EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Mycapssa (octreotide)
Treatment of acromegaly
EU/3/13/1170

Sponsor: Amryt Pharmaceuticals Designated Activity Company

Note

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

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Table of contents

1. Product and administrative information

Product	
Designated active substance	Octreotide acetate (oral use)
Other name(s)	-
International Non-Proprietary Name	Octreotide
Tradename	Mycapssa
Orphan condition	Treatment of acromegaly
Sponsor's details:	Amryt Pharmaceuticals Designated Activity Company 45 Mespil Road Ballsbridge Dublin 4 D04 W2F1 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Larode Ltd
COMP opinion	11 July 2013
EC decision	5 August 2013
EC registration number	EU/3/13/1170
Post-designation procedural history	
Transfer of sponsorship	- Transfer from Larode Ltd to FGK Representative Service GmbH – EC decision of 11 January 2019 - 2nd transfer from FGK Representative Service GmbH to Amryt Pharmaceuticals Designated Activity Company – EC decision of 16 February 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Romaldas Mačiulaitis / Ewa Balkowiec Iskra
Applicant	Amryt Pharmaceuticals Designated Activity Company
Application submission	28 June 2021
Procedure start	19 August 2021
Procedure number	EMA/H/C/005826
Invented name	Mycapssa
Proposed therapeutic indication	Mycapssa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues. Further information on Mycapssa can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Mycapssa
CHMP opinion	15 September 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Vallo Tillmann / Lyubina Racheva Todorova
Sponsor's report submission	17 March 2022
COMP discussion and adoption of list of questions	6-8 September 2022

Oral explanation cancellation by the COMP	4 October 2022
COMP opinion	6 October 2022

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2013 designation was based on the following grounds:

"The sponsor Larode Ltd submitted on 25 March 2013 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing octreotide acetate (oral use) for treatment of acromegaly (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

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 octreotide acetate (oral use) was considered justified based on pharmacokinetic data showing a comparable availability to the currently authorized parenteral formulation of octreotide, and on clinical data showing suppression of growth hormone plasma levels after stimulation with growth hormone releasing hormone;
- the condition is chronically debilitating due to abnormal growth of connective tissue, cartilage, bone, skin, and visceral organs. This results in increased morbidity and mortality due to cardiovascular, cerebrovascular, and respiratory disease;
- the condition was estimated to be affecting less than 2 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing octreotide acetate (oral use) may be of significant benefit to those affected by the condition. The sponsor provided data to support that there are serious and documented difficulties with the formulation or route of administration of the currently authorized octreotide products that are administered via intramuscular or subcutaneous route, e.g., pain and local reactions at the injection site. In addition, there is the need for the authorized products to be administered by healthcare professionals, requiring monthly visits to the hospital. The Committee considered that the possibility of having an oral formulation of octreotide in alternative to the available parenteral formulations constitutes a major contribution to patient care for the patients affected by the condition.

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 fulfilled. The COMP therefore recommends the designation of this medicinal product, containing octreotide acetate (oral use), 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 "Mycapssa 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 Committee for Medicinal Products for Human Use (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 designation, the prevalence (P) was agreed to be less than 2 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 1.37 per 10,000.

The sponsor performed a systematic literature search to determine the prevalence of acromegaly in the EU, including publications from registry databases. It is also indicated that data from cancer registries or isolated tertiary referral centres were not assessed.

A rather recent metanalysis of population studies on the epidemiology of acromegaly was identified (Lavrentaki 2017). The review systematically analyses the epidemiological profile of acromegaly based on recently published population studies from various geographical areas. In this study, a total prevalence is estimated to range between 2.8 and 13.7 cases per 100,000 people and the annual incidence rates range to be between 0.2 and 1.1 cases/100,000 people.

Furthermore, the search yielded prevalence and incidence estimates for acromegaly across European countries (Table 1). For studies reporting incidence (e.g., Holdaway 1999), the sponsor assumed a mean age at diagnosis of 44 years and a conservative mean life expectancy of acromegaly patients to be 75 years, resulting in a lifetime with acromegaly of 30 years. It is noted that some of these studies correspond to national registries (e.g., Daly 2006; Dal 2016; Bex 2007; Mestron 2004; Gruppetta 2013).

Table 1. (Table 4 from sponsors' application)**.** Prevalence of acromegaly as reported in population studies conducted in Europe.

Reference	Region/country covered	Reference population	Total prevalence (per 10,000)
Daly 2006	Province of Liege, Belgium	71,972	1.25
Tjornstrand 2014	Sweden	1,590,640	0.33
Agustsson 2015	Iceland	321,857	1.37
Hoskuldsdottir 2015	Iceland	316,075	1.33
Raappana 2010	Finland	722,000 – 733,000	0,90
Dal 2016	Denmark	5,534,738	0.85
Bex 2007	Belgium and the Grand Duchy of Luxembourg	10,850,000	0.4
Mestron 2004	Spain	Population of Spain in 2001	0.34
Gruppetta 2013	Malta	417,608	1.24

Taking into consideration the available sources from different European countries the prevalence is proposed to fall within the range from 0.33 to 1.37 in 10,000. As a conservative approach, the sponsor opted for the highest prevalence rate reported to reflect the total prevalence in the EU, concluding a final prevalence of 1.37 in 10,000.

The COMP concluded that the proposed figure of 1.37 in 10,000 persons in the EU could be consider as valid and could be rounded to 1.4 in 10,000.

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.

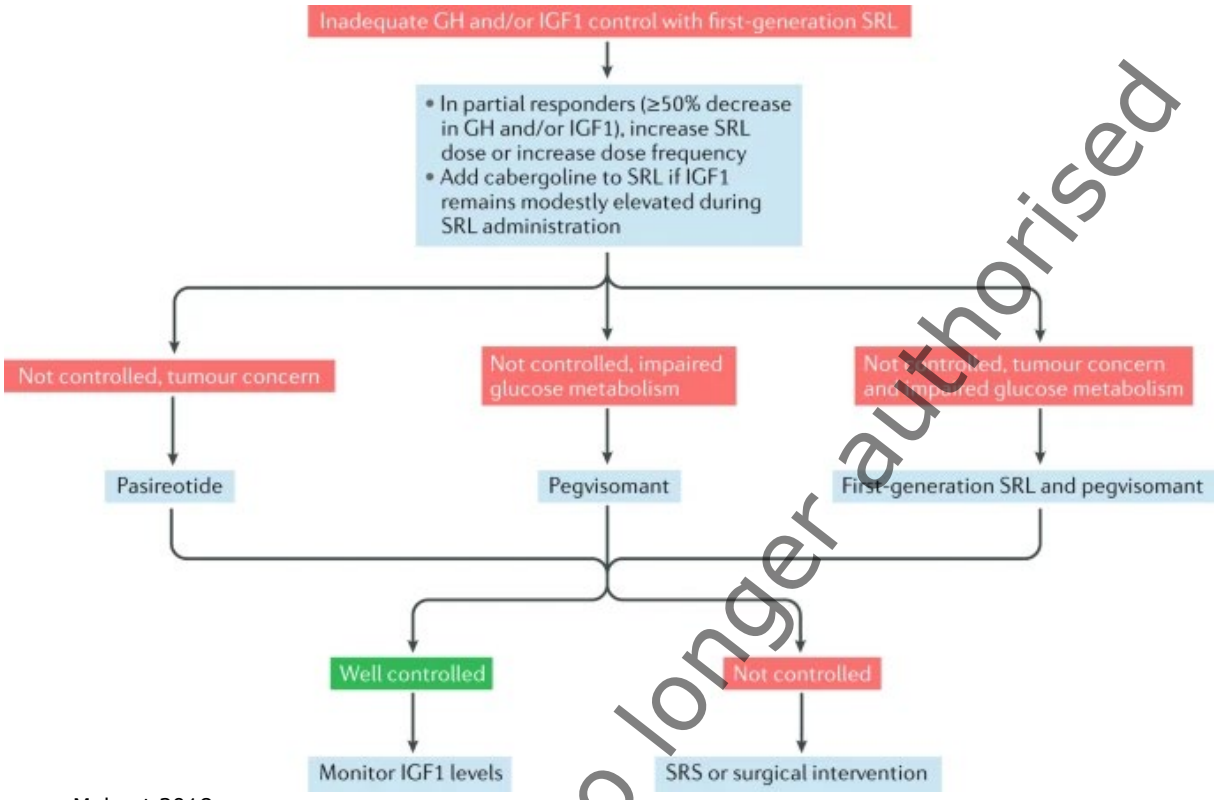
For patients with persistent disease after surgery, a first-generation long-acting SRL is recommended as first-line medical therapy. The choice between octreotide LAR and Lanreotide autogel is determined by availability, convenience of administration and patient preference. Cabergoline can be attempted 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 proposed product Mycapssa is indicated for: "*Mycapssa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues*". 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
Bromocriptine	As an adjunct to surgery and/or radiotherapy to reduce circulating growth hormone levels in the management of acromegalic patients.	No
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

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 Mycapssa in their indications. The medicines Signifor (Pasireotide), Bromocriptine, and Somavert are not considered satisfactory methods, as these target different patient population and lack complete overlap with Mycapssa.

Significant benefit

The sponsor's product is an oral formulation of commercially available octreotide. The sponsor argued that Mycapssa will be of significant benefit based on a clinically relevant advantage (CRA) in terms of the clinical efficacy and clinical safety, and of major contribution to patient care (MCPC) compared to existing treatment methods for the target patient population. Although superiority to injectable SRL is claimed (i.e., octreotide LAR [IM] and lanreotide autogel [SC]), the CHMP concluded that Mycapssa is non-inferior to these other products.

The sponsor requested initial EMA scientific advice dated 22 August 2011 to obtain feedback on the overall development program of Mycapssa (EMEA/H/SA/2206/1/2011/SME/III). Subsequently, Follow-up Protocol Assistance was sought on the 16 September 2013 (EMEA/H/SA/2206/1/FU/1/2013/PA/SME/III), and on the 29 June 2015 (Procedure No.: EMEA/H/SA/2206/1/FU/3/2015/PA/SME/II). In the latter, the sponsor raised a question regarding the evidence needed to justify significant benefit over existing standard of care parenteral treatment which was addressed by the COMP. In particular, the COMP clarified that:

'"Significant benefit on the grounds of 'major contribution to patient care' could generally only be judged if the new product would be comparable in efficacy and safety to currently authorized products. When assessing the potential major contribution to patient care of this new oral formulation, the COMP would therefore have to weigh a potential loss of efficacy against advantages in patient convenience, which then would have to be compelling. In this context, should improved convenience of the oral formulation translate into improved compliance, this could support significant benefit.

At the time of marketing authorization the sponsor of a designated orphan medical product will be required to demonstrate, that significant benefit is confirmed in order to maintain orphan status. In the context of orphan designation "significant benefit" is defined as "a clinically relevant advantage or a major contribution to patient care" (Commission regulation (EC) No 847/2000 Article 3). The Applicant should also bear in mind that their dossier for MAA will be evaluated considering the most recent therapeutic alternatives (including approaches which are not approved currently but may have been approved at the time of MAA)."

The primary data to support the basis of significant benefit stems from the Phase 3 study OOC-ACM-302; a randomised, open-label, active-controlled, preceded by a run-in phase, followed by an open label extension (OLE) phase and a follow-up phase.

Eligible patients had a confirmed diagnosis of acromegaly, had been treated with SRL injections (octreotide LAR or lanreotide monotherapy) for at least 6 months and had been on a stable dose for the last 4 months, and were biochemically controlled (IGF-1 < 1.3 x upper limit of normal [ULN] and mean integrated GH < 2.5 ng/mL over 2 hours) on their current dose of SRL. IGF-1 and GH were analysed centrally throughout the study. Eligible patients were switched to octreotide capsules for a 26-week run-in phase. During this phase, the effective dose for each patient was determined through dose titration. The octreotide capsule dose was to be increased per investigator's discretion in the case of increased IGF-1 levels, worsening of acromegaly symptoms, or both. Patients whose acromegaly was controlled biochemically on octreotide capsules at the end of the run-in phase entered a 36-week open-label randomized controlled treatment (RCT)phase, where they were randomised in a 3:2 ratio to 1 of 2 treatment arms: continue treatment with octreotide capsules (treatment arm 1) or revert to injectable SRL treatment (treatment arm 2) as received prior to screening. Following completion of the core study (screening, run-in, and RCT phases), or study OOC-ACM-303 OLE phase, eligible patients were offered entry into the OOC-ACM-302 OLE phase to receive octreotide capsules for up to 5 years or until product marketing, or termination of the study by the sponsor.

The treatment groups were octreotide capsules: 40 mg/day (20 mg bid), 60 mg/day (40 mg in the morning, 20 mg in the evening), or 80 mg/day (40 mg bid). One hundred and forty-six (146) patients were recruited of which 92 were included in the RCT phase: 55 on octreotide capsules and 37 on SRL injections (octreotide LAR or lanreotide monotherapy). The mean age at screening was 54.1 years (range: 28 to 73 years), and 64.4% of patients were female. Diagnosis at inclusion was acromegaly patients biochemically controlled (defined as IGF-1 <1.3 x ULN and mean integrated GH <2.5 ng/mL over 2 hours) on injectable SRLs. Acromegaly baseline characteristics for the FAS are presented in table 3 indicating that the composition of the RCT phase SRL injection group consisted of 16 patients treated with lanreotide and 21 patients with octreotide LAR.

Table 3. (Table 16 from sponsors' clinical study report). Summary of Acromegaly Baseline Characteristics for the RCT Phase (Full Analysis Set) FAS.

Characteristics	Octreotide Capsule[1] Total (N = 55)	SRL Injection[2] Total (N = 37)	Overall (N = 92)
Baseline IGF-1 (ULN)			
n	55	37	92
Mean (SD)	0.8 (0.25)	0.8 (0.24)	0.8 (0.25)
Median (P25, P75)	0.8 (0.6, 1.0)	0.7 (0.6, 1.0)	0.8 (0.6, 1.0)
Min, max	0.3, 1.3	0.3, 1.5	0.3, 1.5
≤ 1 ULN	43 (78.2)	28 (75.7)	71 (77.2)
> 1 to < 1.3 ULN	11 (20.0)	8 (21.6)	19 (20.7)
≥ 1.3 ULN	1 (1.8)	1 (2.7)	2 (2.2)
RCT Baseline IGF-1 (ULN)			
n	55	37	92
Mean (SD)	0.9 (0.35)	0.8 (0.21)	0.9 (0.30)
Median (P25, P75)	0.9 (0.7, 1.1)	0.8 (0.7, 1.0)	0.9 (0.7, 1.0)
Min, max	0.3, 2.6	0.4, 1.2	0.3, 2.6
≤ 1 ULN	37 (67.3)	29 (78.4)	66 (71.7)
> 1 to < 1.3 ULN	12 (21.8)	8 (21.6)	20 (21.7)
≥ 1.3 ULN	6 (10.9)	0	6 (6.5)
Baseline GH (ng/mL)			
n	55	37	92
Mean (SD)	0.77 (0.601)	0.79 (0.757)	0.78 (0.664)
Median (P25, P75)	0.70 (0.2, 1.1)	0.40 (0.3, 1.0)	0.50 (0.3, 1.1)
Min, max	0.1, 3.0	0.1, 2.9	0.1, 3.0
≤ 1 ng/mL	38 (69.1)	25 (67.6)	63 (68.5)
> 1 to < 2.5 ng/mL	16 (29.1)	10 (27.0)	26 (28.3)
≥ 2.5 ng/mL	1 (1.8)	2 (5.4)	3 (3.3)
RCT Baseline GH (ng/mL)			
n	55	37	92
Mean (SD)	0.55 (0.544)	0.62 (0.634)	0.58 (0.579)
Median (P25, P75)	0.40 (0.2, 0.8)	0.30 (0.2, 0.9)	0.40 (0.2, 0.9)
Min, max	0.1, 2.8	0.1, 3.4	0.1, 3.4
≤ 1 ng/mL	44 (80.0)	28 (75.7)	72 (78.3)
> 1 to < 2.5 ng/mL	10 (18.2)	8 (21.6)	18 (19.6)
≥ 2.5 ng/mL	1 (1.8)	1 (2.7)	2 (2.2)
Prior parenteral somatostatin analog treatment			
Octreotide LAR (n [%])			
Low	4 (7.3)	3 (8.1)	7 (7.6)
Middle	14 (25.5)	10 (27.0)	24 (26.1)
High	11 (20.0)	8 (21.6)	19 (20.7)
Lanreotide (n [%])			
Low	6 (10.9)	6 (16.2)	12 (13.0)
Middle	5 (9.1)	4 (10.8)	9 (9.8)
High	15 (27.3)	6 (16.2)	21 (22.8)
Prior parenteral somatostatin analog treatment overall (n [%])			
Low	10 (18.2)	9 (24.3)	19 (20.7)
Middle	19 (34.5)	14 (37.8)	33 (35.9)
High	26 (47.3)	14 (37.8)	40 (43.5)

Characteristics	Octreotide Capsule[1] Total (N = 55)	SRL Injection[2] Total (N = 37)	Overall (N = 92)
Medical treatment on randomization			
Octreotide LAR (n [%])			
Low	0	3 (8.1)	3 (3.3)
Middle	0	10 (27.0)	10 (10.9)
High	0	8 (21.6)	8 (8.7)
Lanreotide (n [%])			
Low	0	6 (16.2)	6 (6.5)
Middle	0	4 (10.8)	4 (4.3)
High	0	6 (16.2)	6 (6.5)

Baseline was defined as the last value recorded prior to or equal to the date of the first dose of octreotide capsules anytime during Screening or Baseline visit. Baseline RCT was defined as week 26 value. In case of missing values at week 26, the last available value on study drug, prior to week 26 and not earlier than week 20, was used.
1) Dose was set to the highest achieved during the run-in phase.
2)"Low" was any octreotide dose < 20 mg total/month or lanreotide < 90 mg total/month; "Middle" was any octreotide dose < 30 mg total/month or lanreotide < 120 mg total/month; "High" was any octreotide dose ≥ 30 mg total/month or lanreotide ≥ 120 mg total/month.
3) Microadenoma was defined as tumor size ≤ 10 mm, macroadenoma was defined as tumor size > 10 mm, undetermined and not visible were defined as "other".
4) Patients could have reported multiple items in this summary.
5) Complete Responder (CR): IGF-1 ≤ 1 times ULN and GH < 2.5 ng/mL; Partial Responder (PR): 1 times ULN< IGF-1 < 1.3 times ULN and GH < 2.5 ng/mL; Non-Responder (NR): IGF-1 ≥ 1.3 times ULN or GH ≥ 2.5 ng/mL.
AIS = Acromegaly Index of Severity; CI = confidence interval; FAS = Full Analysis Set; GH = growth hormone; IGF-1 = insulin-like growth factor 1; Min, max = minimum, maximum; P25 = 25th percentile; P75 = 75th percentile; RCT = randomized, controlled treatment; SD = standard deviation; SRL = somatostatin receptor ligand; ULN = upper limit of normal.
Source: sponsors' clinical study report.

The study aimed to assess maintenance of biochemical control and safety of octreotide capsules compared to parenteral SRLs in patients with acromegaly. Since all enrolled patients were required to be responders to injectable SRLs on screening, the objective of the RCT phase was to compare long-term maintenance of biochemical control in patients responding to octreotide capsules at the end of the run-in phase to patients responding to injectable SRLs (on screening).

In addition, the design of this study is enriching the acromegaly population by excluding non-responders after the switch from parenteral SRL to oral octreotide. The maintenance of biochemical control after switch from standard of care in Study 302 was therefore assessed in an enriched patient population of patients responding to the Mycapssa after the switch.

Efficacy

The primary endpoint was the proportion of patients who were biochemically controlled throughout the RCT phase: octreotide capsules: 90.9% and SRL injections: 100%. Adjusted 2 difference in proportions: -9.1 (95% CI: -19.9, 0.5).

The secondary efficacy endpoints included, among others, outcomes such as the proportion of patients who were biochemically controlled, overall number of active acromegaly symptoms, overall acromegaly index of severity (AIS) score, results in the acromegaly treatment satisfaction questionnaire, and other biochemical surrogates (e.g., change in GH, IGF-1). Exploratory Efficacy Endpoints included the assessment of improvement in the overall AIS score, acromegaly symptoms change, proportion of patients with TWA IGF-1 ≤ 1 times ULN and others.

Data on adverse reactions, vital signs, electrocardiograms, physical and instrumental (e.g., ultrasound) examination and clinical laboratory assessments were also collected during this study.

As seen in the symptom control results from the RC part of the study, results were comparable between cohorts. Overall, 72.7% of patients in the octreotide capsules group and 67.6% of patients in

the SRL injections group maintained or improved their overall AIS score at the end of the RCT phase compared to week 26 (adjusted treatment difference: 5.4%; 95% CI: -13.2, 25.2; Table 4).

Table 4 .(Table 2 from sponsors' application). Proportion of patients who maintained or reduced their overall AIS score at the end of the RCT phase compared to Week 26 in study OOC-ACM-302 (FAS).

	Octreotide capsules[1]				**SRL injections [2]**			
Parameter	40 mg (N = 23)	60 mg (N = 13)	80 mg (N = 19)	Total (N = 55)	Low (N = 9)	Middle (N = 14)	High (N = 14)	Total (N = 37)
Responder	16 (69.6)	11 (84.6)	13 (68.4)	40 (72.7)	8 (88.9)	10 (71.4)	7 (50.0)	25 (67.6)
95% CI [3]				(59.0, 83.9)				(50.2, 82.0)
Improved	4 (17.4)	4 (30.8)	3 (15.8)	11 (20.0)	4 (44.4)	4 (28.6)	3 (21.4)	11 (29.7)
Maintained	12 (52.2)	7 (53.8)	10 (52.6)	29 (52.7)	4 (44.4)	6 (42.9)	4 (28.6)	14 (37.8)
Non-responder	7 (30.4)	2 (15.4)	6 (31.6)	15 (27.3)	1 (11.1)	4 (28.6)	7 (50.0)	12 (32.4)
Difference in un-adjusted proportions				5.2				
95% CI [4]				(-13.4, 24.6)				
Difference in adjusted proportions [5]				5.4				
95% CI [5]				(-13.2, 25.2)				

If a patient had not discontinued but was missing their Week 62/AIS assessment, then the LOCF approach was used to impute their AIS score

1 Dose was set at the highest achieved during the run-in phase.

2 Low: any octreotide dose <20 mg total/month or lanreotide <90 mg total/month; middle: any octreotide dose <30 mg total/month or lanreotide <120 mg total/month; high: any octreotide dose ≥30 mg total/month or lanreotide ≥120 mg total/month.

3 Clopper-Pearson method

4 M&N method

5 The adjusted difference and CI were obtained using the M&N method with M&N weights (where the stratum was defined in the randomisation process).

Safety

It is indicated by the sponsor that in the group of patients who were switched back to injectable SRLs in the randomized control phase of study, 17 of the 36 patients (47.2%) who completed the Acro-TSQ reported injection site reactions at the end of the RCT phase, and 13 of these patients (81.3%; data were missing for 1 patient) reported that the injection site reactions interfered with daily activities. Other than the lack of injection site reactions, the safety profile of Mycapssa is indicated to be consistent with that of injectable SRLs.

Conclusion on efficacy and safety

As the CHMP has established that there is non-inferiority between the oral formulation and the injectable SRL formulations of octreotide and lanreotide, no clinically relevant advantage can be supported for Mycapssa.

Major Contribution to Patient Care: Differentiation from SRL injection therapies and PROs results

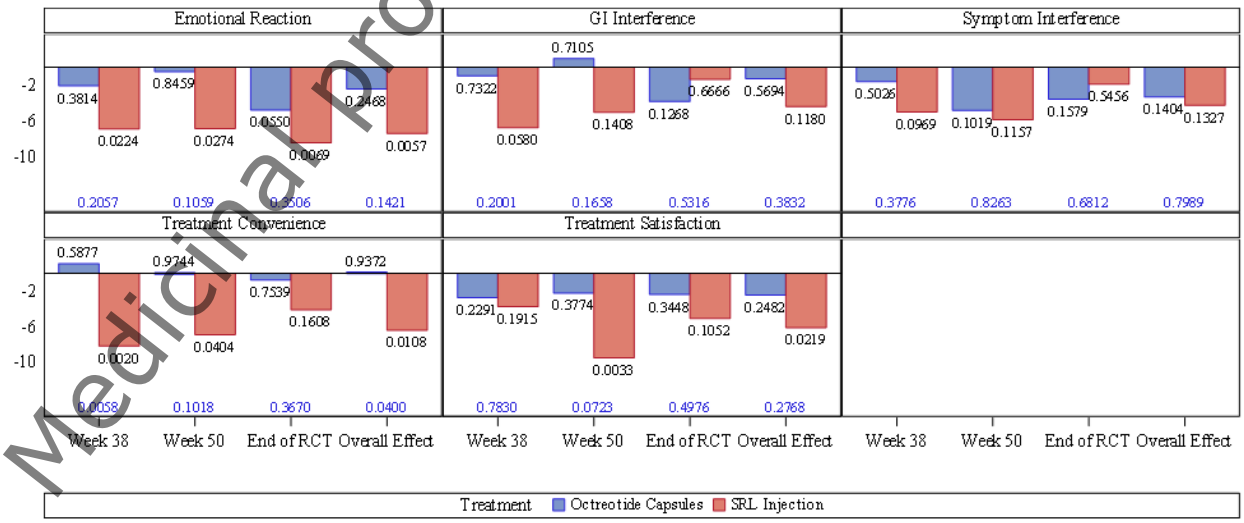
The sponsor has provided data in support of the MCPC from study OOC-ACM-302 and indicated that the criteria agreed with the COMP during protocol assistance was followed. Several PRO questionnaires were used in the study: Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ); EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L) and the work productivity questionnaire (WPAI). WPAI:SHP is a standardized and validated PRO questionnaire to measure health outcomes in clinical trial settings (Reilly 1993). The results of each are summarised below.

The overall proportion of patients with a reduced overall number of active acromegaly symptoms at the end of the run-in phase compared to baseline was 30.8% (95% CI: 23.3, 38.3), the number of symptoms was maintained in 35.6% of patients. Thus, the proportion of patients with a maintained or reduced overall number of active acromegaly symptoms at the end of the run-in phase compared to baseline was 66.4% (95% CI: 58.8, 74.1). Overall, 74.5% of patients in the octreotide capsules group and 70.3% of patients in the SRL injections group maintained or reduced their overall number of active acromegaly symptoms at the end of the RCT phase compared to Week 26 (adjusted treatment difference: 4.6%; 95% CI -13.6, 23.9).

- Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ):

Mean Acromegaly Treatment Satisfaction Questionnaire ACRO-TSQ scales during RCT phase were generally comparable between the 2 treatment groups. However, while numerical changes in Emotional Reaction, Treatment Convenience, and Treatment Satisfaction favoured octreotide capsules; numerical changes in GI interference and Symptom Interference favoured SRL injections. A significant difference between treatment groups was seen for treatment convenience, where a significantly greater deterioration was found in the SRL injections group for the average effect during the RCT phase (p = 0.040).

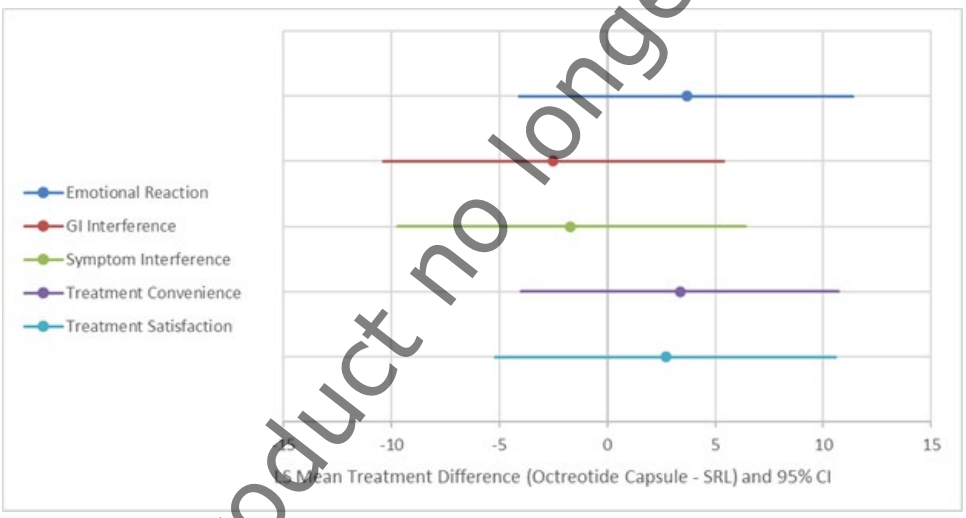
Figure 2. (Figure 5 from sponsors' application). ACRO-TSQ scales change during the RCT phase of study OOC-ACM-302 by treatment group and visit (FAS).



Least squares mean change from baseline to week 38, week 50, and week 62 based on an MMRM model which included treatment arm, scheduled visits (week 38, week 50, week 62), the interaction between the treatment arm and scheduled visits, as fixed factors, and the score at baseline (week 26) as a covariate. An unstructured covariance structure was assumed, and the denominator degrees of freedom were computed using the Kenward-Roger method. Numbers in black at the end of each bar represent within group p-value. Number in blue that spans visit represents between groups p-value.

The LSM treatment differences for the change from baseline (end of the Run-in period value) in ACRO-TSQ scale scores at the end of the RCT phase are presented in Figure 3, with positive numbers favouring octreotide capsules and negative numbers favouring SRL injections. The results reported from the RCT phase reflect the change in the PRO from the end of the run-in-period (week 26, when all patients were treated with OOC) to the end of the RCT (week 62). ACRO-TSQ scale scores were generally comparable between treatment groups at the end of the RCT phase, however, numerical changes in emotional reaction, treatment convenience, and treatment satisfaction favoured octreotide capsules while numerical changes in GI interference and symptom interference favoured SRL injections: emotional reaction (LSM difference = 3.67; 95% CI -4.11, 11.44), treatment convenience (LSM difference = 3.36; 95% CI -4.01, 10.74), treatment satisfaction (LSM difference = 2.71; 95% CI -5.19, 10.61), GI Interference (LSM difference = -2.49; 95% CI -10.36, 5.39), and symptom interference (LSM difference = -1.66; 95% CI -9.68, 6.35). None of the differences between baseline and the end of the RCT phase were statistically significant.

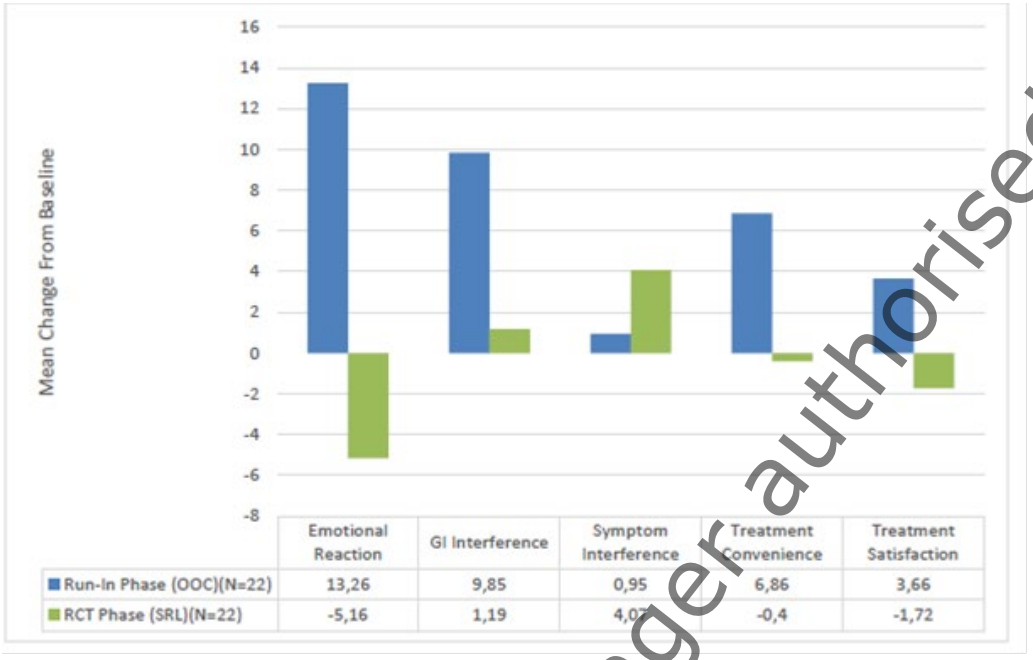
Figure 3. (Figure 6 from sponsors' application). Forest plot of the LSM difference (octreotide capsules – SRL injections) and 95% CI for the ACRO-TSQ scales at the end of the RCT phase of study OOC-ACM-302 (FAS).



Additional analyses were conducted combining data from both the run-in and RCT Phases, which are claimed to be of specific interest for patients randomized to injectable SRLs during the RCT. The descriptive analysis shows improvement at end of run-in (while treated with OOC) followed by worsening or maintenance at end of RCT (while treated with injectables) for Emotional Reaction, Treatment Convenience, Treatment Satisfaction and GI Interference scales (Figure 4). However, only 22 patients were part of the analysis.

Symptom interference showed improvement at both end of run-in and end of RCT, with larger improvements noted during the RCT.

Figure 4. (Figure 7 from sponsors' application). Summary of Mean Changes in Acro-TSQ domains by Study Phase for patients Randomized to injectable SRLs.



	Emotional Reaction	GI Interference	Symptom Interference	Treatment Convenience	Treatment Satisfaction
Run-In Phase (OOC)(N=22)	13,26	9,85	0,95	6,86	3,66
RCT Phase (SRL)(N=22)	-5,16	1,19	4,07	-0,4	-1,72

- EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L)

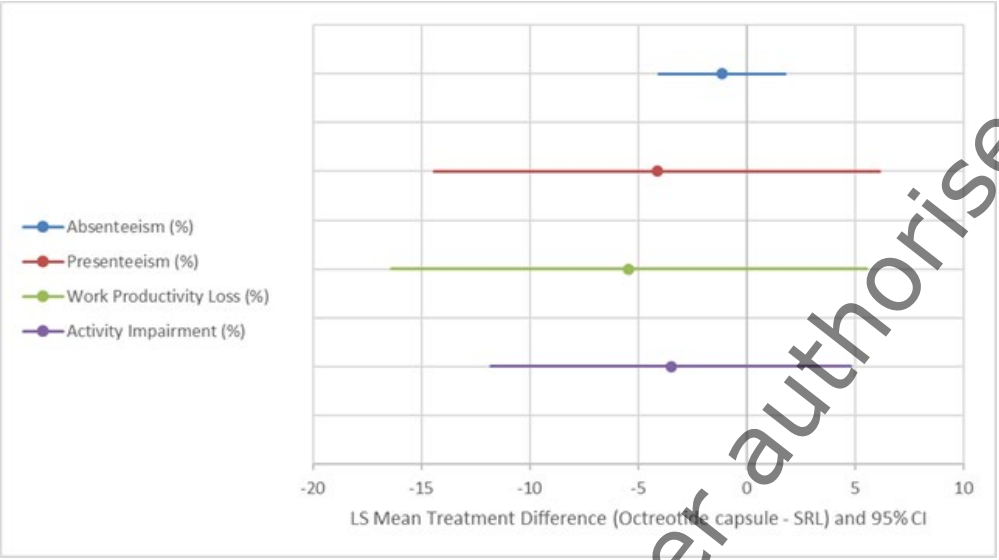
EQ-5D-5L Index scores during the RCT phase were generally comparable between treatment groups, and the 95% CIs for change from baseline (end of the Run-in period value) at the end of the RCT phase included zero for both treatment groups. Similar results were obtained for all EQ-5D-5L dimension ratings.

Based on a mixed effect model repeated measures analysis, ED-5D-5L Index scores were not significantly different between treatment arms at the end of the RCT phase (LSM treatment difference -0.04, 95% CI -0.12, 0.04). EQ-5D-5L VAS scores were also generally comparable between treatment arms at the end of the RCT phase.

- The work productivity questionnaire (WPAI) results

WPAI:SHP domain scores were generally comparable between the 2 treatment groups at the end of the RCT phase; none of the differences was statistically significant (Figure 5).

Figure 5. (Figure 8 from sponsors' application). Forest plot of the LSM difference (octreotide capsules - SRL injections) in changes from baseline (95% CI) from RCT baseline to the end of the RCT phase for the WPAI scores in randomised patients of study OOC-ACM-302 (FAS).



Conclusion on major contribution to patient care

Overall, the data submitted by the sponsor could not conclusively show MCPC at the time of initial assessment. While significant differences are observed in the run-in phase, results do not reach statistical significance in most RCT sub scores. Further, no subgroup analysis was presented for the octreotide LAR (intramuscular) and lanreotide (subcutaneous) groups. This would require further discussion in order to allow an understanding of any difference based on the route of administration – intramuscular compared to subcutaneous.

In addition, and of particular relevance, doubts were raised concerning the main study OOC-ACM-302, in regard to the methodology and the statistical analysis that is being presented on the PRO analysis. Elements such as how the run-in phase patients were defined (whether the results reflect all patients or only those who qualified as responders to treatment), and the sample sized used in this phase. An overview table for these results with a clarification would be useful. It was unclear what baseline is being referred to in Figure 5 in terms of whether it refers to the beginning of the Run-in phase or randomisation and how the different timepoints are defined (e.g., week 38, week 50) since these do not appear to be aligned with specific study endpoints.

The sponsor addressed the above concerns from the COMP which could be summarized on: the main clinical study design and collection of results, the results observed as part of the Patient-reported outcomes (PROs), the details of the statistical analysis, and the possible impact of the route of administration of each of the two products used in the control group (i.e., SLR injections). The sponsor further justified the claim for significant benefit of Mycapssa over existing treatments and provided clarity on the clinical study design and statistical methodology.

Regarding the study methodology, the sponsor clarified that the Acro-TSQ questionnaire was administered during the RCT phase of the study every 12 weeks, starting at baseline on week 26 (end of Run-in/beginning of RCT) through the end of RCT phase (week 62). The reference timepoints (e.g., week 38, week 50 and week 62) were selected so that the assessments were equally spaced throughout the RCT phase. Data from the Acro-TSQ at weeks 38, 50 and 62 were compared to the week 26 baseline value.

The sponsor also elaborated on the reasons why a more pronounced effect as measured by the PROs is observed during the Run-in phase compared to the randomized controlled phase of the study. It was clarified that the Run-in phase was included to identify the eligible population for the RCT phase, that is, those patients who responded to and tolerated both OOC. Analysis of PRO data during the Run-in period was performed by comparing each patient to their own baseline value. For each patient, the baseline value provides PRO data while treated with iSRLs, while the end of the Run-in period value provides PRO data while on OOC. Therefore, the results of the PRO during the run-in period (change from baseline to end of run-in) reflect the change in patient perception of treatment convenience and burden when changing from parenteral to oral SRL treatment. As this is their first experience with oral treatment, the sponsor argued that this is the analysis for which most pronounced changes would be observed.

The results reported from the RCT phase, however, reflect the change in the PRO from the end of the run-in-period (week 26, when all patients were treated with OOC) to the end of the RCT (week 62). Therefore, for patients randomized to OOC the PRO results from the RCT phase reflect a potential further change after already being on OOC for 6 months. In that situation it is indicated that no additional pronounced patients benefit, reflected as changes in the PRO outcome, are expected. On the contrary, for patients randomized to iSRLs, the PRO results from the RCT phase reflect the changes after being switched from OOC back to injectables.

It is finally concluded that the study was not powered to detect differences between treatment groups for any of the PROs during the RCT phase. As such and as indicated by the sponsor, the comparison between groups did not demonstrate any statistically significant differences in those Acro-TSQ domains where there were significant differences within patients during the Run-in phase (with the exception of treatment convenience). Of interest, the same three Acro-TSQ domains (emotional reaction, treatment convenience and treatment satisfaction) that improved on switching to OOC during the Run-in worsened for patients that were randomized to return to the prior iSRL therapy in the RCT. In comparison, the group randomized to remain on OOC therapy during the RCT phase showed no significant changes in these three domains, with stable results maintained as measured by overall effect. The COMP agreed with the sponsor that the totality of the PRO data demonstrates a consistency in improved outcomes within patients when receiving OOC therapy compared to their experience on iSRLs which can be considered a major contribution to patient care.

Regarding the possible impact of the route of administration, it was clarified that analysis of PRO data based on treatment with either octreotide LAR or lanreotide autogel during the RCT was not assessed, since according to the sponsor the sample size would not allow for a robust subgroup analysis among patients randomized to iSRLs (N=37) (21 patients were treated with octreotide LAR and 16 patients were treated with lanreotide autogel during the RCT). Based on a similarly reasoning, such analysis was neither performed during the Run-in phase. It is, however, indicated that randomization was used to minimize any potential imbalances between groups (OOC vs. iSRLs). It was further argued that documented experience does not reflect notable differences on patient-reported or other outcomes between the different products and their SRL Injection routes of administration (Giustina, 2014; Katznelson, 2014; Fleseriu, 2021 Feb). In particular, the sponsor refers to indicators such as acromegaly symptom burden, physical or emotional burden or overall treatment effect. Some notable exceptions were differences between octreotide and lanreotide on injection site pain (worse with octreotide LAR), skin pathologies, e.g., skin nodules, swelling, bruising and dermatitis (more with lanreotide autogel), and bowel problems (worse with lanreotide autogel) (Strasburger, 2016). The COMP accepted this explanation by the sponsor.

In conclusion, the COMP considered that the totality of evidence could be sufficient to clarify the existing doubts regarding the results obtained in the enriched patient population of patients responding to Mycapssa and agreed to recommend maintaining the orphan designation based on the patient reported outcomes and therefore a significant benefit based on a major contribution to patient care.

4. COMP position adopted on 6 October 2022

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 1.4 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 Mycapssa may be of potential significant benefit to those affected by the orphan condition still holds.
- the sponsor provided data from the pivotal clinical trial showing non-inferiority of Mycapssa vs injectable somatostatin receptor ligands (iSRLs) (octreotide LAR or lanreotide autogel) in an enriched patient population. However, improvements were shown in the treatment satisfaction domain of the Acromegaly Treatment Satisfaction Questionnaire for patients on Mycapssa as compared to the control with iSRLs. In addition, the results from other patient-reported outcomes (PROs) administered during the pivotal clinical trial trended towards improved results with Mycapssa as compared to iSRLs. The totality of evidence supports a conclusion on a major contribution to patient care.

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 Mycapssa, octreotide acetate (oral use) for treatment of acromegaly (EU/3/13/1170) is not removed from the Community Register of Orphan Medicinal Products.