale for paltusotine as resting on (i) improved efficacy and (ii) a major contribution to patient care relative to injected SRLs. For improved efficacy, the sponsor highlights two post hoc analyses supporting benefit versus octreotide acetate and lanreotide acetate depot therapies: the retrospective reclassification analysis in PATHFNDR-2 indicating disease control in approximately 60% of participants characterised as prior non-responders to any medical therapy and disease control in 50% of those previously not controlled on octreotide acetate or lanreotide acetate depot injections, and the PATHFNDR-1 intra-subject analysis suggesting improved stability of symptom control with paltusotine, reflected by reduced breakthrough symptom exacerbation frequency. For major contribution to patient care, the sponsor emphasises stakeholder input and published patient survey findings indicating substantial injection-related burden, arguing that an effective once-daily oral therapy would address this burden by eliminating the need for repeated long-acting injections.

Overall, based on the totality of the evidence presented, the Committee considered that the argument for significant benefit was adequately substantiated. In particular, the post hoc analyses provided supportive evidence of clinically meaningful responses in patients previously characterised as unresponsive or inadequately controlled on existing somatostatin receptor ligand (SRL) therapies, with disease control observed in a substantial proportion of these individuals. In addition, the intra-subject data suggesting improved stability of symptom control, including a reduction in breakthrough symptom exacerbations, further supported the claim of improved efficacy in a population with ongoing unmet need.

Furthermore, the Committee acknowledged that the argument for a major contribution to patient care was reasonably supported. The availability of an effective once-daily oral therapy has the potential to alleviate the well-documented burden associated with repeated long-acting injectable SRLs, including injection-related discomfort, logistical challenges, and healthcare resource utilisation. Stakeholder input and patient-reported evidence consistently highlight the impact of chronic injectable treatment on quality of life.

Taken together, the Committee concluded that the criteria for significant benefit could be considered fulfilled.

4. COMP position adopted on 5 March 2026

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of acromegaly (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to abnormal skeletal, tissue, and organ growth, which leads to multisystem morbidities and terminal cardiovascular, cerebrovascular, and respiratory disease;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Palsonify (paltusotine) may be of potential significant benefit to those affected by the orphan condition still holds;
- the sponsor provided data from a pivotal clinical trial demonstrating that treatment with Palsonify led to biochemical responses in patients with acromegaly who had an absence of disease control on prior injectable somatostatin receptor ligands (iSRLs), including octreotide LAR and lanreotide autogel. The sponsor also provided additional data indicating a reduction in the frequency of breakthrough symptom exacerbations relative to the screening period. The totality of evidence supports a conclusion on a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Palsonify, paltusotine for treatment of acromegaly (EU/3/25/3035) is not removed from the Community Register of Orphan Medicinal Products.