20 May 2025
EMA/OD/0000242010
EMADOC-1700519818-2149851
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

of an orphan medicinal product submitted for marketing authorisation application

Oczyesa (octreotide)
Treatment of acromegaly
EU/3/09/645

Sponsor: Camurus AB

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Octreotide hydrochloride
Other name(s)	--
International Non-Proprietary Name	Octreotide
Tradename	Oczyesa
Orphan condition	Treatment of acromegaly
Sponsor's details:	Camurus AB Rydbergs Torg 4 224 84 Lund Skane Lan Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Camurus AB
COMP opinion	5 May 2009
EC decision	12 June 2009
EC registration number	EU/3/09/645
Post-designation procedural history	
Transfer of sponsorship	Transfer from Camurus AB, Sweden, to Novartis Europharm Limited, United Kingdom – EC decision of 28 April 2014
	Transfer from Novartis Europharm Limited, United Kingdom to Novartis Europharm Limited, Ireland – EC decision of 25 May 2018
	Transfer from Novartis Europharm Limited, Ireland to Camurus AB – EC decision of 25 July 2018
Marketing authorisation procedural history	
Rapporteur	Jean-Michel Race
Applicant	Camurus AB
Application submission	26 April 2024
Procedure start	23 May 2024
Procedure number	EMA/H/C/006322
Invented name	Oczyesa
Proposed therapeutic indication	Oczyesa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues. Further information on Oczyesa can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/oczyesa
CHMP opinion	25 April 2025

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Vallo Tillmann / Zsofia Gyulai
Sponsor's report submission	18 December 2024
COMP discussion and adoption of list of questions	14-15 April 2025
Oral explanation	13 May 2025
Sponsor's removal request	15 May 2025
Removal from the Community Register	20 May 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2009 was based on the following grounds:

"Whereas the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- for the purpose of orphan designation, the COMP considered that the active ingredient should be renamed as "octreotide chloride (lipid depot solution)";
- acromegaly (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.2 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and may be life-threatening, in particular due to joint arthropathy, risk for cardiovascular disease, and reduced life-expectancy;
- although satisfactory methods of treatment of the condition have been authorised in the Community, sufficient justification has been provided that octreotide chloride may be of significant benefit to those affected by the condition.

the COMP recommends the designation of this medicinal product, containing octreotide chloride, as an orphan medicinal product for the orphan indication: 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 "Oczyesa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues" 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

At the time of the orphan drug designation for acromegaly in 2009, the prevalence of acromegaly was estimated to be less than 2 per 10,000.

A PubMed literature search was performed on 04-Oct-2024 to determine the prevalence of acromegaly in the EU based on population studies, including publications from registry databases. The search was limited to literature published in English in 2014 to 2024.

Estimates of the prevalence of acromegaly in the EU based on population studies published in 2014 up to 04-Oct-2024 ranged from 0.8 to 1.4/10,000 people in the EU (Table 1).

In addition, three meta-analyses published during this period were identified:

- A recent meta-analysis assessed the global epidemiology of acromegaly and found prevalence estimates ranging from 0.18 to 1.41/10,000 persons (Rosendal 2024).
- Another meta-analysis assessed the global epidemiology of acromegaly. The pooled prevalence of acromegaly in the 22 studies was 0.59 (95% CI: 0.44, 0.79) per 10,000 persons (Crisafulli 2021).
- The total prevalence was estimated to range between 0.28 and 1.37 cases per 10,000 people in a meta-analysis of population the epidemiology of acromegaly from various geographical areas (Lavrentaki 2017).

As reviewed by Fleseriu et al, published data indicate that the prevalence of acromegaly is increasing (from 0.5 to 0.6 per 10,000 people between 1971 and 1989 to 1.3 to 1.4 per 10,000 people between 2012 and 2014), probably due to improved diagnostic techniques, including development of more sensitive GH assays and shifts in biochemical diagnostic criteria allowing for diagnosis of milder cases, improved disease awareness, and increased survival of patients receiving improved surgical and pharmacological treatments (Fleseriu 2022).

Table 1. Prevalence of acromegaly as reported in population studies conducted in the EU and published in 2014 to 04-Oct-2024

Reference	Region/Country (Study period)	Source	Reference population	Prevalence (per 10,000)
Robèrt 2024	Sweden (1991–2018)	National Patient Register	Swedish 2000 standard population	1.40[a]
Fauchier 2024	France (2012-2021)	National cohort (PMSI French hospital database)	Not reported	1.04
Rosendal 2024	Denmark (1997-2021)	National cohort	5,867,412	1.08
Falch 2023	Norway (1999-2019)	Regional Cohort	3,000,000	0.83
Aagaard 2022	North Denmark Region (1992–2021)	Regional Cohort (Danish National Patient Registry)	600,000	1.22
Arnardóttir 2022	Sweden (1991-2011)	Swedish Pituitary Register	Population Census in Sweden 2000	1.30[b]
Caputo 2019	Piedmont, Italy (2012-2016)	Regional Cohort (Health search databases)	4,400,000	0.83
Gatto 2018	Piedmont, Italy (2000-2014)	General practice database	1,066,871	0.69
Dal 2016	Denmark (1991-2010)	National cohort (Hospital medical charts)	5,534,738	0.85
Gruppetta 2016	Malta (2014)	National cohort (Secondary care electronic medical records)	394,640 – 425,384	1.36
Hoskuldsdottir 2015	Iceland (1955-2013)	National cohort (Secondary care electronic medical records)	316,075	1.34
Agustsson 2015	Iceland (1955-2012)	National cohort (Pituitary adenoma database)	321,857	1.37
Tjörnstrand 2014	Västra Götaland, Sweden (2001-2011)	Regional cohort (Swedish Pituitary Registry and hospital records)	1,590,640	1.22[c]

a Based on an incidence rate of 4.0/million/year in the entire population as reported in Robèrt et al 2024.
b Based on an incidence rate of 3.7/million/year as reported in Tjörnstrand et al 2014.
c Based on an incidence rate of 0.35/100,000 as reported in Tjörnstrand et al 2014.

To calculate the prevalence, the incidence rate was multiplied by an estimated disease duration of 35 years, where the mean age at diagnosis of acromegaly is assumed to be 45 years (Maione 2019) and the mean life expectancy is conservatively assumed to be 80 years.

In conclusion, based on published population studies in different countries in the EU during the last 10-year period, the reported prevalence of acromegaly is estimated to range from 0.7 to 1.4 in 10,000

people. As a conservative approach, i.e., based on the highest prevalence rate reported, the total prevalence is concluded to be 1.4 in 10,000 people in the EU, i.e., less than 2 per 10,000 as reported at the time of the designation.

The COMP concluded that the proposed figure of 1.4 in 10,000 persons in the EU is considered acceptable.

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 (Figure 1):

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.

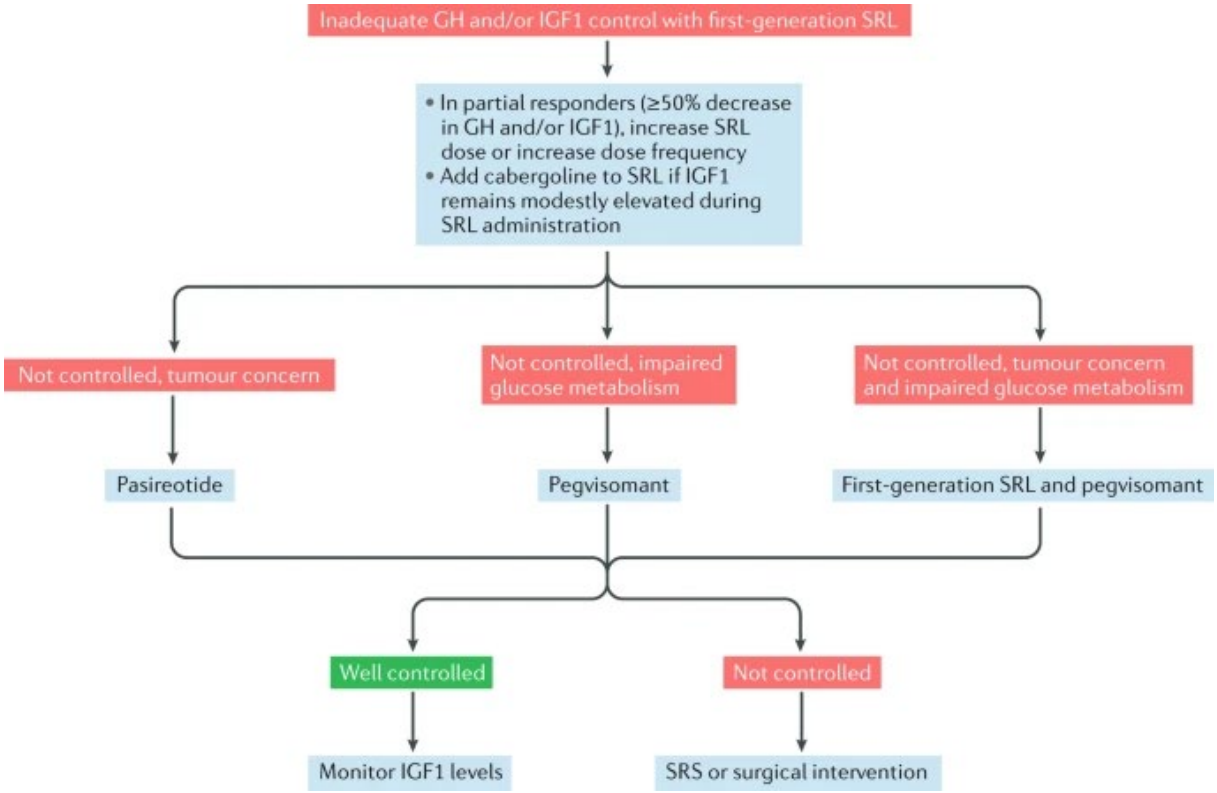
For patients with persistent disease after surgery, a first-generation long-acting SRL is recommended as first-line medical therapy. The choice between octreotide LAR and Lanreotide autogel is determined by availability, convenience of administration and patient preference. Cabergoline can be attempted 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.

Figure 1. A proposed algorithm for the treatment of acromegaly in patients inadequately controlled with first-generation somatostatin receptor ligands lanreotide autogel and octreotide long-acting release.



Source: Melmet 2018.
Abbreviations: GH, growth hormone; IGF-I, insulin-like growth factor I; SRL, somatostatin receptor ligand; SRS, stereotactic radiosurgery.

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
Sandostatin (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, as patients have to be inadequately controlled on treatment with another somatostatin analogue
Bromocriptine	As an adjunct to surgery and/or radiotherapy to reduce circulating growth hormone levels in the management of acromegalic patients.	No, different target 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, as patients have to be inadequately controlled on treatment with another somatostatin analogue

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.

Oczyesa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues. In this specific therapeutic area, Sandostatin (octreotide) and Somatuline (lanreotide) are considered satisfactory methods, as these medicines are approved for treatment of acromegaly and have complete overlap with Oczyesa in their indications.

The medicines Signifor (Pasireotide), Bromocriptine, and Somavert are not considered satisfactory methods.

Significant benefit

Background information

CAM2029 has been the subject of multiple rounds of protocol assistance (PA) with the European Medicines Agency (EMA), addressing the requirements for establishing significant benefit in the context of orphan designation.

In the initial protocol assistance provided in 2009 (EMEA/CHMP/SAWP/717378/2009), the Committee for Orphan Medicinal Products (COMP) acknowledged that CAM2029 might offer potential advantages related to its posology and method of administration, particularly the proposed use of a ready-to-use pre-filled syringe for subcutaneous delivery. COMP noted that improvements in ease of use, convenience, and administration method could potentially contribute to a claim of significant benefit, particularly in terms of enhancing patient quality of life, adherence, and autonomy.

This discussion was further developed during protocol assistance in 2013 (EMA/CHMP/SAWP/431986/2013), due to updates to the clinical development programme and the refinement of the CAM2029 administration format.

According to the Commission Notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000, a product may demonstrate significant benefit through either a clinically relevant advantage (CRA) or a major contribution to patient care (MCPC).

A CRA may include improved efficacy for the overall population or for a defined subgroup, or a superior safety or tolerability profile, all of which must be substantiated by clinical data.

An MCPC may be supported by improvements in self-administration, convenience, or treatment adherence — particularly when such features address known limitations of existing therapies and lead to better outcomes or improved quality of life. However, to be regarded as offering a major contribution to patient care, a product is generally expected to be at least comparable in terms of efficacy, safety, and overall benefit-risk profile to already authorised medicinal products.

CAM2029 (Oczyesa) is currently under evaluation for the maintenance of its orphan designation for the treatment of acromegaly, for which satisfactory treatment options already exist — namely octreotide LAR (Sandostatin LAR) and lanreotide autogel (Somatuline ATG). To support the claim of significant benefit, the sponsor has submitted data from two Phase 3 trials: the placebo-controlled pivotal study HS-18-633, and the supportive, long-term open-label study HS-19-647. The marketed product is a 20 mg fixed-dose, subcutaneous pre-filled pen.

CAM2029 Clinical Development Programme

Two Phase 3 studies: HS-18-633, a randomized, double-blind, placebo-controlled trial evaluating short-term efficacy and safety; and HS-19-647, an open-label extension study assessing long-term outcomes.

HS-18-633: Placebo-Controlled Pivotal Study

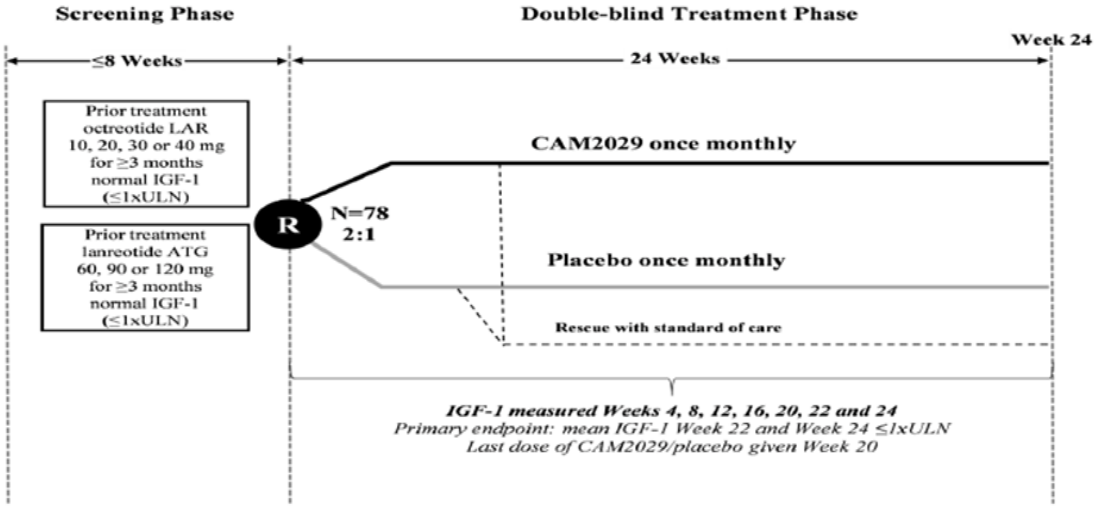
HS-18-633 was a 24-week, multicentre, randomised, double-blind, placebo-controlled Phase 3 trial in adults with acromegaly. Eligible patients had received a stable monthly dose of octreotide LAR or lanreotide ATG for at least 3 months and had achieved IGF-1 levels ≤1×ULN. Patients were randomised 2:1 to receive CAM2029 (20 mg) or placebo administered subcutaneously every 4 weeks

using a pre-filled syringe. The design was intended to evaluate the maintenance of biochemical control following the switch from standard SRLs. No active comparator arm was included. The HS-18-633 study scheme is shown in Figure 2.

The placebo device used in this trial was a matching subcutaneous formulation device, in appearance, volume (1.0 mL), and administration method to CAM2029. This ensured blinding and maintained consistency in the route, schedule, and setting of administration between treatment groups.

A total of 72 patients were randomised in a 2:1 ratio to receive CAM2029 20 mg (n=48) or placebo (n=24) via subcutaneous injection every 4±1 weeks for 24 weeks. Dose reduction to 10 mg was permitted for tolerability reasons, though no such reductions were necessary. Administration was either by patients themselves,caregivers, and healthcare professionals (HCPs) beginning from the first dose.

Figure 2. HS-18-633 Study Scheme.



The most frequently used prior medications for acromegaly (taken at any time before enrolment in the trial) in patients in the ITT analysis set were octreotide LAR (43 patients [59.7%]), lanreotide ATG (35 patients [48.6%]), and cabergoline (5 patients [6.9%]); 2 patients (2.8%) had received pegvisomant and 1 patient (1.4%) had received pasireotide.

At screening, 39 out of 72 patients (54.2%) were receiving octreotide LAR and 33 patients (45.8%) were receiving lanreotide ATG. Most patients (76.4%) were on mid-to-high doses of SRLs, including octreotide LAR at 20, 30, or 40 mg and lanreotide ATG at 90 or 120 mg. The remaining 23.6% were on lower doses (octreotide LAR 10 mg or lanreotide ATG 60 mg).

The primary endpoint was the proportion of patients with mean IGF-1 ≤1×ULN at Weeks 22 and 24. Results showed:

- CAM2029: 72.2%
- Placebo: 37.5%
- Difference: 34.6% (95% CI: 11.3, 57.9); p=0.0018

Stratified analysis by prior treatment (octreotide LAR vs lanreotide ATG) showed consistent response rates across subgroups (Table 3). Among patients previously treated with octreotide LAR, 72.0%

(18/25) of those receiving CAM2029 were responders, compared with 35.7% (5/14) in the placebo group. Similarly, among patients previously treated with lanreotide ATG, 72.4% (16.7/23) of patients receiving CAM2029 were responders, compared to 40.0% (4/10) of those on placebo. These results indicate a treatment effect of CAM2029 regardless of prior SRL therapy.

Table 3. Primary efficacy endpoint analysis – proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 by treatment arm in HS-18-633 (ITT analysis set).

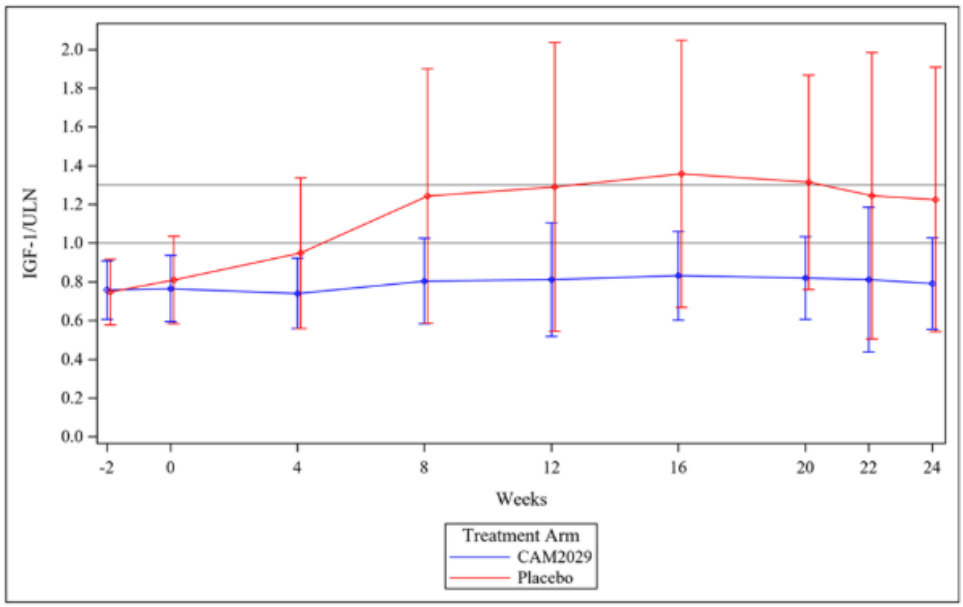
Previous Treatment	**CAM2029 Mean Responders n/N (%)**	**Placebo Mean Responders n/N (%)**	**Difference in Proportions [%][a] (CAM2029-Placebo) (95% CI)**	**Upper-tailed p-value[b]**	**Odds Ratio[c] (CAM2029/ Placebo) (95% CI)**
Octreotide LAR	18.0/25 (72.0)	5.0/14 (35.7)			
Lanreotide ATG	16.7/23 (72.4)	4.0/10 (40.0)			
Overall	34.7/48 (72.2)	9.0/24 (37.5)	34.6 (11.3, 57.9)	0.0018	4.31 (1.52, 12.27)

ATG: autogel; CI: confidence interval; IGF-1: insulin-like growth factor-1; ITT: intention-to-treat; LAR: long-acting repeatable; n: mean number of responders; N: number of patients in the analysis; ULN: upper limit of normal
a. Mantel-Haenszel-type common difference in proportions across strata, stratified by prior treatment (octreotide LAR or lanreotide ATG).
b. Upper-tailed p-value of the common risk difference test using Mantel-Haenszel stratum weights (octreotide LAR or lanreotide ATG). The significance level was 0.025.
c. Mantel-Haenszel-type common odds ratio across strata, stratified by prior treatment (octreotide LAR or lanreotide ATG).
Patients with intercurrent events were regarded as non-responders independently of their (missing or non-missing) Week 22 and Week 24 data.
Overall proportions of responders were not weighted.
Source: HS-18-633 CTR, Table 14.2.2.1

A key secondary endpoint (IGF-1 ≤1×ULN and GH <2.5 µg/L at Week 24) was also met (CAM2029: 70.0% vs placebo: 37.5%; p=0.0035).

The mean IGF-1/ULN remained stable and below 1×ULN in the CAM2029 treatment arm throughout the 24-week treatment period. In the placebo treatment arm, the mean values increased above 1×ULN at Week 8 and remained above ULN up to Week 24 (Figure 3).

Figure 3. IGF-1/ULN over time (mean ± SD) by treatment arm in HS-18-633 (ITT analysis set).

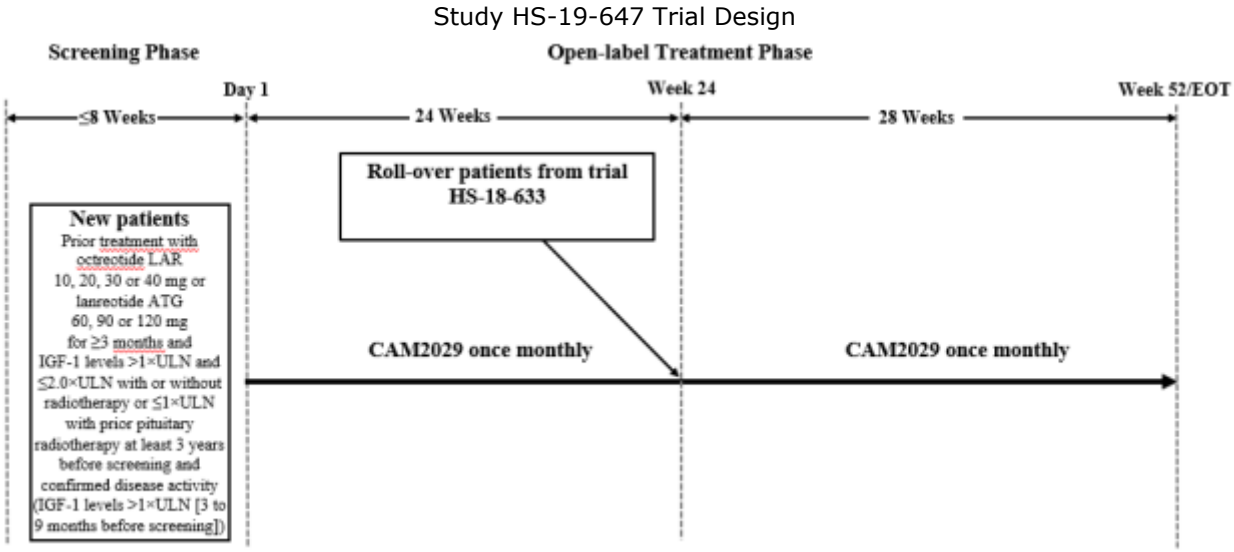


The median time to loss of response was not reached in the CAM2029 arm, compared to 8.4 weeks in the placebo arm (p<0.0001). CAM2029 was well tolerated with a high completion rate (95.8%).

HS-19-647: Long-Term Open-Label Study

HS-19-647 is a 104-week open-label Phase 3 trial assessing long-term safety and efficacy of CAM2029. It enrolled 135 patients, including 81 new and 54 roll-over patients from HS-18-633. All received CAM2029 20 mg subcutaneously every 4 weeks; dose reduction to 10 mg was permitted based on tolerability. A pre-filled syringe and a pre-filled pen were used. The scheme of study HS-19-647 is shown in Figure 4.

Figure 4.



Main part of the Trial ATG: autogel; EOT: End of trial (refers to end of the main part of the trial); IGF-1: insulin-like growth factor-1; LAR: long-acting release; N= planned number of enrolled patients; ULN: upper limit of normal.

In HS-19-647, two baselines were defined for the purpose of analysis:

- Standard-of-Care (SoC) Baseline / Cumulative Baseline: For new patients, this baseline was defined as the average of IGF-1 values from Week -2 and pre-dose Day 1 prior to receiving their first dose of CAM2029. For roll-over patients from HS-18-633 who had previously received CAM2029, the same approach applied. This baseline represents the patient's condition while on their previous SoC treatment (e.g., octreotide LAR or lanreotide ATG).
- Active Baseline / Placebo Baseline: This baseline was used for placebo roll-over patients and defined as the average of IGF-1 values from Week 22 and pre-dose Week 24—representing the patient's state immediately prior to initiating CAM2029 treatment in HS-19-647.

For IGF-1 values, when one of the two required measurements was missing, the available value was used. GH baselines were similarly defined using cycle mean values, with fallback to screening or previous visits if needed. ECG baselines were defined by the mean of triplicate measurements.

These dual baseline definitions were designed to enable within-patient comparisons and to differentiate the treatment effects of CAM2029 from prior therapies or placebo exposure.

Key findings at Week 52 included:

- IGF-1 ≤1×ULN increased from 45.9% to 59.1% in the overall population.
- New patients: 14.8% to 36.5%.
- Placebo roll-over: 27.8% to 94.4%.

Mean GH levels remained <1.0 µg/L across all groups. The results support the long-term biochemical efficacy of CAM2029.

Conclusion on efficacy of Study HS-18-633 and Study HS-19-647

As concluded by the Committee for Medicinal Products for Human Use (CHMP), the pivotal study HS-18-633 demonstrated the superiority of CAM2029 over placebo with regard to both the primary endpoint — the proportion of patients with mean IGF-1 levels ≤1×ULN at Weeks 22 and 24 — and the key secondary endpoint evaluating IGF-1 levels at those same timepoints. Among patients who were biochemically controlled at baseline (IGF-1 ≤ ULN), CAM2029 maintained this control significantly more effectively than placebo.

However, it is important to note that CAM2029 was not directly compared to other authorized somatostatin receptor ligands (SRLs) such as octreotide LAR or lanreotide ATG in any of the Phase 3 studies. As a result, the relative efficacy of CAM2029 in comparison to these existing treatments remains uncertain. Available data comparing CAM2029 to prior SRL treatments are limited to intra-patient comparisons from baseline to Week 24 or Week 52 and do not support robust conclusions regarding comparative efficacy.

In the context of an application for orphan maintenance based on a major contribution to patient care (MCPC), it is expected that the product should be shown to be at least comparable in terms of efficacy, safety, and overall benefit-risk balance to currently authorized alternatives (Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products). In the absence of direct comparative data with approved SRLs, further clarification may be warranted to establish whether CAM2029 has comparable efficacy to the approved products and meets the threshold for being considered as making a major contribution to patient care under the applicable regulatory framework.

Patient-reported outcomes (PROs) and Quality of Life (QoL) data in Study HS-18-633 and Study HS-19-647

Patient-reported outcomes (PROs) were systematically assessed in both pivotal Phase 3 studies — HS-18-633 and HS-19-647 — using validated instruments designed to capture multiple dimensions of the patient experience. These included assessments of quality of life (QoL), treatment satisfaction, and the practicality of self-administration.

Instruments used included the Acromegaly Quality of Life Questionnaire (AcroQoL), which measures disease-specific QoL, and the Treatment Satisfaction Questionnaire for Medication (TSQM), which evaluates satisfaction across domains such as effectiveness, convenience, and side effects. Additionally, the Self-Injection Assessment Questionnaire (SIAQ) was used to capture patient perspectives on the self-injection process in relevant study populations. Results are presented for each of the two studies HS-18-633 and HS-19-647.

Study HS-18-633

- TSQM (Treatment Satisfaction Questionnaire for Medication)

Treatment satisfaction was assessed using the TSQM, a validated instrument comprising four domains: convenience, effectiveness, global satisfaction, and side effects. Scores in each domain range from 0 to 100, with higher values indicating greater satisfaction. In this study, baseline scores reflected patient satisfaction with their previous standard of care (SoC), namely octreotide LAR or lanreotide ATG. Figure 5 summarizes the results.

Convenience Domain

Statistically significant improvements in the convenience domain were observed in both treatment arms from baseline to Week 24. Least Squares (LS) Mean changes were:

- **CAM2029**: +13.85 (95% CI: 9.45, 18.25)
- **Placebo**: +9.90 (95% CI: 4.06, 15.75)

These increases suggest a perceived enhancement in convenience following the switch from SoC, likely reflecting the administration method. No difference was observed between treatment arms, potentially due to both groups using the same subcutaneous delivery device.

Effectiveness, Global Satisfaction, and Side Effects Domains

For the **effectiveness** domain, no relevant changes were observed:

- CAM2029: -2.72 (95% CI: -9.94, 4.51)
- Placebo: -3.11 (95% CI: -12.09, 5.86)
- Mean difference (CAM2029 – Placebo): 0.40 (95% CI: -10.80, 11.60)

In the **global satisfaction** domain:

- CAM2029: +0.10 (95% CI: -7.00, 7.20)
- Placebo: -2.77 (95% CI: -11.60, 6.06)
- Mean difference: 2.87 (95% CI: -8.23, 13.97)

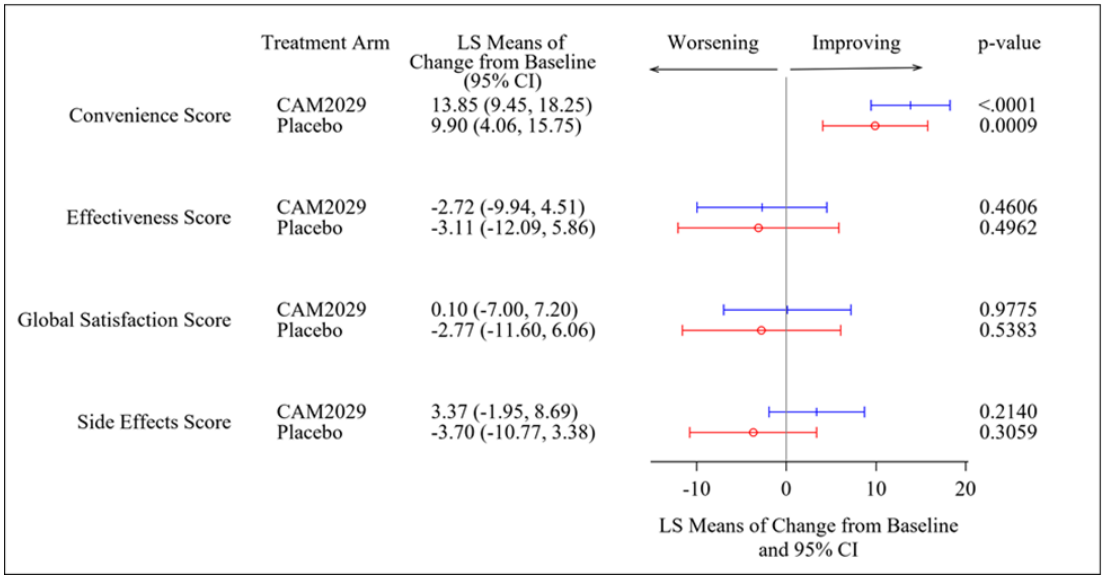
In the **side effects** domain (where higher scores denote fewer side effects):

- CAM2029: +3.37 (95% CI: -1.95, 8.69)

- Placebo: -3.70 (95% CI: -10.77, 3.38)
- Mean difference: 7.07 (95% CI: -1.63, 15.76)

These findings indicate **numerical trends** favouring CAM2029 across several domains. However, the overlapping confidence intervals and absence of statistical significance limit definitive conclusions regarding comparative treatment satisfaction.

Figure 5. Forest plot of LS Means for change from baseline to Week 24 in TSQM scores by treatment arm in HS-18-633 (ITT analysis set)



ANCOVA: analysis of covariance; CI: confidence interval; LS: least square; TSQM: Treatment Satisfaction Questionnaire for Medication
ANCOVA model with treatment arm and prior treatment as factors and baseline TSQM domain scores as covariate.
Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing also for other reasons. Missing data were imputed.
The TSQM domain scores ranged from 0 to 100, where higher scores indicated higher treatment satisfaction.
Source: HS-18-633 CTR, Figure 14.2.10.1

- Patient Satisfaction Scale Scores at Week 24

At Week 24, patients were asked to rate their overall treatment experience with CAM2029 or placebo, compared to their previous standard of care (SoC) treatment with octreotide LAR or lanreotide ATG. The Patient Satisfaction Scale used a 5-point Likert scale that ranged from 1 "*much worse*" to 5 "*much better*", where higher score indicated higher patient satisfaction.

A total of 44 out of 48 patients in the CAM2029 arm and all 24 patients in the placebo arm completed the questionnaire. Patients receiving CAM2029 reported high satisfaction with the treatment compared to their previous treatment with SoC (Table 4 and Table 5).

- **CAM2029 group**:
  - *Much better*: 29.2%
  - *Slightly better*: 18.8%
  - *About the same*: 29.2%
  - *Slightly worse*: 4.2%

- **Placebo group**:
  - *Much better*: 12.5%
  - *Slightly better*: 33.3%
  - *About the same*: 25.0%
  - *Slightly worse*: 16.7%

These results suggest a numerically greater proportion of CAM2029-treated patients perceived the treatment as "much better" compared to their prior therapy. In contrast, a larger proportion of patients in the placebo arm reported only slight improvement or no change.

Mean Satisfaction Scores at Week 24/EOT

- **CAM2029**: **3.9** (95% CI: 3.6, 4.2)
- **Placebo**: **3.4** (95% CI: 2.9, 3.8)

While formal statistical comparison was not performed, the mean score was numerically higher in the CAM2029 group, suggesting a positive treatment experience relative to previous therapies.

Table 4. Number of single answers to the patient satisfaction scale at Week 24/EOT by treatment arm and previous treatment (ITT analysis set)

	CAM2029			Placebo		
Answer Category	Octreotide LAR (N=25) n (%)	Lanreotide ATG (N=23) n (%)	Overall (N=48) n (%)	Octreotide LAR (N=14) n (%)	Lanreotide ATG (N=10) n (%)	Overall (N=24) n (%)
Much worse	0	0	0	1 (7.1)	0	1 (4.2)
Slightly worse	0	2 (8.7)	2 (4.2)	2 (14.3)	2 (20.0)	4 (16.7)
About the same	5 (20.0)	9 (39.1)	14 (29.2)	4 (28.6)	2 (20.0)	6 (25.0)
Slightly better	7 (28.0)	2 (8.7)	9 (18.8)	3 (21.4)	5 (50.0)	8 (33.3)
Much better	7 (28.0)	7 (30.4)	14 (29.2)	2 (14.3)	1 (10.0)	3 (12.5)

EOT: end of trial; ITT: intention-to-treat; n: number of patients within the category; N: number of patients in the analysis set; %: percentage of patients
Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing for other reasons.
Source: Table 14.2.13.2

Table 5. Patient satisfaction scale scores at Week 24/EOT by treatment arm and previous treatment (ITT analysis set)

	CAM2029			Placebo		
Statistics	Octreotide LAR (N=25)	Lanreotide ATG (N=23)	Overall (N=48)	Octreotide LAR (N=14)	Lanreotide ATG (N=10)	Overall (N=24)
n	19	20	39	12	10	22
Mean (SD)	4.1 (0.8)	3.7 (1.1)	3.9 (1.0)	3.3 (1.2)	3.5 (1.0)	3.4 (1.1)
95% CI of Mean	3.7, 4.5	3.2, 4.2	3.6, 4.2	2.5, 4.0	2.8, 4.2	2.9, 3.8

CI: confidence interval; EOT: end of trial; ITT: intention-to-treat; n: number of patients within the category N: number of patients in the analysis set; SD: standard deviation
Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing for other reasons.
Source: Table 14.2.13.1

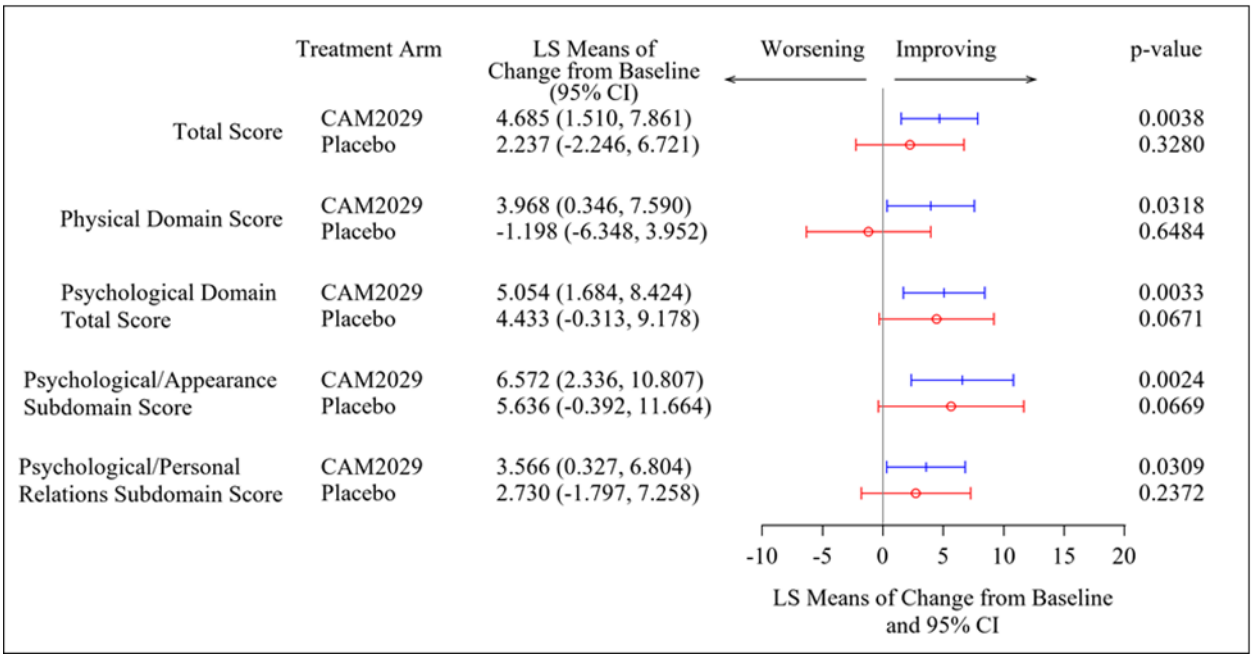
- Change from Baseline in AcroQoL Scores

AcroQoL (Acromegaly Quality of Life Questionnaire) domain scores range from 0 to 100, with higher scores indicating better quality of life (QoL). In the ANCOVA analysis of change from baseline to Week 24 (end of treatment), baseline scores reflect patients' QoL under their previous standard of care (SoC), i.e., octreotide LAR or lanreotide ATG.

In the CAM2029 treatment arm, the AcroQoL Total Score showed a numerical improvement from baseline to Week 24. Improvements were also observed in both the Physical Domain and Psychological Domain Total Scores, including the associated psychological subdomains. In contrast, no significant changes were seen in the placebo arm (Figure 6).

There were no statistically significant differences between treatment arms for any of the AcroQoL domains. According to the sponsor, this outcome was expected due to the identical administration device (pre-filled syringe) used in both arms, which may have neutralized any perceived difference in convenience, and the fact that the study was not powered to detect differences in patient-reported outcome measures.

Figure 6. Forest plot of LS Means for change from baseline to Week 24 in AcroQoL scores by treatment arm in HS-18-633 (ITT analysis set)



AcroQoL: Acromegaly Quality of Life Questionnaire; ANCOVA: analysis of covariance; CI: confidence interval; LS: least square
ANCOVA model with treatment arm and prior treatment as factors and baseline AcroQoL domain scores as covariate.
Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing also for other reasons. Missing data were imputed.
The AcroQoL domain scores ranged from 0 to 100, where higher scores indicated better QoL.
Source: HS-18-633 CTR, Figure 14.2.11.1

- EQ-5D-5L Scores (EuroQoL5-dimension 5-level)

An EQ-5D-5L index value of 0 represents death and 1 represents full health. Values below 0 can occur. The EQ-5D-5L VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

No significant changes in the EQ-5D-5L index value or in the VAS scores from baseline to Week 24/EOT were observed in either treatment arm.

- Self-Administration and Self-Injection Assessment Questionnaire (SIAQ) Scores

Patient experience with self-administration was evaluated using the SIAQ. This tool includes several domains assessing emotional and practical aspects of self-injection, with scores ranging from 0 to 10, where higher scores reflect a more positive experience.

Prior to their first self-injection, patients completed the SIAQ PRE module, typically on Day 1 (CAM2029: 23/28; placebo: 12/17), although a few completed it at later timepoints (Week 4 or Week 8). Post-injection experiences were captured via the SIAQ POST modules, administered 20 to 40 minutes after the first injection (Post-treatment 1) and again after the last injection at Week 20 (Post-treatment 2).

In total, 45 patients (62.5%) and 3 caregivers (4.2%) performed self-injections at least once during the study, and all 45 patients who self-administered completed the SIAQ assessments.

At baseline, mean SIAQ scores in the domains of 'feelings about injections', 'satisfaction with current way of taking medication', and 'self-confidence' ranged from 6.4 to 8.0 in the CAM2029 group and from 5.9 to 6.7 in the placebo group, indicating a slightly more favourable initial perception in the CAM2029 arm. Across both treatment arms, scores improved progressively over time, with the greatest increases observed by Post-treatment 2, reflecting growing familiarity and comfort with the injection process. These improvements were more pronounced in the CAM2029 group, suggesting a positive user experience associated with the product's administration.

For the domains assessed only post-treatment — including 'self-image', 'injection site reactions', 'ease of use', and overall 'satisfaction with self-injection' — mean scores in the CAM2029 arm fell within the higher range (approximately 6.5 to 9.2). Notably, the highest scores were observed for 'injection site reactions' and 'self-image', indicating minimal local discomfort and a generally positive perception of self-injection.

Overall, the data suggest that self-administration of CAM2029 was feasible, well-tolerated, and associated with a favourable patient experience, with improvements over time in both emotional and practical aspects of self-injection. However, these findings should be interpreted with caution, as confidence intervals were wide and often overlapped across treatment groups, highlighting a degree of uncertainty and variability in the observed outcomes.

Table 6. Self-injection scores (SIAQ) by treatment arm and previous treatment (ITT analysis set)

			CAM2029			Placebo		
Domain/Scale	**Visit**	**Statistics**	**Octreotide LAR (N=25)**	**Lanreotide ATG (N=23)**	**Overall (N=48)**	**Octreotide LAR (N=14)**	**Lanreotide ATG (N=10)**	**Overall (N=24)**
Feelings about Injections	Pre-treatment	n	14	14	28	10	7	17
		Mean (SD)	8.274 (2.027)	7.679 (2.557)	7.976 (2.284)	6.333 (2.428)	7.262 (1.782)	6.716 (2.174)
		95% CI of Mean	7.103, 9.444	6.202, 9.155	7.090, 8.862	4.596, 8.070	5.614, 8.910	5.598, 7.834
	Change from Pre-treatment to Post-treatment 1	n	13	14	27	10	7	17
		Mean (SD)	0.321 (0.870)	0.833 (2.468)	0.586 (1.861)	1.083 (2.723)	0.119 (0.891)	0.686 (2.170)
		95% CI of Mean	-0.205, 0.846	-0.591, 2.258	-0.150, 1.323	-0.865, 3.031	-0.705, 0.943	-0.429, 1.802
	Change from Pre-treatment to Post-treatment 2	n	8	12	20	8	4	12
		Mean (SD)	0.521 (0.884)	0.694 (2.353)	0.625 (1.871)	1.354 (3.052)	0.417 (0.481)	1.042 (2.491)
		95% CI of Mean	-0.218, 1.260	-0.800, 2.189	-0.251, 1.501	-1.197, 3.905	-0.349, 1.182	-0.541, 2.624
Self-confidence	Pre-treatment	n	14	14	28	10	7	17
		Mean (SD)	6.548 (2.809)	6.190 (2.258)	6.369 (2.507)	6.333 (2.552)	6.548 (2.227)	6.422 (2.353)
		95% CI of Mean	4.926, 8.170	4.887, 7.494	5.397, 7.341	4.508, 8.159	4.488, 8.607	5.212, 7.631
	Change from Pre-treatment to Post-treatment 1	n	13	14	27	10	7	17
		Mean (SD)	0.192 (1.988)	0.536 (1.291)	0.370 (1.640)	0.583 (1.472)	0.000 (1.273)	0.343 (1.384)
		95% CI of Mean	-1.009, 1.394	-0.210, 1.281	-0.278, 1.019	-0.470, 1.637	-1.177, 1.177	-0.368, 1.055
	Change from Pre-treatment to Post-treatment 2	n	8	12	20	8	4	12
		Mean (SD)	0.313 (1.539)	0.764 (2.055)	0.583 (1.836)	0.729 (0.938)	0.833 (1.521)	0.764 (1.093)
		95% CI of Mean	-0.974, 1.599	-0.542, 2.070	-0.276, 1.442	-0.055, 1.514	-1.588, 3.254	0.070, 1.458
Satisfaction with current way of taking medication	Pre-treatment	n	14	14	28	10	7	17
		Mean (SD)	6.964 (2.004)	7.143 (1.926)	7.054 (1.931)	6.000 (2.108)	5.714 (3.450)	5.882 (2.643)
		95% CI of Mean	5.807, 8.122	6.031, 8.255	6.305, 7.802	4.492, 7.508	2.523, 8.905	4.523, 7.241
	Change from Pre-treatment to Post-treatment 1	n	13	14	27	10	7	17
		Mean (SD)	1.154 (2.419)	0.893 (1.243)	1.019 (1.868)	0.750 (2.372)	1.429 (2.835)	1.029 (2.509)
		95% CI of Mean	-0.308, 2.615	0.175, 1.611	0.279, 1.758	-0.947, 2.447	-1.193, 4.050	-0.261, 2.320

			CAM2029			Placebo		
Domain/Scale	**Visit**	**Statistics**	**Octreotide LAR (N=25)**	**Lanreotide ATG (N=23)**	**Overall (N=48)**	**Octreotide LAR (N=14)**	**Lanreotide ATG (N=10)**	**Overall (N=24)**
	Change from Pre-treatment to Post-treatment 2	n	8	12	20	8	4	12
		Mean (SD)	0.625 (2.216)	0.208 (2.911)	0.375 (2.600)	0.625 (3.953)	3.750 (4.330)	1.667 (4.174)
		95% CI of Mean	-1.228, 2.478	-1.641, 2.058	-0.842, 1.592	-2.680, 3.930	-3.140, 10.000	-0.986, 4.319
Self-image	Post-treatment 1	n	13	14	27	10	7	17
		Mean (SD)	8.462 (1.920)	8.036 (3.279)	8.241 (2.669)	8.500 (1.748)	8.571 (1.967)	8.529 (1.781)
		95% CI of Mean	7.301, 9.622	6.143, 9.929	7.185, 9.296	7.250, 9.750	6.752, 10.000	7.614, 9.445
	Post-treatment 2	n	8	12	20	8	4	12
		Mean (SD)	9.063 (1.860)	7.917 (3.168)	8.375 (2.724)	7.813 (1.602)	8.125 (2.394)	7.917 (1.794)
		95% CI of Mean	7.507, 10.000	5.904, 9.930	7.100, 9.650	6.473, 9.152	4.316, 10.000	6.777, 9.057
Injection site reactions	Post-treatment 1	n	13	14	27	10	7	17
		Mean (SD)	9.279 (0.780)	9.196 (0.679)	9.236 (0.716)	8.813 (1.029)	8.795 (1.482)	8.805 (1.191)
		95% CI of Mean	8.807, 9.750	8.804, 9.589	8.953, 9.520	8.076, 9.549	7.424, 10.000	8.193, 9.418
	Post-treatment 2	n	8	12	20	8	4	12
		Mean (SD)	8.984 (0.831)	7.786 (1.924)	8.266 (1.661)	6.992 (1.315)	8.125 (0.675)	7.370 (1.239)
		95% CI of Mean	8.290, 9.679	6.564, 9.009	7.488, 9.043	5.893, 8.091	7.051, 9.199	6.583, 8.157
Ease of use	Post-treatment 1	n	13	14	27	10	7	17
		Mean (SD)	7.046 (1.400)	6.943 (1.337)	6.993 (1.342)	7.080 (1.148)	7.371 (1.512)	7.200 (1.273)
		95% CI of Mean	6.200, 7.892	6.171, 7.715	6.462, 7.524	6.259, 7.901	5.973, 8.770	6.546, 7.854
	Post-treatment 2	n	8	12	20	8	4	12
		Mean (SD)	7.700 (1.314)	6.900 (1.536)	7.220 (1.471)	6.500 (1.166)	7.800 (1.681)	6.933 (1.430)
		95% CI of Mean	6.602, 8.798	5.924, 7.876	6.532, 7.908	5.525, 7.475	5.125, 10.000	6.024, 7.842
Satisfaction with self-injection	Post-treatment 1	n	13	14	27	10	7	17
		Mean (SD)	7.830 (1.224)	7.168 (1.544)	7.487 (1.413)	6.929 (1.027)	7.704 (1.108)	7.248 (1.099)
		95% CI of Mean	7.090, 8.569	6.277, 8.060	6.928, 8.046	6.194, 7.663	6.680, 8.728	6.683, 7.813
	Post-treatment 2	n	8	12	20	8	4	12
		Mean (SD)	7.589 (1.263)	7.292 (1.947)	7.411 (1.675)	6.786 (1.161)	8.125 (1.607)	7.232 (1.413)
		95% CI of Mean	6.534, 8.645	6.055, 8.529	6.627, 8.194	5.815, 7.757	5.568, 10.000	6.334, 8.130

CI: confidence interval; ITT: intention-to-treat; max: maximum; min: minimum; N: number of patients in the analysis set; n: number of patients within the category; SD: standard deviation

Only questionnaires completed at self-administration were included in the analysis

Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing for other reasons.

Source: Table 14.2.16.1

- Feasibility of Self-Administration

A total of 57 patients or partners (79.2%) expressed willingness to self-administer the investigational medicinal product (IMP) during the trial. Interestingly, the proportion of participants opting for self-administration was higher in the placebo arm (91.7%) compared to the CAM2029 arm (72.9%). Among those who received training in self-administration, 52 out of 57 individuals (91.2%) were assessed as competent by site personnel (CAM2029: 91.4%; placebo: 90.9%).

Throughout the study, 42 patients (58.3%) received the IMP from site personnel on at least one occasion, while 45 patients (62.5%) and 3 partners (4.2%) successfully self-administered the IMP at least once.

Difficulties with self-injection were infrequent and generally minor, with isolated incidents reported at Week 4 (1 patient), Week 8 (1 partner), Week 12 (1 patient), and Week 16 (3 patients).

HS-19-647

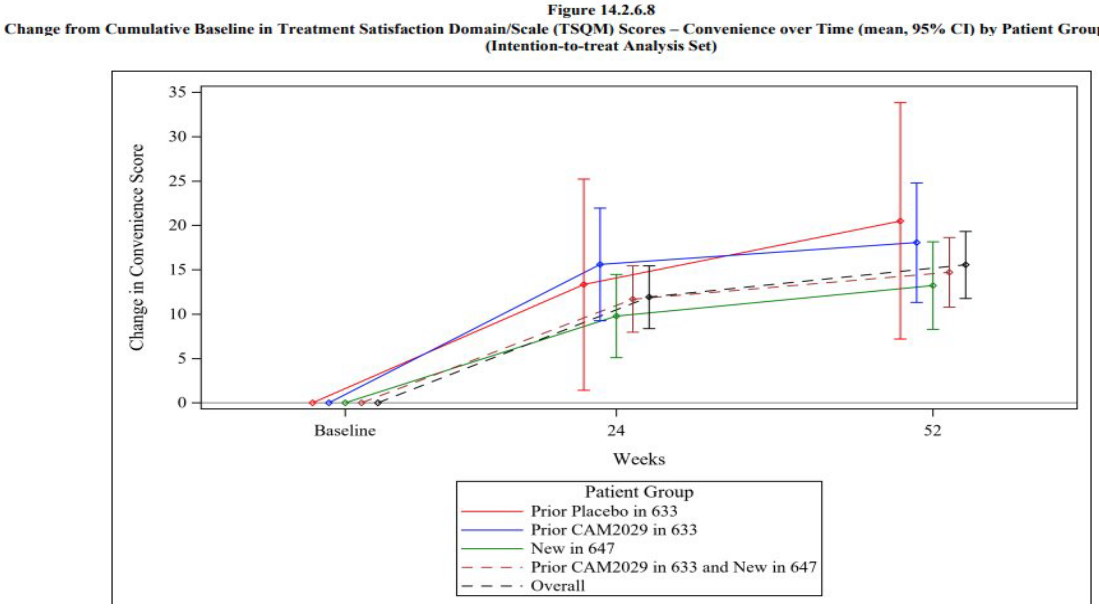
- Treatment Satisfaction (TSQM)

In study HS-19-647, patient-reported treatment satisfaction was evaluated using the TSQM questionnaire at Week 24 and Week 52. Completion rates were high, with 129 out of 130 patients completing the questionnaire at Week 24, and 126 out of 127 at Week 52 (Table 14.2.11.1).

Significant improvements were observed across multiple TSQM domains from the standard-of-care (SoC) baseline to Week 52, particularly in convenience, effectiveness, and global satisfaction.

- **Convenience Domain**: This domain showed the greatest improvement. The overall mean change from SoC baseline to Week 52 was **+15.38** (95% CI: 11.98, 18.77). All patient groups demonstrated significant improvements (Figure 7):
  - CAM2029 roll-over patients: +17.78 (95% CI: 10.96, 24.59)
  - Placebo roll-over patients: +18.52 (95% CI: 6.79, 30.24)
  - New patients: +13.60 (95% CI: 9.35, 17.85)

Figure 7. Change from SoC Baseline in Treatment Satisfaction Domain/Scale (TSQM) Scores – Convenience over Time (mean, 95% CI) by Patient Group – Main Part (Intention-to-treat Analysis Set)



Further improvements were seen following the introduction of the **pre-filled pen**, with mean convenience scores increasing from the last use of the pre-filled syringe to the last use of the pen:

- Overall population: +12.16 (95% CI: 7.83, 16.48)
- New patients: +11.67 (95% CI: 5.89, 17.44)

- **Effectiveness Domain**: The overall mean change from SoC baseline to Week 52 was **+5.43** (95% CI: 2.12, 8.75). The greatest increase was observed in new patients (+6.34 [95% CI: 1.66, 11.03]). In roll-over groups:
  - CAM2029 roll-over patients: +3.33 (95% CI: -1.94, 8.60)
  - Placebo roll-over patients: +5.56 (95% CI: -4.29, 15.40)

Effectiveness scores also increased after transitioning to the pre-filled pen:

- Overall: +5.76 (95% CI: 2.26, 9.26)
- New patients: +6.02 (95% CI: 1.05, 10.98)

- **Global Satisfaction Domain**: From SoC baseline to Week 52, the overall mean change was **+3.98** (95% CI: 0.78, 7.18). The highest improvement was seen in CAM2029 roll-over patients (+8.10 [95% CI: 1.07, 15.13]), followed by:
  - New patients: +2.88 (95% CI: -0.80, 6.56)
  - Placebo roll-over patients: +0.89 (95% CI: -10.64, 12.43)

Notably, among placebo roll-over patients, an increase in global satisfaction was observed from their placebo baseline to Week 52 (+11.11 [95% CI: -0.78, 23.00]). However, no clear improvement was seen when comparing scores from the pre-filled syringe to the pre-filled pen in this domain.

- **Side Effects Domain**: A modest improvement was observed in the overall population from SoC baseline to Week 52 (+3.04 [95% CI: -0.67, 6.76]). Subgroup changes were:
  - CAM2029 roll-over: +6.88 (95% CI: 0.50, 13.25)
  - New patients: +2.71 (95% CI: -2.48, 7.89)
  - Placebo roll-over: -2.73 (95% CI: -12.69, 7.22)

From the placebo baseline to Week 52, side effect scores improved modestly in the placebo roll-overs (+4.17 [95% CI: -4.02, 12.36]). A positive trend was also seen following the transition from the pre-filled syringe to the pre-filled pen in the overall population (+3.17 [95% CI: -0.42, 6.76]).

Of note, improvements in patient-reported outcomes were more pronounced in the supportive study HS-19-647 compared to the pivotal trial HS-18-633. The longer study duration (52 weeks) and the introduction of the pre-filled pen may have contributed to the observed increases in treatment satisfaction. However, the open-label, single-arm design of HS-19-647 introduces potential bias in the perception of benefit. Moreover, without a comparator, it is difficult to attribute improvements solely to the intervention. The absence of formal statistical comparisons further limits conclusions regarding the magnitude of benefit relative to other treatments. The sponsor should further justify the benefits.

- Patient Satisfaction Scale Scores

At Week 24, 126 out of 130 patients, and at Week 52, 123 out of 127 patients completed the patient satisfaction questionnaire. Overall, patient satisfaction was high across treatment groups, with mean scores increasing from 3.9 (95% CI: 3.7, 4.1) at Week 24 to 4.1 (95% CI: 4.0, 4.3) at Week 52, on a scale from 1 ("much worse") to 5 ("much better") [HS-19-647].

The lowest satisfaction was observed at Week 24 in the placebo roll-over group (mean: 3.4; 95% CI: 2.8, 4.0), while the highest was reported at Week 52 among CAM2029 roll-over patients (mean: 4.2; 95% CI: 3.9, 4.5).

Notably, by Week 52, 87 out of 127 patients (68.5%) indicated that their experience with CAM2029 was better than with their previous standard of care: 56 patients (41.5%) rated it as "much better" and 31 patients (23.0%) as "slightly better".

- Acromegaly Quality of Life Questionnaire (AcroQoL)

Improvements in AcroQoL scores were observed from baseline to Week 52 across the study population, with the largest gains reported in CAM2029 roll-over patients. The total score increased by +2.99 (95% CI: 0.96, 5.02) overall, with a notable improvement in roll-over patients (+6.79; 95% CI: 2.48, 11.10). Changes in new and placebo roll-over patients were smaller and not statistically significant.

Physical and psychological domain scores followed a similar pattern, with more pronounced improvements in CAM2029 roll-over patients and minimal or no changes in other groups.

AcroQoL Total Scores increased over time from the last use of the pre-filled syringe to the last use of the pre-filled pen increased (mean change of 2.61, 95% CI: 0.03, 5.20) in the overall population, and was 1.59 (95% CI: -2.67, 5.85) in placebo roll-over patients, 4.62 (95% CI: -0.08, 9.33) in CAM2029 roll-over patients, and 1.19 (95% CI: -3.08, 5.45) in new patients, although confidence intervals overlapped in all subgroups.

- Self-Administration and Self-Injection Assessment Questionnaire (SIAQ) Scores

A high proportion of participants expressed willingness to self-administer CAM2029, with 91.1% (123/135) opting in. Of these, 94.3% were assessed as competent to do so by healthcare professionals.

During the trial, 70.4% of patients (n=95) and 13.3% of caregivers (n=18) administered the treatment at least once. Improvements were noted in SIAQ domains such as 'feelings about injections' and 'self-confidence' from pre- to post-treatment assessments, indicating a positive experience with self-injection.

Instances of injection difficulties were rare and all patients experiencing issues were ultimately able to complete administration successfully.

Conclusion on MCPC of Study HS-18-633 and Study HS-19-647

The evaluation of patient-reported outcomes (PROs), including the Acromegaly Quality of Life Questionnaire (AcroQoL), the Treatment Satisfaction Questionnaire for Medication (TSQM), and the Self-Injection Assessment Questionnaire (SIAQ), provides valuable insights into the patient experience with CAM2029 across both pivotal trials (HS-18-633 and HS-19-647). However, limitations affect the interpretation of these findings in support of a significant benefit claim.

In the pivotal HS-18-633 trial, patients in the CAM2029 arm demonstrated numerical improvements from baseline in AcroQoL total score and both the physical and psychological domains over the 24-week treatment period. Similar improvements were observed in TSQM, particularly in the convenience domain, which likely reflects the transition from previous standard of care (octreotide LAR or lanreotide ATG) to CAM2029 using the pre-filled syringe. However, no improvements from baseline were observed in the TSQM domains of effectiveness, side effects, or global satisfaction. These observed gains should be interpreted with caution, as the study was not powered to detect formal statistical significance for PRO endpoints.

The long-term, open-label HS-19-647 study offers additional information on the effect in patient-reported measures over 52 weeks. Increases from baseline were observed in TSQM domains of convenience, effectiveness, and global satisfaction, alongside sustained or enhanced AcroQoL scores. These patterns were most pronounced in the CAM2029 roll-over group, suggesting potential additive benefits with prolonged treatment. Improvements were also noted in emotional and practical aspects of self-injection, as captured by the SIAQ. This contrasts with the already discussed results from the pivotal HS-18-633 study, where numerical improvements from baseline in TSQM were limited primarily to the convenience domain, with little to no change observed in the effectiveness, side effects, or global satisfaction domains. The reasons for this discrepancy remain unclear. Potential contributing factors may include the longer treatment duration and the introduction of the pre-filled pen device in HS-19-647, which could have enhanced perceived convenience and autonomy over time. However, given the open-label, single-arm design of HS-19-647 and the lack of formal comparator, these trends are not fully substantiated and require further discussion.

Overall, important limitations remain. Both studies relied on descriptive comparisons to baseline, with no formal hypothesis testing of PROs. The supportive study lacked a comparator arm, and confidence intervals for several endpoints were too broad, indicating uncertainty around the estimates. While the improvements over time appear positive, the open-label design of HS-19-647 also introduces potential bias.

Overall conclusion

To support a claim of major contribution to patient care (MCPC), a product must demonstrate at least comparable efficacy, safety, and benefit–risk balance relative to authorised treatment options. Based on the current submission, this standard has not yet been clearly met for CAM2029. No direct or indirect comparisons were provided against established somatostatin analogues such as octreotide LAR or lanreotide ATG. The data submitted rely solely on intra-patient comparisons from baseline to Week 24 or 52, which are not sufficient to substantiate the claim of at least equivalent efficacy, safety and benefit/risk of CAM2029 relative clinical efficacy. As such, the comparative effectiveness of CAM2029 remains uncertain, and further discussion in this regard would be appropriate.

With respect to patient-reported outcomes (PROs), improvements from baseline were reported across multiple instruments — including TSQM, AcroQoL, and SIAQ — in both the pivotal (HS-18-633) and supportive (HS-19-647) trials. However, interpretation is limited by several factors, including the absence of formal statistical comparisons, the open-label and single-arm nature of the supportive study, and the use of different injection devices across time points. These methodological constraints limit the conclusions that can be drawn from the PRO findings. The sponsor is therefore invited to provide further clarification on how the observed changes are considered to support a claim of significant benefit.

Moreover, the absence of subgroup analyses by prior therapy — specifically differentiating between patients previously treated with intramuscular (octreotide LAR) versus deep subcutaneous (lanreotide ATG) injections — limits the ability to assess whether observed outcomes are influenced by route of prior administration. The role of the delivery device also warrants further clarification. In particular, the sponsor is requested to submit additional analyses of PRO data stratified by (i) the injection mechanism used in prior treatment and (ii) the injection device used for CAM2029 (pre-filled syringe versus pre-filled pen), in order to better understand the potential contribution of administration method to patient experience.

These uncertainties highlight the need for additional justification and supportive data to substantiate a claim of major contribution to patient care. Taken together, the sponsor is invited to further clarify whether the efficacy of CAM2029 may be considered at least equivalent to authorised comparators, and to explain how the available PRO findings — given their exploratory nature and inherent limitations — support the overall claim of significant benefit.

4. COMP list of issues

To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorized medicinal products. Although certain endpoints demonstrated statistically significant differences, it remains unclear how these results compare directly to the efficacy of existing somatostatin analogues. The COMP would therefore welcome further discussion on whether CAM2029 may be considered comparable in terms of maintaining sustained biochemical control and achieving long-term clinical outcomes.

In relation to patient-reported outcomes (PROs), improvements from baseline were noted across multiple domains of the TSQM, AcroQoL, and SIAQ instruments in both the pivotal (HS-18-633) and supportive (HS-19-647) studies. However, interpretation of these results is constrained by limitations in study design, including the lack of formal statistical comparisons between treatment arms, the non-randomised, open-label nature of the supportive trial, and not differentiating the different devices used

for the products delivery. The sponsor is therefore invited to elaborate on how the available PRO data are considered to support the MCPC claim, particularly in light of these methodological constraints.

Additionally, the absence of subgroup analyses by prior treatment — specifically between patients previously treated with octreotide LAR (intramuscular) and lanreotide ATG (deep subcutaneous) — limits interpretation of potential differences based on route of administration. Clarification regarding the role of the injection device, and whether improvements in patient experience are attributable to the switch to subcutaneous administration via CAM2029, would also be informative.