EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2022
EMA/796198/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mycapssa

International non-proprietary name: octreotide

Procedure No. EMEA/H/C/005826/0000

Note

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

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List of abbreviations

AIS	Acromegaly Index of Severity
ANOVA	Analysis of variance
AE	Adverse event
ASMF	Active Substance Master File
AUC	Area under the curve
AUCx-y	Area under the curve from time x to time y
AUC0-inf	Area under the curve from time 0 extrapolated to infinity
AUC0-t	Area under the curve from time 0 to the last concentration above the limit of quantitation
CAV	Average concentration
Bid	Twice daily
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CL/F	Oral clearance
Cmax	Maximum plasma concentration
CrCl	Creatinine clearance
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
DAD	Diode-Array Detection
DDI	Drug-drug interaction
DTT	Dihiotheidol
ECL	Electrochemiluminescent
eCLcr	Estimated creatinine clearance
EOT	End of treatment
ESRD	End-stage renal disease
ET	Early termination
F	Female
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GEP	Gastroenteropancreatic
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMC	Glyceryl monocaprylate
GMR	Geometric Mean Ratio
GTC	Glyceryl tricaprylate
HCTZ	Hydrochlorothiazide
HDPE	High Density Polyethylene
HF	Hydrophilic fraction
HFC	Crude hydrophobic fraction
HFS	Hydrophobic fraction suspension
HPLC	High-performance liquid chromatography
HV	Healthy volunteer
HVPG	Hepatic venous pressure gradient

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ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IGF-1	Insulin-like growth factor 1
IgG	Immunoglobulin G
IR	Immediate Release
Λz	Elimination rate constant
L/M	Lactulose/Mannitol
LAR	Long-Acting Release
LF	Lipophilic fraction
LOQ	Limit of quantitation
M	Male
MAA	Marketing Authorisation Application
MDRD	Modification of Diet in Renal Disease
MHC	Major histocompatibility complex
MoA	Mode of action
NA	Not applicable
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OS	Oily suspension
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamic(s)
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
PVC	Polyvinyl chloride
QTPP	Quality target product profile
PVP-12	Polyvinylpyrrolidone
Sc	subcutaneous
SD	Standard deviation
SmPC	Summary of Product Characteristics
SRI	Severe renal impairment
SRL inj	parenteral somatostatin receptor ligand
SSTR	Somatostatin receptor
t½	Elimination half-life
Tlag	Absorption lag time
Tmax	Time of maximum plasma concentration
TJ	tight junction
TPE	Transient Permeability Enhancer™
TSH	Thyroid stimulating hormone
TWA	Time-weighted average
ULN	Upper limit of normal
USP	United States Pharmacopoeia
UV	Ultraviolet
Vz/F	Apparent oral volume of distribution

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant FGK Representative Service GmbH submitted on 28 June 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Mycapssa, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 10 December 2020.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Mycapssa as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Mycapssa

The applicant applied for the following indication:

"Mycapssa is indicated for long-term maintenance treatment in patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues."

Mycapssa, was designated as an orphan medicinal product EU/3/13/1170 on 05 August 2013, in the following condition: treatment of acromegaly.

The CHMP granted the following indication:

"Mycapssa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues."

With their response to Day 120 List of Questions, the MAA was transferred to Amryt Pharmaceuticals DAC.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Sandostatin IR 50 µg/100 µg/500 µg/1000 µg
- Marketing authorisation holder: Novartis Pharma
- Date of authorisation: 06 October 1995
- Marketing authorisation granted by:

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- Member State (EEA): Germany
  - National procedure
  - MRP/DCP
- Marketing authorisation number: 29423.00.00; 29423.01.00; 29423.02.00; 29423.03.00;

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Sandostatin IR 50 µg/100 µg/500 µg/1000 µg
- Marketing authorisation holder: Novartis Pharma
- Date of authorisation: 06 October 1995
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
    - MRP/DCP
- Marketing authorisation number: 29423.00.00; 29423.01.00; 29423.02.00; 29423.03.00;

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance/Scientific advice

The applicant received the following Protocol assistance/Scientific Advice on the development relevant for the indication:

Date	Reference	SAWP co-ordinators
20/10/2011	EMEA/H/SA/2206/1/2011/SME/III	Elmer Schabel and Helgi Helgason
21/11/2013	EMEA/H/SA/2206/1/FU/1/2013/PA/SME/III	Kolbeinn Gudmundsson and Kerstin Westermar
22/05/2014	EMEA/H/SA/2206/1/FU/2/2014/II	Kolbeinn Gudmundsson and Kerstin Westermar
24/09/2015	EMEA_H_SA_2206_1_FU_3_2015_PA_SME_II	Andreas Kirisits and Kerstin Westermark

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The applicant received scientific advice on four occasions, as mentioned in the table above for the development of Mycapssa for treatment of acromegaly. The scientific advice pertained to the following quality, pre-clinical and clinical aspects:

- API sourcing strategy
- Choice of excipients, specifications and supporting documentation
- Drug product specifications and release testing
- Stability testing strategy
- General non-clinical strategy
- Data requirements for bridging s.c. to oral route of administration
- Need for thorough QT study
- Overall strategy for evidence generation regarding clinical pharmacology and clinical efficacy and safety
- Phase 3 plans: number of Phase 3 studies, type of control (baseline-comparison or active comparator), study population including enrichment design of biochemically controlled patients after run-in phase for one Phase 3 study, inclusion of subjects who participated in prior phase 3 study, dose, dose regimen, co-administration of cabergoline in patients with modestly elevated IGF-1 levels, treatment duration, efficacy and safety endpoints, sample size, statistical analysis plan.
- Evaluation of treatment satisfaction using a PRO
- Safety database and assessment, acceptability of a comparison to the safety profile of authorised octreotide with a subcutaneous route of administration
- Adequacy of envisaged evidence to support Significant Benefit in the context of the Orphan Designation

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Silvijus Abramavicius Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	28 June 2021
The procedure started on	19 August 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 November 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 November 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 November 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 December 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions	29 April 2022

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to all CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 May 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 May 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	31 August 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Mycapssa on	15 September 2022

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2. Scientific discussion

2.1. Introduction

The legal basis of MAA for Mycapssa is Article 10(3) of Directive 2001/83/EC, a so-called "hybrid" application to the reference medicinal product sc Sandostatin IR (MA number 29423.00-03.00), which was first approved in the European Union on 06 October 1995. The applicant set the main objective of the Mycapssa development to change the route of administration in order to address the unmet medical need of an efficacious oral octreotide treatment. As a consequence, full quality and pivotal clinical development was foreseen as well as partially derogated non-clinical development.

For quality development, the pharmaceutical form needed to be adjusted to allow oral administration and the strength had to be adjusted to reach comparable systemic exposure with oral Mycapssa therapy as with the subcutaneous reference medicinal product. The applicant has developed octreotide capsules, a new formulation of octreotide for oral delivery. The enteric-coated capsule is filled with an oily suspension of unmodified octreotide formulated with transient permeability enhancer (TPE®) excipients, a proprietary mixture that permits oral administration. The enteric coating allows the intact capsule to pass through the stomach and disintegrate when it reaches the higher pH of the small intestine. The TPE excipients facilitate local transit across the intestinal wall and allows the intact peptide (i.e., octreotide) to be absorbed into the systemic circulation.

For non-clinical development, three main non-clinical studies were conducted (safety pharmacology of the formulation, PK studies *in vivo* and comparative toxicology studies of 9 months duration).

For clinical development, this hybrid application is not based on bioequivalence between Mycapssa and the reference medicinal product Sandostatin, but on non-clinical and clinical data supporting the safety and efficacy of the new route of administration, pharmaceutical form, and strength. In total 11 (eleven) clinical studies were conducted with the same intent, addressing PK in healthy volunteers (HV), in patients with liver and renal impairments and 8 interaction studies (drug-food and DDI) in HV.

2.2. Disease or condition

The applicant was applying for the following indication:

"MYCAPSSA is indicated for long-term maintenance treatment in patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues."

This indication is part of the indication for treatment of acromegaly (ACM) approved for Sandostatin s/c that is: "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."

In addition to acromegaly, Sandostatin is indicated also for Gastro-entero-pancreatic endocrine tumours, Bleeding gastro-oesophageal varices, Treatment of TSH-secreting pituitary adenomas. These other indications are not a subject to this application.

The CHMP approved the following indication:

"Mycapssa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues."

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2.3. Epidemiology

The annual incidence of acromegaly is 3 to 5 cases per million individuals, and the estimated prevalence is 40 to 70 cases per million, with men and women equally affected. Owing to its insidious onset it is often diagnosed late (4 to more than 10 years after onset), at an average age of about 40 years

2.4. Aetiology and pathogenesis

At diagnosis, patients generally exhibit coarsened facial features, exaggerated growth of hands and feet, and soft tissue hypertrophy. The diagnosis of acromegaly requires demonstration of dysregulated and enhanced GH secretion or elevated IGF-1 levels, reflective of peripheral tissue exposure to tonically elevated GH concentrations. Acromegaly comorbidities occur especially with uncontrolled GH/IGF-1 hypersecretion, and most comorbidities are ameliorated by controlling GH/IGF-1 levels.

2.5. Clinical presentation, diagnosis

Acromegaly, a serious and life-threatening rare disease usually caused by a growth hormone (GH)-secreting pituitary adenoma, is an inexorable chronic condition with significant morbidity and mortality. Acromegaly mortality determinants include GH >2.5 ng/mL and elevated IGF-1, hypertension, cardiovascular and cerebrovascular disease, requirement for glucocorticoid replacement, and prior pituitary radiation.

Effective surgical, radiation, and medical strategies to improve comorbidity and mortality require control of GH/IGF-1.

2.6. Management

Treatment options for acromegaly include surgical resection of the pituitary adenoma, radiotherapy, and drug therapy to reduce GH and IGF-1 levels to normal values. 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.

Currently, there are 3 drug classes available for the treatment of acromegaly: SRLs or somatostatin analogues (SSAs; octreotide, lanreotide, and pasireotide), dopamine agonists (bromocriptine and cabergoline), and a GH receptor antagonist (pegvisomant). At present, SRLs are the most widely used drugs to control acromegaly. Current injectable therapies for acromegaly are suboptimal for multiple reasons. The injections are poorly tolerated. Patients experience long-term sequelae associated with their injection, including persistent pain (lasting days), nodules, haemorrhage, inflammation, and scarring. At an emotional level, anxiety, frustration, and loss of independence due to assistance required in receiving injections compounds the physical impact. Work time is lost in scheduling and traveling for injections, and from adverse events (AEs) associated with injections or symptom exacerbation towards the end of the injection interval. The medical literature, the EMA and US FDA and WHO post-marketing AE databases, and patient-reported outcome (PRO) studies all support these burdens of existing SRL injection treatment and the unmet medical need for safer, less burdensome treatment.

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2.7. About the product

Mode of action. Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits pathologically increased secretion of GH and of peptides and serotonin produced within the gastro-entero-pancreatic (GEP) endocrine system.

Pharmacological classification. Somatostatin and analogues, ATC code: H01CB02

Mycapssa is presented in new dosage form: enteric-coated hard gelatin capsule, containing an oily suspension of octreotide acetate corresponding to 20 mg of the free peptide octreotide.

Considering non-clinical development, as stated by the applicant with respect to non-clinical studies because octreotide capsules are administered by a route that has not previously been approved for octreotide acetate, a series of primary pharmacodynamic, pharmacokinetic (PK), and repeat-dose toxicity studies were conducted to characterise the mode of action of the octreotide-TPE formulation, the oral bioavailability of octreotide after administration of octreotide capsules, and the safety of octreotide capsules. Since the combination of excipients in the TPE formulation is novel, the applicant also qualified the excipients in octreotide capsules in the repeat-dose toxicity studies. The safety of the individual excipients in octreotide capsules is also supported by published information and by their use in marketed pharmaceuticals.

The applicant states that primary pharmacodynamic effects of the somatostatin analogue octreotide and its potential effects on safety pharmacology parameters have been established during development of sc Sandostatin IR. Additional primary pharmacodynamic (non-GLP) studies conducted by the applicant in rats have characterised the enhancement of permeability in the GI tract induced by the TPE formulation.

No identical compositions of to-be-marketed TPE (CH-906-4) formulations in octreotide test articles were used in all non-clinical studies.

To quantify octreotide plasma concentrations in the battery of repeat-dose toxicity studies in cynomolgus monkeys the validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was used. In part of studies used LC-MS/MS and enzyme-linked immunosorbent assay (ELISA) methods followed in-house validation.

As PK studies, the applicant performed oral octreotide bioavailability evaluations in rats and monkeys. Different test article application approach was used (bulk formulation via intestinal cannulas, gavage compared with intrajejunal administration, administration of octreotide-TPE to the stomach, duodenum, jejunum, ileum, or colon, capsules in monkeys) in comparison with parenteral octreotide.

Concerning toxicity evaluation, the applicant relies in part on non-clinical data for sc Sandostatin and has conducted additional toxicological studies in cynomolgus monkeys to demonstrate the safety of octreotide capsules in comparison to sc Sandostatin IR and to qualify product-related impurities.

The applicant provided justifications on absence of studies in CTD Modules 3, 4, and 5 of dossier that are provided in Table 1.1.1.

Table 1.1.1 Justifications for the quality, non-clinical and clinical sections not included in the CTD Module 4 and 5

CTD Section, Title	Justification	Assessment

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Quality		
None	N/A	N/A
Nonclinical		
4.2.1.2 Secondary Pharmacodynamics	This is a hybrid MAA according to Article 10(3) of Directive 2001/83/EC. Secondary pharmacodynamic studies conducted during development of sc Sandostatin IR are referred to.	No independent Secondary Pharmacodynamics studies of octreotide capsules were conducted. These studies conducted during development of Sandostatin are referred to (FDA, 1988). Approach is acceptable.
4.2.1.3 Safety pharmacology	This is a hybrid MAA according to Article 10(3) of Directive 2001/83/EC. Safety pharmacology studies conducted during development of sc Sandostatin IR are referred to.	No dedicated safety pharmacology studies of octreotide capsules were conducted. Safety pharmacology studies conducted during development of Sandostatin are referred to (FDA, 1988). In addition, cardiovascular parameters and general behaviour were monitored in repeat-dose toxicity studies in monkeys. No cardiovascular or neurological effects were observed in these studies. Concerning capsule excipients safety, the Applicant qualifies them as safe, possessing food and pharmacopoeial grade and provide literature overview. Approach is acceptable.
4.2.1.4 Pharmacodynamic Drug Interactions	This is a hybrid MAA according to Article 10(3) of Directive 2001/83/EC. Pharmacodynamic drug interactions investigated during development of sc Sandostatin IR are referred to.	Omission of Pharmacodynamic Drug Interactions of octreotide capsules data in NC part of the dossier is acceptable.

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4.2.2.3 Distribution	The results of Study 75-30-13 suggested that delivery of octreotide-TPE via the intestine does not result in significant hepatic extraction. Based on this data, the distribution of octreotide after oral administration of octreotide capsules is expected to be identical to that of injected octreotide acetate. Distribution data generated during development of sc Sandostatin IR are referred to.	Omission of distribution studies in this hybrid application is acceptable.
4.2.2.4 Metabolism	The results of Study 75-30-13 suggested that delivery of octreotide-TPE via the intestine does not result in significant hepatic extraction. Based on this data, the metabolism of octreotide after oral administration of octreotide capsules is expected to be identical to that of injected octreotide acetate. Metabolism data generated during development of sc Sandostatin IR are referred to.	Missing of biotransformation studies in this hybrid application is acceptable.
4.2.2.5 Excretion	The results of Study 75-30-13 suggested that delivery of octreotide-TPE via the intestine does not result in significant hepatic extraction. Based on this data, the excretion of octreotide after oral administration of octreotide capsules is expected to be identical to that of injected octreotide acetate. Excretion data generated during development of sc Sandostatin IR are referred to.	Omission of excretion studies in this hybrid application is acceptable.
4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)	Relevant pharmacokinetic drug interactions were investigated in clinical studies of octreotide capsules (see Module 2.7.2)	The applicant provide drug-drug interaction studies with octreotide capsules in Clinical part of the dossier, therefore omission of these data in NC part is acceptable.
4.2.2.7 Other Pharmacokinetic Studies	No further pharmacokinetic studies were conducted.	Lacking other pharmacokinetic studies in this hybrid application is acceptable.
4.2.3.1 Single-dose Toxicity	Octreotide capsules are intended for repeated administration. Therefore, no single-dose toxicity studies were conducted.	Omission single-dose toxicity studies in this hybrid application is acceptable.
4.2.3.3 Genotoxicity	This is a hybrid MAA according to Article 10(3) of Directive 2001/83/EC. Genotoxicity studies conducted during development of sc Sandostatin IR are referred to.	Omission of genotoxicity studies in this hybrid application is acceptable.

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4.2.3.4 Carcinogenicity	This is a hybrid MAA according to Article 10(3) of Directive 2001/83/EC. In the absence of proliferative signals in the chronic toxicity study of octreotide capsules in cynomolgus monkeys, carcinogenicity studies conducted during development of sc Sandostatin IR are referred to.	Omission of carcinogenicity studies in this hybrid application is acceptable.
4.2.3.5 Reproductive and Developmental Toxicity	This is a hybrid MAA according to Article 10(3) of Directive 2001/83/EC. Reproductive and developmental toxicity conducted during development of sc Sandostatin IR are referred to.	Omission of reproductive and developmental toxicity studies in this hybrid application is acceptable.
4.2.3.6 Local Tolerance	The local tolerance of octreotide capsules was investigated as part of repeat-dose toxicity studies in cynomolgus monkeys	No separate local tolerance studies were conducted. It is acceptable.
4.2.3.7.1 Antigenicity	No signs of antigenicity were identified during development of sc Sandostatin IR. No further studies are therefore needed	Omission of antigenicity studies in this hybrid application is acceptable.
4.2.3.7.2 Immunotoxicity	No signs of immunotoxicity were identified during development of sc Sandostatin IR. No further studies are therefore needed.	Omission of immunotoxicity studies in this hybrid application is acceptable.
4.2.3.7.3 Mechanistic studies	The safety profiles of octreotide capsules and sc Sandostatin IR were shown to be comparable. Mechanistic studies were therefore not conducted.	Omission of mechanistic studies in this hybrid application is acceptable.
4.2.3.7.4 Dependence	There was no indication from the clinical use of sc Sandostatin IR that octreotide has any dependence potential. Studies to investigate the dependence potential are therefore not needed.	Omission of dependence studies in this hybrid application is acceptable.
4.2.3.7.5 Metabolites	The metabolism of octreotide has been investigated during development of sc Sandostatin IR. There are no pharmacologically active or toxic metabolites that needed further investigation.	Lack of studies with metabolites in this hybrid application is acceptable.
4.2.3.7.7 Other	No other studies were conducted.	Acceptable.
Clinical		
Reports of Biopharmaceutic Studies		
5.3.1.3 *In vitro – In vivo* Correlation Study Reports	No rationale is provided	Approach is acceptable.

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Reports of Studies Pertinent to Pharmacokinetics (PK) using Human Biomaterials		
5.3.2.1 Plasma Protein Binding Study Report	No rationale is provided	Approach is acceptable, as this was analysed in reference product development.
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies	No rationale is provided	Approach is acceptable, as this was analysed in reference product development.
5.3.2.3 Reports of Studies Using Other Human Biomaterials	All PK studies were performed on blood samples and are reported as part of the clinical studies in Modules 5.3.1.1, 5.3.1.2, 5.3.2.2, 5.3.3.3, and 5.3.3.4.	Approach is acceptable
Reports of Studies Pertinent to Pharmacokinetics (PK) using Human Biomaterials		
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	PK in healthy subjects was investigated as part of the clinical studies in Modules 5.3.1.1, 5.3.1.2, 5.3.3.3, and 5.3.3.4	Approach is acceptable
5.3.3.2 Patient PK and Initial Tolerability Study Reports	PK in patients was investigated as part of study CH-ACM-01. The results are included in Module 5.3.5.2.	Approach is acceptable
5.3.3.5 Population PK Study Reports	No population PK studies have been performed for octreotide capsules.	Approach is acceptable
Reports of Human Pharmacodynamic (PD) Studies		
5.3.4.2 Patient PD and PK/PD Study Reports	PD in patients was investigated as part of study CH-ACM-01. The results are included in Module 5.3.5.2	Approach is acceptable
Case Report Forms and Individual Patient Listings		
5.3.7	Patient listings are provided in the individual CSRs. Case report forms are available upon request	Approach is partially acceptable and additional information was requested at D120

Medicinal product no longer authorised

2.8. Quality aspects

2.8.1. Introduction

The finished product is presented as gastro-resistant hard capsules containing octreotide acetate equivalent to 20 mg octreotide as active substance.

Other ingredients are: povidone, sodium caprylate, magnesium chloride, polysorbate 80, glyceryl monocaprylate, glyceryl tricaprylate, gelatine, titanium dioxide (E171), methacrylic acid - ethyl acrylate copolymer (1:1), talc, triethyl citrate, silica, colloidal anhydrous, sodium hydrogen carbonate, and sodium laurilsulfate.

The product is available in polychlorotrifluoroethylene [PCTFE]/polyethylene [PE]/polyvinylchloride [PVC]-aluminium blisters.

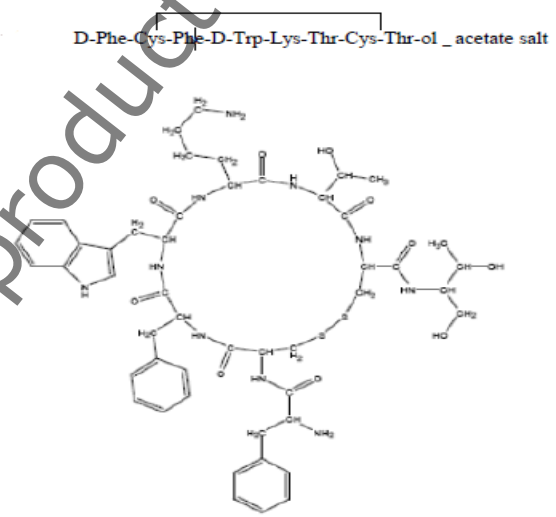
2.8.2. Active substance

General information

The active substance octreotide is described in the Ph. Eur. monograph No. 01/2020:2414.

The chemical name of the active substance is L-cysteinamide, D-phenylalanyl-L-cysteyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2- hydroxy-1-(hydroxymethyl)propyl]-,cyclic(2-7) disulfide acetate salt corresponding to the molecular formula $C_{49}H_{66}N_{10}O_{10}S_2$. It has a relative molecular weight of 1019.3 (calculated for freebase) and the following structure:

Figure 1: Active substance structure



The chemical structure of the active substance was elucidated by a combination of FT-IR, ^{1}H-NMR, ^{13}C-NMR, mass, MS/MS spectrum, amino acid analysis, chiral amino acid analysis, elemental analysis , and physico-chemical properties

The active substance is a hygroscopic white to off white powder (it is characterised by needle shape particles) freely soluble in water pH 2.0, pH 4.0, pH 7.0, slightly soluble in water pH 10.0, soluble in AcOH and MeOH.

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The active substance exhibits stereoisomerism due to the presence of 10 chiral centres. The active substance has a specific optical rotation between -14.5° and -18.5°. Enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has not been observed for the active substance.

Manufacture, characterisation and process controls

The active substance is supplied by two manufacturers.

Octreotide acetate is synthesised using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in polyethylene bag as direct packaging.

General information and specifications of the plastic materials are provided. The release specification and compliance statement to the European Regulation 10/2011/EC, as amended, on plastic materials and articles intended to come into contact with food are submitted in the dossier. The confirmation of compliance to current Ph. Eur. requirements is presented.

Specification

The active substance specification includes tests for: appearance (visual), identification (HPLC, ^{1}H NMR), special rotation (Ph. Eur.), assay (HPLC), acetic acid content (Ph. Eur.), related compounds (HPLC), water content (Ph. Eur.), microbial enumeration (Ph. Eur.), and residual organic solvents (GC).

The parameters tested are in line with the Ph. Eur. monograph for octreotide and do not need additional justification. The use of alternative method for content and related peptides related has been satisfactorily justified and supported by comparability study.

Each specification parameter has been justified individually.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (-20ºC±5ºC) and for up to 6 months under accelerated conditions (2-8ºC) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, assay, water determination, related peptides, microbial tests, and bacteria; endotoxins tests*.* The analytical methods used were the same as for release and were stability indicating.

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The purity profile results remained within specifications at all intervals during long-term and accelerated conditions. No trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. According to the obtained results, octreotide acetate powder is not photostable under the tested conditions.

Results on stress conditions (alkaline, oxidation, sunlight solution, sunlight powder, acidic, heat solution, and humidity) were also provided on one batch. According to presented information octreotide active substance was found to be stable when stressed by heat, light and acid, minimal degradation was observed for alkaline conditions and oxidation stress (14% and 12% accordingly).

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable.

2.8.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a white, size 0 enteric-coated hard gelatin capsules.

The finished product has been developed as a formulation to enable the oral delivery of the peptide which otherwise has limited oral bioavailability. The Transient Permeability Enhancer (TPE) system is a combination of excipients assembled in a proprietary process.

The formulation objective was to develop an oral dosage form finished product. It was necessary to protect the oral dosage form during its passage through the acidic environment of the stomach and have the dosage form rapidly dissolve when it reached the intestines. An enteric coated capsule was the preferred oral dosage form among many which were considered.

An extensive and systematic formulation development exercise led to an octreotide capsule final formulation and process which has been consistently used for the manufacture of clinical supply batches, toxicology supplies, and primary registration stability batches and is also the formulation which has been scaled up to commercial scale. This finished product formulation has demonstrated good stability and has the desired bioavailability as evaluated in animal and human studies. Octreotide capsules have consistently met specifications and are stable long term under cold chain conditions and at controlled room-temperature conditions throughout a 30-day in-use stability period.

Stability data was generated with the commercial octreotide capsules formulation in aluminium-Aclar blisters. The stability data from these studies demonstrated acceptable compatibility of the active substance with the excipients at long-term storage conditions. A binary compatibility study was also carried out which demonstrated the product remained stable at the proposed long-term storage conditions.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The manufacturing of octreotide capsules uses standard pharmaceutical unit operation and equipment. The process involves the proprietary preparation of the fill mass, filling into hard gelatin capsules, employing an automated encapsulation filling machine. Concurrently with encapsulation, the filled capsules are banded with a gelatin solution to seal the body and cap of the hard gelatin capsules. The dried banded capsules are then enteric coated and cured at room temperature.

The primary packaging is polychlorotrifluoroethylene PCTFE/polyethylene (PE)/polyvinylchloride (PVC)-aluminium blisters. The material complies with Ph.Eur. and EC requirements. The choice of the

Medicinal product no longer authorised

container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by two manufacturing sites.

The manufacturing process is considered to be a non-standard manufacturing process. It involves the proprietary combination of the excipients with the active, filling, into gelatine capsules, banding, enteric coating and blister packaging.

During evaluation the CHMP considered as Major Objection (MO) that the proposed acceptance range for sodium caprylate assay in the intermediate was not acceptable. The applicant has introduced a limit for routine sodium caprylate testing in the release specification, what it is considered acceptable.

Major steps of the manufacturing process have been validated by a number of studies on 3 commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC-UV, HPLC/UV-DAD), assay (HPLC-UV), impurities (HPLC-fluo), uniformity of dosage (Ph. Eur.), dissolution (Ph. Eur.), microbial limits (Ph. Eur.), and sodium caprylate assay (HPLC-UV).

The tests selected and the methods used to verify the identity, strength, purity, and quality of the finished product are consistent with those for delayed-release oral capsule drug products as per ICH Q6A. The specifications were developed using compendial and the ICH guidance, information from the active substance manufacturer, and finished product release and stability data. The proposed specification is considered adequately justified.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested as MO) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for twenty-one batches that include six primary registration stability batches (precommercial scale) and fifteen commercial-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 6 commercial scale batches of finished product stored for up to 36 months under long term conditions (2°C – 8°C) and for up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, octreotide assay, impurities/degradation products, sodium caprylate content, and dissolution. Water content is performed for information only. The analytical procedures used are stability indicating.

The stability data does not show any significant changes under long-term conditions. The 6-month accelerated data clearly show the need to keep the drug product refrigerated. Under accelerated conditions, there is significant degradation of the finished product by the 6-month test point.

For convenience during the drug use period, and to allow storage of the blisters at room temperature for up to 1 month, an end-use study was included. No significant changes were observed in the parameters studied.

Based on available stability data, the proposed shelf-life of 3 years and storage condition "store in a refrigerator (2 °C – 8 °C)" and "do not freeze" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.8.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Two MOs that had been raised about the proposed acceptance range for sodium caprylate assay in the intermediate and the risk evaluation on the presence of nitrosamine impurities. Both were resolved by provision of additional information or justification. Overall, during the procedure, the information of the dossier has been updated and improved as requested.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.8.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

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2.8.6. Recommendations for future quality development

Not applicable.

2.9. Non-clinical aspects

2.9.1. Introduction

Octreotide is the acetate salt of a cyclic octapeptide. It is long-acting and has pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide displays a high affinity for somatostatin receptor subtypes 2 and 5, effectively suppressing GH hypersecretion in up to ~60% of patients with acromegaly (Colao 2004; Chanson 2008; Melmed 2009a; Fleseriu 2014; Melmed 2014).

Current somatostatin therapies (Sandostatin®, Sandostatin long-acting release (LAR), Somatuline® Autogel (lanreotide)) for acromegaly are to be injected by intravenous, subcutaneous, deep subcutaneous or intramuscular route. There are currently no licenced oral formulations of somatostatin analogues, octreotide, lanreotide, or pasireotide.

The applicant has developed octreotide capsules, a new formulation of octreotide for oral delivery. The enteric coated capsule is filled with an oily suspension of unmodified octreotide formulated with transient permeability enhancer (TPE®) excipients, a proprietary mixture that permits oral administration. The enteric coating allows the intact capsule to pass through the stomach and disintegrate when it reaches the higher pH of the small intestine to discharge octreotide capsules suspension.

To support a hybrid MAA the applicant relies on nonclinical data for the EU-approved medicinal product Sandostatin® and on information in the published literature for sc Sandostatin IR. In addition, the applicant conducted 5 pharmacology studies (with rat), 7 pharmacokinetic studies (rat and monkey), and 6 toxicity studies, 2 of which bridged to the safety of sc Sandostatin IR (monkey). The safety of the excipients in octreotide capsules was evaluated in the 1-, 3-, and 9-month oral toxicology studies in cynomolgus monkeys.

The dedicated studies conducted by the applicant focused on the following key areas and objectives:

1. Enhancement of intestinal absorption of octreotide with the TPE formulation, including duration and extent of absorption.

2. The pharmacokinetics of octreotide following oral dosing with octreotide capsules or octreotide-TPE, including the potential extent of liver sequestration.

3. The safety of octreotide acetate and the TPE excipients, administered as octreotide capsules, on the gastrointestinal (GI) tract, cardiovascular system, and other major organs after chronic exposure.

4. Establishment of a bridge in terms of exposure and safety with sc Sandostatin IR.

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2.9.2. Pharmacology

2.9.2.1. Primary pharmacodynamic studies

As to the primary pharmacodynamics data of octreotide acetate, it is referred to the identical active substance of the EU-approved medicinal product sc Sandostatin IR, which mode of action is well established: inhibition of growth hormone (GH) secretion. The effects of octreotide were found to be similar to those of the natural hormone somatostatin. Octreotide displayed greater potency and selectivity for GH and glucagon suppression and a longer duration of action than the native hormone. As this application is a hybrid MAA according to Article 10(3) of Directive 2001/83/EC the approach to not conduct separate NC primary pharmacodynamics studies was considered acceptable.

To increase octreotide acetate GI absorption the applicant developed a capsule formulation with a transient permeability enhancer (TPE®) using Medium Chain Fatty Acids salts (MCFAS). According to sources MCFAS exert their permeation effect mainly via the paracellular route by inducing tight junction (TJ) opening. The selection of the formulation excipients and their concentration in the final formulation was based on absorption of octreotide acetate in an animal model and desirable physico-chemical properties supporting stability and manufacturability. During development of the octreotide capsule formulation, several combinations of the excipients were studied resulting in selection of the final TPE formulation components with the main component for enhancing GI permeation – sodium caprylate. Presented in the NC PD part studies focused on different compositions (classes) of TPE permeability-enhancing properties and action reversibility. Through the development process, in PD experiments conducted by the applicant, combinations of the TPE excipients (class CH-809, CH-811-1, CH-906-1, CH-906-2) differed from those chosen for final commercial formulation of Mycapssa capsules (class CH-906-4).

In its own *in vivo* studies with rats the applicant focuses on the mode of action of TPE-induced permeability, pharmacokinetic properties and evaluation of the magnitude, duration, and long-term reproducibility of the effects of the TPE system on GI permeability.

In the study (75-30-12) with rats' effect of TPE on intestinal epithelial TJs, the permeation pathway (paracellular or transcellular), and the reversibility of TPE's effect on intestinal epithelial TJs were investigated. Results showed that following TPE administration, TJ protein localisation is altered in a reversible fashion as demonstrated for ZO-1 and Cla-3 proteins in rat intestine, suggesting a TPE permeation effect and its reversibility. The paracellular marker LC-Biotin was able to penetrate through the opened TJs of the intestinal barrier, binding to the cell membranes around the epithelial cells in the intestine. These results indicate paracellular permeability enhancement by TPE. Administration of biotin-labelled octreotide in TPE to the jejunum of rats resulted in a pattern of localisation of the octreotide similar to that seen for the LC-Biotin paracellular marker. It is worth mentioning that TPE formulation in one component differed from that of commercial capsule TPE formulation and study results should be regarded with certain reserve.

In one study (75-30-05) the applicant evaluated octreotide-TPE absorption after gavage and direct intrajejunal administration. Gavage shoved limited octreotide absorption. In contrast, plasma octreotide levels were greater than 50-fold following administration directly to the intestine. The TPE formulations were different from that of commercial Mycapssa capsule composition.

In *in vivo* study (75-30-08) in rats determined octreotide-TPE absorption along the different segments of the GI tract. Direct administration of octreotide-TPE to the stomach resulted in the lowest absorption. The TPE enhancing effect was highest at the proximal region of the intestine (duodenum-jejunum). The TPE formulation in one component differed from that of the commercial capsule TPE formulation.

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The study 75-30-02 evaluated the size limit of molecules that can penetrate from the intestinal lumen into the blood in rats during TPE-induced permeation. Fluorescein isothiocyanate-labelled dextran molecules of increasing size were used to determine (in a rat model) the size of molecules that can penetrate into the blood. Results show that molecules in size of 10-40 kDa penetrated in systemic circulation in higher amounts whereas those of >70 kDa in size were scarcely absorbed. This leads to the applicant conclusion that during the TPE action penetration of the majority of pathogens is precluded.

The applicant performed a study (75-30-03) evaluating the duration of TPE induced intestinal permeability in rats using FITC-labelled dextran marker. Obtained results point to a decrease of permeation induced by TPE after 60 and 90 min. The TPE formulations were different from that of the commercial Mycapssa capsule composition.

The non-GLP study (75-30-10) assessed intestinal permeation effect after repeat dosing intra-intestinally (daily for 14 days) of octreotide-TPE formulation and found that prolonged dosing did not impact absorption rate and it remained steady during all two weeks. The TPE formulation in two components differed from that of the commercial capsule TPE formulation.

In the dossier the applicant provides an overview of published literature on the capacity of different substances to improve absorption of drugs with poor permeability. From the literature data it can be seen that the gastrointestinal tract (GIT) is not static, its permeability can be influenced by different external substances. In addition, orally administered permeability enhancement can be influenced by many factors (e.g., gastric acidity); it cannot assure complete bioavailability of concomitantly administered medicine, it could act adversely. It is not evident with certainty how to measure local tight junction (TJ) permeability and the absorption with permeability enhancement can be considered as erratic.

2.9.2.2. Secondary pharmacodynamic studies

No independent secondary pharmacodynamics studies of octreotide capsules were conducted. The applicant relies on literature data from earlier octreotide secondary pharmacodynamics investigations. The approach was considered acceptable.

2.9.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies of octreotide capsules were conducted. Concerning capsule excipients safety, the applicant qualifies them as safe, possessing food and pharmacopoeial grade and provides a literature overview. This approach was considered acceptable. More details on excipients safety evaluation are provided in Toxicology 3.2.4.8 Other toxicity studies section.

2.9.2.4. Pharmacodynamic drug interactions

The applicant did not perform dedicated NC studies related with pharmacodynamic drug interactions. This is acceptable.

2.9.3. Pharmacokinetics

The applicant evaluated PK of octreotide-TPE in studies with Sprague-Dawley rats and cynomolgus monkeys. The TPE formulation used in the final Mycapssa capsule product is CH-906-4, and 20 mg of octreotide. Through the development process, in some NC experiments combinations of the TPE excipients were different from those in CH-906-4 and the API concentration varied.

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The study (75-30-05) in rats when octreotide-TPE absorption parameters were evaluated after gavage and upon intra-jejunal administration showed 53-fold higher AUC0-90 level after direct intra-intestinal test article dosing compared to gavage administration. Results should be interpreted with reserve as composition of TPE formulation differed significantly.

Investigation for octreotide-TPE quantitative evaluation of absorption from different segments of GIT in rats (75-30-08) resulted in evidence that highest absorption was in the duodenum and the jejunum. Calculated PK parameters as Cmax/dose and AUC/dose were higher for octreotide-TPE than those of octreotide solution. The octreotide-TPE formulation (CH-906-2) differed in one component compared to final CH-906-4 composition.

The comparison study in rats (75-30-06) after octreotide injection s.c., i.v. or octreotide-TPE intra-jejunal administration showed dose-related increase of PK parameters. However, calculated absolute bioavailability of octreotide-TPE ranged from 1.93% to 4.89% and F relative to a sc octreotide - from 3.46% to 10.3%, suggesting weak absorption to systemic blood. Moreover, results should be interpreted with caution as three TPE formulation classes (CH-809, CH-906-1 and CH-906-2) of octreotide acetate used in this study were different from the final formulation.

Study results in rats (75-30-17) after intrajejunal administration of different doses of octreotide-TPE (with CH-906-4 as final formulation) depicted linear increase of PK parameters (AUC, Cmax) over doses ranging from 15 to 50 mg/g and smaller increase at 66 mg/g dose. The used Sprague Dawley rat model attests to octreotide-TPE absorption after direct intra-intestinal administration but results should be translated with caution to oral administration as capsules.

Study 75-30-13 evaluated octreotide-TPE (with CH-906-4 as final formulation) PK parameters after single jejunal (j.j.) or subcutaneous(s.c.) administration comparing hepatic portal (HPV) and systemic blood octreotide concentrations. After a single s.c. octreotide injection, mean plasma octreotide concentrations were similar in HPV and systemic circulation. Similar results were observed following a single i.j. administration of octreotide-TPE formulation, although mean plasma octreotide concentrations were slightly higher in HPV plasma than in systemic plasma samples. Although, the differences in AUCs were not statistically significant, calculated 17.5% disparity indicated a certain rate of first-pass biotransformation. The applicant does not make evaluation of the equivalence (e.g., compared to HED) of the applied doses s.c. (289 micrograms/kg) and i.j. (29 770 micrograms/kg).

The octreotide-TPE pharmacokinetics were evaluated in study (75-30-04) in rats during repeated once daily intra-jejunal application. The octreotide-TPE formulation (CH-906-2) differed in one component compared to final CH-906-4 composition. Obtained results show comparable octreotide plasma concentration-time profiles over the 12 days of dosing and absence of prolonged impact of TPE on the gut permeability in rats.

The applicant in study (75-30-01, 1300-003, Appendix B) in monkeys compared PK of octreotide-TPE capsule coated with Acryl-Eze® at different thickness upon its oral administration versus s.c. administration of octreotide acetate. The TPE formulations were CH 811-1 and CH-906-1. The first one differed significantly in composition from CH-906-4 as final formulation and the second in one component. Study depicted that in animals dosed with 0.5 and 8 mg octreotide-TPE dose concentrations measured up to 240 min were likely confounded and results are not discussed. In the group dosed with 5 mg, blood sampling time was extended until 585 min. Individual monkeys' oral octreotide plasma concentration curves showed significant dispersion in Cmax, Tmax and AUC, suggesting non-consistent, erratic absorption rate and very small bioavailability (F only 1.5%) calculated from s.c. octreotide data. Results from this study in monkey send certain signals of possible weak and non-consistent absorption of oral octreotide in capsule with TPE in humans. Data from published literature (Fricker, 1991, 1992) confirms negligible octreotide oral bioavailability.

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2.9.4. Toxicology

2.9.4.1. Single dose toxicity

No single-dose toxicity studies were conducted with octreotide. Octreotide capsules are intended for repeated administration. Therefore, the lack of single dose toxicity studies was considered acceptable.

2.9.4.2. Repeat dose toxicity

The potential toxicity of octreotide capsules was evaluated in 28-day (Study 1300-002), and the 3-month (Study 1300-007) and 9-month (Study 1300-009) GLP toxicology studies, which were conducted using clinical trial batches of octreotide capsules containing 20 mg of octreotide, except the 28-day toxicity study, where the formulation used did not contain magnesium chloride. The monkey was selected for repeat-dose toxicity studies because it is considered the most appropriate species to study absorption with enteric-coated drugs, such as the octreotide capsules, due to the difficulty in delivering capsules to the stomach of animals of a small size. No clinical signs of test article-related toxicity were observed during the dosing period in any dose groups of the toxicity studies. Few monkeys from the control group and the treatment groups died or were euthanised during the study. All deaths were unequivocally attributed to complications occurring in the dosing and handling process. The NOAEL was determined at the highest dose used in the studies – 20 mg/day (4,9 mg/kg/d). The 20 mg/day dose of octreotide acetate administered in toxicity studies corresponds to approximately 5.0 mg/kg/day for monkeys weighing 4 kg, which represents a human equivalent dose (HED) of 1.62 mg/kg/day, or a total human dose of approximately 113 mg/day of octreotide based on a human body weight of 70 kg. This provides a safety margin of 1.4 for the maximum human dose of 80 mg/day.

Therefore, the data from the repeat-dose toxicity study in monkeys suggested that no novel toxicities will be associated with oral administration of octreotide capsules at doses that produce systemic exposures similar to those obtained following sc Sandostatin IR. Thus, the local gastrointestinal and the systemic toxicity profiles of Octreolin, Sandostatin and negative control olive oil capsules were comparable without any adverse events noted.

Based on results of a 28-day oral dose toxicology study conducted in cynomolgus monkeys, the NOAEL of octreotide capsules was the highest dose tested, 19.5 mg/day or 4.9 mg/kg/day. Moreover, no safety issues related to the TPE excipients were reported. However, due to oesophageal injury some animals did not receive all doses. Therefore, the applicant was asked to present analysis of results of Study 1300-002 excluding animal no. 126. However, the conclusions of the study that administration of Octreolin to male and female cynomolgus monkeys at doses of 9.75 mg/animal/day (Group 3) and 19.5 mg/animal/day (Group 4) has demonstrated a trend toward a decrease in exposure with continued dosing and a decrease after the afternoon dose compared to the morning dose, and that the latter appears to be somewhat less in female than in male animals, did not change.

2.9.4.3. Genotoxicity

No additional genotoxicity testing with octreotide capsules has been conducted and the applicant relies on data from sc Sandostatin IR. The Lack of studies was considered acceptable.

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2.9.4.4. Carcinogenicity

The applicant did not conduct any carcinogenicity study and refers to studies conducted during development of sc Sandostatin IR using the generated data for product labelling (SmPC section 5.6). Lack of carcinogenicity studies was considered acceptable.

2.9.4.5. Reproduction toxicity and developmental toxicity

The applicant did not evaluate reproductive and developmental toxicity of octreotide-TPE and refer to studies conducted during development of sc Sandostatin IR using the generated data for product labelling (SmPC section 5.6). Lack of reproductive and developmental toxicity studies was considered acceptable.

2.9.4.6. Toxicokinetic data

Systemic exposure in terms of AUC0-t and Cmax showed high variability among study days and between animals, indicating day-to-day differences in oral bioavailability and very low bioavailability. While on Day 90 in the study 1300-009, octreotide plasma concentrations in animals receiving octreotide capsules were low, measurements on Days 1, 180, and 270 indicated continuous systemic exposure to octreotide. For sc Sandostatin IR, the mean values for AUC0-t were comparable at each sampling time point. A consistently longer Tmax was observed following treatment with octreotide capsules compared with sc Sandostatin IR. However, this had no effect on overall exposure (AUC0-t) to octreotide which was comparable for oral administration of 20 mg of octreotide capsules and sc administration of 0.1 mg of sc Sandostatin IR.

2.9.4.7. Local tolerance

The local tolerance of octreotide capsules was investigated as part of repeat-dose toxicity studies in cynomolgus monkeys. No signs of GI toxicity were detected at approximately 10-fold greater local exposure in monkeys compared to humans.

2.9.4.8. Other toxicity studies

Since the TPE formulation in its exact composition is a novel pharmaceutical formulation, it was necessary to provide safety data for the TPE formulation contained in octreotide capsules (EMEA/CHMP/QWP/396951/2006). The excipients included in the TPE system are polyvinylpyrrolidone (PVP-12), sodium caprylate, polysorbate 80, glyceryl monocaprylate (GMC), glyceryl tricaprylate (GTC), and magnesium chloride. The applicant has provided the safety assessment protocols for each excipient considering that they are not novel by EMA, as they all have been included in drugs approved for marketing. Also, metabolism and function of each excipient was explained in these protocols, safety is assessed referring to 3-month and 9-month repeat toxicity studies *in vivo*. All the excipients are pharmacopoeial grade or made of pharmacopoeial ingredients. It was considered acceptable.

The applicant conducted an additional 28-day toxicity study in cynomolgus monkeys (Study 1300-015) to qualify the impurities according to ICH guideline Q3B(R2). The drug product batch used in the study was exposed to stress conditions (7 months at 25°C/60%RH followed by 12 months at 2°C to 8°C) to enrich product-related impurities. The octreotide capsules enriched with product-related impurities were well tolerated. No signs of toxicity were observed in in-life and post-mortem analyses. The lack of toxicity in this study qualified impurity levels at the specified acceptance limits and the maximum human dose of 80 mg/subject. According to the ICH Q3B(R2) guideline, a minimum duration of 14

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days for the toxicity study is appropriate for the continuous treatment drug product. Also, a minimum screen (e.g., genotoxic potential), should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both *in vitro*, are considered an appropriate minimum screen. The applicant has tested the specified impurities in octreotide capsules for structural alerts for genotoxicity using two quantitative structure–activity relationship (QSAR) prediction methodologies (DEREK and Leadscope). The purpose of this assessment is to meet the ICH M7 (R2) requirements, which states that two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based (i.e., DEREK) and the second methodology should be statistical-based (i.e., Leadscope Model Applier). The applicant has evaluated the potential genotoxicity and mutagenicity of the five Octreotide degradants structures provided: octreotide linear, n-acetyl octreotide, lys(ac)- octreotide, n-octanoyl-octreotide and lys(oct)-octreotide in the study 75-69-03 and the 2 degradants - D-Phe-Cys (R-methyl imidazolidinone adduct) Octreotide Isomer and D-Phe-Cys (S-methyl imidazolidinone adduct) Octreotide Isomer in the study 75-69-04). Based on the results of both knowledge-based and statistically based genotoxicity QSAR prediction programs, the overall weight of evidence indicates that none of the potential impurities or degradation products in octreotide capsules should present any potential risk for genotoxicity.

2.9.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Octreotide			
CAS-number: 79517-01-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 shake flask method	-0.49 (neutral pH)	Potential PBT (**N**)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		**not B**
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g., prevalence, literature)	0.008	µg/L	> 0.01 threshold (**N**)
Other concerns (e.g., chemical class)			(**N**)

In Phase I two parameters for octreotide were presented, the distribution coefficient (logD) and Predicted Environmental concentration (PEC).

The applicant refers to Buchwald and Bodor (1998) for determination of the distribution coefficient of octreotide where the octonal-water partition of several peptides including octreotide was evaluated using the shake flask approach. Protocol of the analysis on determination of logD for octreotide has not been provided, but the full refereed article has been provided within the dossier in Module 4.

The log Kow was reported to be -0.49, which does not exceed the EMA partition coefficient limit of 4.5.

Fpen was refined assuming that 100% of the patient population is daily taking the medicinal product for the relevant disease(s), i.e., Fpen = prevalence of the disease. For orphan drug submissions, Fpen can be refined based on the prevalence on which the medicinal orphan drug designation, as adopted by

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the Committee for Orphan Medicinal Product (COMP), was based. Based on the prevalence of the disease, this was equivalent to a total of fewer than 102,000 people or less than 0.02% of the population in the EU. Therefore, the refined PECSW of octreotide is 0.008 µg/L. This value is below the action limit of 0.01 µg/L. As such, according to the EMA guideline (EMEA/CHMP/SWP/4447/00) if the PECSW value is below 0.01 µg/L, then a Phase II environmental fate and effect analysis should not be performed.

2.9.6. Discussion on non-clinical aspects

The applicant seeks to obtain MA for Mycapssa gastro-resistant capsules with octreotide acetate-TPE and presented hybrid Marketing Authorisation Application (MAA) according to Article 10(3) of Directive 2001/83/EC. To support MAA the applicant relies in part on nonclinical data for the medicinal product Sandostatin® and on information in the published literature for sc Sandostatin IR and has conducted additional studies to qualify the safety of its formulation and administration suitability of octreotide acetate by the oral route. The design the nonclinical development programme fulfils regulatory guidance and the European Medicines Agency (EMA) requirements. As this MAA is a hybrid MAA, the applicant provided justifications on absence of studies in CTD Module 4 (NC part) of the dossier. In general justifications to forego specific studies were considered as acceptable. The applicant's non-clinical written and tabulated summary and toxicology study-reports have been used as the basis of the text in this critical assessment. The data submitted were assessed taking into account the legal basis of the application, applicable guidelines and other scientific criteria.

The nonclinical primary pharmacodynamic and pharmacokinetic studies were performed as non GLP-compliant investigations. However, four toxicity studies up to 9 months in duration were Good Laboratory Practice (GLP)-compliant. *In vitro* studies on impurities conducted by the applicant were non-GLP studies. This is in line with official requirements.

Concentrations of octreotide were quantified in mice and monkey plasma by LC-MS/MS, ELISA and fluorescence methods. For GLP studies, validated methods were used for the quantification of octreotide in plasma and validation reports are presented in the dossier. The analytical method was validated for intra- and inter-day accuracy, precision and if necessary, specificity, dilution effect, freeze/thaw stability and storage stability.

For MoA of octreotide acetate, the applicant relies on identical active substance to the medicinal product Sandostatin approved in the EU and on published literature. The approach was considered as completely satisfactory. It is known that octreotide is poorly absorbed given orally, thus, to increase the permeability of the intestine the applicant formulated capsule with excipients collectively called Transient Permeability Enhancer (TPE®). In the dossier published literature data were provided describing that TPE ingredients enhance paracellular enterocyte permeability. Through the development process, in some NC experiments combinations of the TPE excipients were different from those chosen as final formulation (CH-906-4). Subsequently those investigation results should be regarded with caution.

In its own *in vivo* PD studies with rats the applicant focused on the mode of action of TPE-induced permeability, pharmacokinetic properties and evaluation of the magnitude, duration, and long-term reproducibility of the effects of the TPE system on GI permeability. The applicant demonstrated that TPE induced permeability is limited, that repeated administration of octreotide-TPE is transient, reversible and non-refractory; induced permeation is restricted to molecules size of about 70 kDa etc. It is worth mentioning that direct intra-intestinal administration of the test article differs from oral application of capsules and results from the clinical perspective should be read with certain caution. From the literature it can be seen that gastrointestinal tract (GIT) is not static, its permeability can be

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influenced by different external substances. Orally administered permeability enhancement can be influenced by many factors (e.g., gastric acidity, food etc.), cannot assure complete absorption and can act adversely. It is not certain that it can assure local tight junction (TJ) permeability. In addition, absorption supported by enhancement may be considered as erratic.

PK studies conducted by the applicant demonstrated that enteral administration of octreotide-TPE capsules enhances to a certain degree the absorption of octreotide, which is normally very poorly absorbed in the GI tract. Individual monkeys' oral octreotide plasma concentration curves showed significant dispersion in Cmax, Tmax and AUC, suggesting non-consistent, erratic absorption rate and very small bioavailability (F only 1.5%) calculated from s.c. octreotide data. Results from this study in monkeys send certain signals of possible weak and non-consistent absorption of oral octreotide in capsule with TPE.

As toxicological properties following sc administration of octreotide contained in Sandostatin®, are well established, the applicant relies in part on nonclinical data for this reference medical product. Therefore, single-dose, reproductive and developmental toxicity, genotoxicity and carcinogenicity studies were not conducted. The reference data from these studies has been transferred to the appropriate sections of SmPC of octreotide-TPE capsules. This is in line with the guidelines for the hybrid MAA.

The applicant has conducted additional toxicology studies in cynomolgus monkeys to demonstrate the safety of octreotide capsules in comparison to sc Sandostatin IR and to qualify product-related impurities in support of a hybrid MAA according to Article 10(3) of Directive 2001/83/EC. The potential toxicity of octreotide capsules was evaluated in repeat-dose toxicology studies, which almost all were conducted using clinical trial batches of octreotide capsules containing 20 mg of octreotide. The cynomolgus monkey is considered the most appropriate species, selected for repeat-dose toxicity studies, because it would be difficult to deliver capsules to the stomach of animals of a small size. The data from the repeat-dose toxicity study in monkeys suggested that there was no novel systemic toxicities discovered and the local gastrointestinal toxicities will be observed with oral administration of octreotide capsules at doses that produce systemic exposures similar to those obtained following sc Sandostatin IR. Toxicokinetic data confirms that systemic exposure in terms of AUC0-t and Cmax is highly variable among study days and between animals, indicating day-to-day differences in oral bioavailability and very low bioavailability.

Since the TPE formulation in its exact composition is a novel pharmaceutical formulation, according to the EMA Guidelines the applicant was asked to provide adequate information on systemic effects of the excipients, either from published literature or from own studies. The applicant has provided the safety assessment protocols for each excipient considering that they are not novel, as they all have been included in medicinal products approved previously in the EU, they are pharmacopoeial grade or made of pharmacopoeial ingredients. Also, some of the excipients do not reach systemic circulation because either are metabolised in the liver or are poorly absorbed.

Toxicity profile of the drug-related impurities and degradation products identified in clinical trial batches of octreotide capsules were assessed *in vivo* and *in vitro* for potential genotoxicity. A study to detect point mutations and one to detect chromosomal aberrations, both *in vitro*, are considered an appropriate minimum screen according to the guidelines. Based on the results, none of the potential impurities or degradation products in octreotide capsules should present any potential risk for genotoxicity and they seem to be well tolerated.

The assessment of the potential risk to the environment for octreotide has been terminated in Phase I because the PECsurface/water value was below the action limit. The calculations were made based on the prevalence of acromegaly and assuming a market share of 100%, which is in line with the ERA Guideline. According to the same guideline log Know should be determined experimentally by the

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applicant or can be taken from the published literature. The full reference of log Know determination for octreotide has been provided with the dossier.

2.9.7. Conclusion on the non-clinical aspects

Overall, the NC programme was based in part on data generated for sc and iv administration of octreotide during development of Sandostatin. The applicant performed additional primary PD, PK and repeat-dose toxicity studies with octreotide-TPE or octreotide capsules which demonstrated that the novel TPE formulation of octreotide is suitable and safe for oral administration. No additional recommendations for the Product Information are suggested from the nonclinical point of view. All issues revealed as nonclinical concerns were resolved.

2.10. Clinical aspects

2.10.1. Introduction

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of octreotide acetate based on own studies and published literature. The SmPC is partly based on the SmPC of the reference product.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

To support the application, the applicant has submitted the studies listed below.

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Study number (Study location)	Study objectives	Study design	N	Study status
Phase 3 studies in patients with acromegaly				
OOC-ACM-302 (Europe, United States)	Efficacy, safety	Phase 3, randomised, open-label, active-controlled, preceded by a run-in phase, followed by an OLE phase	146 (RCT phase: 92)	Run-in and RCT phases completed, OLE ongoing
OOC-ACM-303 (Europe, North America, Australia/NZ)	Efficacy, safety	Phase 3, randomised, double-blind, placebo-controlled, followed by an OLE phase	56	DPC phase completed, OLE ongoing
CH-ACM-01 (Europe, Israel, Mexico)	Efficacy, safety	Phase 3, single-arm, baseline-controlled, followed by an OLE phase	155	Completed
Pharmacokinetic study in healthy volunteers				
CHI-001 (Israel)	PK, safety	Phase 1, open-label, crossover, followed by dose escalation	12	Completed
Clinical pharmacology studies in special populations				
CH-PHT-01 (Spain)	PK, safety in subjects with liver cirrhosis and portal hypertension (hepatic impairment)	Phase 2, open-label, dose escalation	18	Completed
CHI-007 (United States)	PK, safety in subjects with severe renal impairment/end-stage renal disease on dialysis	Phase 1, open-label	24	Completed
Drug-food or drug-drug interaction studies in healthy volunteers				
CHI-002 (Israel)	Food effect (high-fat meal), safety	Phase 1, open-label, crossover	24	Completed
OCT-01 (Israel)	Food effect (light and standard meal), safety	Phase 1, open-label, crossover	24	Completed
CHI-004 (United States)	Intestinal permeability, PK, safety	Phase 1, open-label, crossover	24	Completed
CHI-005 (Israel)	BA and PK after PPI administration, safety	Phase 1, open-label, crossover	14	Completed
OCT-02 (Israel)	BA and PK with lisinopril and digoxin; BA with ingested water volume; safety	Phase 1, single-blind, placebo-controlled, crossover	18	Completed
CHI-006 (Israel)	BA and PK with warfarin, HCTZ, metformin, and oestradiol; safety	Phase 1, single-blind, placebo-controlled, crossover	20	Completed
OCT-03 (Germany)	BA and PK with metoclopramide, loperamide; BA and PK with body posture; BA after night-time administration	Phase 1, open-label, crossover	18	Completed
OCT-04 (Israel)	BA and PK with cyclosporine, safety	Phase 1, single-blind, placebo-controlled, crossover	18	Completed
		Total number of subjects:	571	

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2.10.2. Clinical pharmacology

2.10.2.1. Pharmacokinetics

The clinical pharmacology development programme for octreotide capsules consisted of 12 studies (11 clinical pharmacology studies and 1 Phase 3 study). Comparative bioavailability bridging results for octreotide capsules and the reference medicinal product (sc Sandostatin IR), as well as the effect of food and water volume on the PK of octreotide capsules (studies CHI-001, CHI-002, OCT-01) were provided.

Overall, a total of 184 healthy subjects participated in the clinical pharmacology programme for octreotide capsules. Subjects were exposed to at least a single dose (3 mg – 40 mg) of octreotide capsules. In study CH-ACM-01 in patients with acromegaly, 65 patients were treated with 40 mg/day,

33 patients were treated with 60 mg/day, and 57 patients were treated with 80 mg/day at the end of the core treatment phase. According to the applicant no definitive ADME studies in humans have been performed for octreotide capsules.

Bioanalytical methods. The methods used here represent standard approaches used in the field. The pre-specified criteria for the different validation parameters are in line with the Guideline on bioanalytical method validation and were fulfilled. The provided validation reports for quantitation of octreotide in human serum and plasma include the necessary information. The measurements with the individual calculated concentrations are presented. The analytical reports contain necessary information on reference and calibration standards, run acceptance criteria are set, adequately detailed descriptions of analytical procedures are provided, information on sample tracking and sample analysis are provided. Necessary certificates of analysis are presented. In general, the applied approaches in designing and implementing the validation of bioanalytical procedures is considered acceptable as the performance of the assay methods in the study met the defined criteria, and could be considered suitable for purpose. Information on the development of anti-octreotide neutralizing antibodies in human serum assays is provided. As there was no evidence for induction of anti-octreotide antibodies during chronic administration of oral octreotide acetate, the development of the neutralizing antibody assay is considered not to be needed.

Several issues were raised. Bioanalytical analysis (clinical study OCT-02 - according to the validation report P1206 Project AHEA2 - Quantitation of Lisinopril) - The long-term storage parameters covering time of the sample storage in study OTC-02 was not found. applicant was asked to submit validation results and time of the sample storage for Lisinopril analysis. Method Validation Report LCMSD 455.2 - Quantitation of Digoxin - The analysis of the effect of haemolysis and lipemia were not found in the dossier. The applicant was asked to submit the missing results. Bioanalytical analysis (clinical study CHI-006 - quantitation of metformin) Long term storage condition for metformin were supposed to be added but the results are missing. applicant was asked to submit the results covering storage of the samples during bioanalysis. The lipemic effect was not addressed during validation of detection methods for warfarin enantiomers, hydrochlorothiazide, metformin and estradiol. The bioanalytical reports for GH and IGF determination could not be identified in the dossier. The applicant submitted the missing results. Lipaemia effect was accounted for in the bioanalytical method used as a routine, and the applicant showed that haemolysis was observed in very few samples and that this effect was unlikely to distort the overall reliability of the results. The final IGF-1 and GH bioanalytical report from ERL for the 3 pivotal studies was provided and is acceptable, therefore, the issue is resolved. Therefore, we conclude that there are no further issues with bioanalytical methods and their validation.

Absorption

Octreotide capsules are designed to withstand the acid environment of the stomach, deliver octreotide to the small intestine, reversibly increase intestinal paracellular absorption without effecting transcellular absorption.

Mechanistic effects of Transient Permeability Enhancer (TPE). Octreotide capsules have a gastric acid resistant enteric coating to deliver octreotide acetate to the small intestine for absorption. The TPE formulation protects the drug molecule from inactivation by the GI environment and at the same time acts on the intestinal wall to induce local, transient, and reversible opening of the tight junctions, allowing permeation of the drug molecules through the intestine. The intestinal permeability induced by octreotide capsules after a single dose of 20 mg, was tested in a study CHI-004 using the lactulose/mannitol (L/M) assay and supported by a literature review.

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The applicant performed a number of studies where bioavailability of Octreotide capsules was analysed in both HV and ACM patients. The results most relevant to bioavailability are presented here from studies CHI-004, CHI-001, CHI-002, OCT-01 and CH-ACM-01 (PK Substudy of pivotal Study 302).

Study CHI-001

Study design. This was a single centre, Phase 1, open, partly randomised, dose-escalation study in 12 healthy male volunteers. The study consisted of 2 stages. Twelve (12) subjects were planned and completed Stage 1 and the first treatment of Stage 2 (10 mg dose). The 20 mg treatment in Stage 2 was conducted after approval of a protocol amendment, and 9 of the 12 subjects returned for that visit and dose. Octreotide plasma concentrations following each Octreolin administration were determined at 0 (pre-dose, up to 60 minutes before administration), every 20 minutes post dosing for the first 4 hours, then at 5, 6, 8, 12 and 24 hours post dosing.

Study results are presented in Table 3.3.1.1.1.

The observed variability of PK parameters followed p.o. administration seems quite high. The applicant did not present the analysis of the sources of significant inter-subject and intra-subject variability. This issue will not be further pursued because administration of this drug will require biochemical monitoring to ascertain efficacy.

Table 3.3.1.1.1. Pharmacokinetic parameters of octreotide after oral administration of octreotide capsules 20 mg under fasted conditions and after subcutaneous administration of 0.1 mg Sandostatin IR in studies CHI-001 and CHI-002

Parameter	Study CHI-001		Study CHI-002	
	0.1 mg sc Sandostatin IR (N = 12)	Octreotide capsules 20 mg (N = 9)	0.1 mg sc Sandostatin IR (N = 14)	Octreotide capsules 20 mg (N = 24)
T_{lag} (h)	[a]	0.835 [0.670 – 1.00] [b]	[a]	0.330 [0.330 – 1.02]
C_{max} (ng/ml)	3.33 ± 0.91	2.938 ± 2.027	3.83 ± 0.86	3.62 ± 1.93
T_{max} (hr)	0.500 [0.167 – 1.00]	1.67 [0.67 – 4.00]	0.50 [0.203 – 4.00]	2.50 [0.330 – 4.33]
AUC_{0-t} (h*ng/mL)	10.0 ± 2.23	13.4 ± 11.6	12.0 ± 1.53	15.2 ± 8.73
AUC_{inf} (h*ng/mL)	10.2 ± 2.32	13.6 ± 11.5	12.3 ± 1.57	15.4 ± 8.74
λz (1/h)	0.3156 ± 0.0371	0.3018 ± 0.0776	0.3083 ± 0.0331	0.2799 ± 0.0783
$t_{½}$ (h)	2.23 ± 0.28	2.45 ± 0.68	2.27 ± 0.25	2.66 ± 0.73

AUC_{0-inf}: area under the plasma concentration-time curve extrapolated to infinity; AUC_{0-t}: area under the plasma concentration-time curve from 0 until the last measurable concentration; C_{max}: Maximum observed drug concentration; T_{lag}: Absorption lag time; T_{max}: time to maximum plasma concentration; $t_{½}$: terminal half-life λz: terminal elimination rate constant
[a] There was no lag time after sc administration.
[b] N= 2

Source: CSR CHI-001, Appendix 16.2.6, PK Report Amendment I, Table 1; CSR CHI-002, Appendix 16.2.6, PK Report Amendment I, Table 1

Study CHI-002

Study design

This was a phase 1, open-label, 2-period, 2-sequence crossover, food-effect bioavailability study (N=24), followed by open-label assessment bioavailability after single octreotide acetate (Sandostatin) injection in healthy subjects. Octreotide plasma concentrations following oral Octreolin administrations were determined on each dosing day at 0 (pre-dose, up to 60 minutes before administration), every 20 minutes post dosing for the first 5 hours, then after 6, 8, 12, and 24 hours post dosing.

Study results are presented in Table 3.3.1.1.2 and Table 3.3.1.1.4

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Mean plasma concentrations, Cmax, AUC0 t, and AUC0-inf increased in a dose-related manner following administration of different octreotide capsule doses (3 mg, 10 mg, and 20 mg).

• Octreotide capsules showed an apparent lag time and considerable within- and between-subject variability in the octreotide plasma concentration-time profile.

• Median Tmax and mean t½ were not dependent on octreotide capsule dose.

• Octreotide capsule (20 mg) was comparable to 0.1 mg octreotide sc in systemic exposure (AUC).

Table 3.3.1.1.2. Summary of Pharmacokinetic Parameters for Octreotide after Subcutaneous Administration of Octreotide 0.1 mg and Administration of Octreolin 3 mg, 10 mg, and 20 mg to Healthy Volunteers under Fasted Conditions

Parameter*	Octreotide 0.1 mg SC	Octreolin 3 mg PO	Octreolin 10 mg PO	Octreolin 20 mg PO
Tlag (h)†	—‡	0.670 (10) [0.670 – 0.687]	0.670 (4) [0.670 – 0.670]	0.835 (2) [0.670 – 1.00]
Cmax (ng/mL)	3.33 ± 0.91 (12)	0.443 ± 0.256 (12)	1.799 ± 0.995 (12)	2.938 ± 2.027 (9)
Tmax (h)	0.500 (12) [0.167 – 1.00]	0.843 (12) [0.670 – 4.00]	0.670 (12) [0.330 – 4.00]	1.67 (9) [0.670 – 4.00]
AUC(0-t) (h×ng/mL)	10.0 ± 2.23 (12)	1.701 ± 1.194 (12)	5.87 ± 3.16 (12)	13.4 ± 11.6 (9)
AUC(inf) (h×ng/mL)	10.2 ± 2.32 (12)	1.822 ± 1.220 (12)	6.41 ± 3.18 (11)	13.6 ± 11.5 (9)
λz (1/h)	0.3156 ± 0.0371 (12)	0.3778 ± 0.0704 (12)	0.3099 ± 0.0355 (11)	0.3018 ± 0.0776 (9)
t½ (h)	2.23 ± 0.28 (12)	1.90 ± 0.37 (12)	2.26 ± 0.24 (11)	2.45 ± 0.68 (9)

*Mean ± standard deviation (N) except T_{lag} and T_{max} for which the median (N) [Range] is reported.
†A lag time was not calculated if the first concentration ≥ LOQ occurred at the first sample time.
‡There was no lag time after SC administration.
Source: Appendix 16.2.6, Pharmacokinetic Report Appendix V.

Bioavailability is calculated as AUC oral/AUC IV*Dose IV/Dose oral, under assumption nothing else impacts clearance and F(u)b fraction unbound in blood. The applicant claims that after correcting for dose, the octreotide apparent BA from fasted oral administration of octreotide capsules relative to sc Sandostatin IR was 0.63%. Study CHI-002 Demographic information are given as a mean for all subjected enrolled to the study, regardless treatment groups. That approach hinders analysis of any imbalance according to the initial demographic parameters that could affect PK, between treatment groups. The applicant was asked to submit the demographic description for age, body weight, BMI, height, sex according to treatment arms. The data were provided and the issue was resolved.

Study CHI-004

Study design. This was a phase 1, open-label, 4-period, 2-sequence crossover study designed to assess the Transient Permeability Enhancer (TPE) induced intestinal permeability effect, PK, and safety in healthy subjects (N = 24) after a single dose of 20 mg octreotide capsules using the L/M test that measures the ability of 2 non-metabolised sugar molecules (mannitol and lactulose), to permeate the intestinal mucosa.

Subjects received the following treatments during the study:

A = Control: L/M test and GHRH-Arginine test at the same time

B = Octreolin 20 mg at t = 0 plus L/M test at 2 hours post Octreolin dosing

C = Octreolin 20 mg at t = 0 plus L/M test at 5.5 hours post Octreolin dosing and GHRHArginine test at t = 2 h

D = Octreolin 20 mg at t = 0 plus L/M test at 10 hours post Octreolin dosing

Octreotide plasma concentrations were determined within 20 minutes pre-dose, and then post-dose at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 6, 8, and 12 hours.

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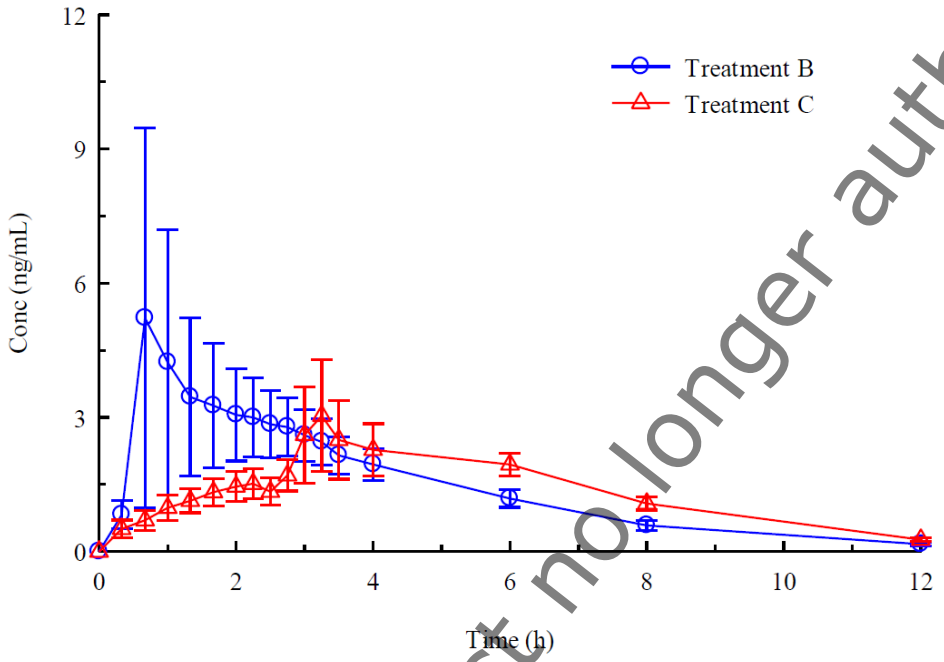
Of the 19 subjects who completed both Treatment B and Treatment C, 2 subjects, 110001 and 110015, had plasma octreotide concentrations that were aberrantly high. The PK data were thus analysed with (N = 19) and without (N = 17) those 2 subjects. The analyses without Subjects 110001 and 110015 are presented as the primary results, and the analyses including the 2 aberrant subjects are presented as secondary results.

Figure 2. Mean ± Standard Error Plasma Concentrations of Octreotide After Oral Administration of Octreolin on 2 Occasions: All Completing Subjects: Linear Axes



GHRH = growth hormone releasing hormone; L/M = lactulose/mannitol; Treatment B = Octreolin plus L/M test at 2 hours post Octreolin; Treatment C = Octreolin plus L/M test at 5.5 hours post Octreolin and GHRH-Arginine test

Table 3.3.1.1.3. Summary of Pharmacokinetic Parameters for Octreotide After Oral Administration of Octreolin on 2 Occasions: All Completing Subjects

Parameter*	Octreolin	
	Treatment B	Treatment C
Cmax (ng/mL)	7.13 ± 18.08 (19)	3.71 ± 4.68 (19)
Tmax (h)	2.25 (19) [0.333 – 6.00]	3.29 (19) [0.677 – 6.04]
AUC(0-t) (h×ng/mL)	17.7 ± 24.6 (19)	15.8 ± 11.4 (19)
AUC(inf) (h×ng/mL)	23.8 ± 30.6 (19)	23.3 ± 20.3 (18)
λz (1/h)	0.3399 ± 0.0379 (19)	0.3347 ± 0.0583 (18)
t½ (h)	2.07 ± 0.27 (19)	2.14 ± 0.43 (18)
Tlag (h)†	0.67 (4) [0.67 – 1.33]	1.90 (2) [1.00 – 2.79]

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration <= LOQ occurred at the first sample time.

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Lambda z = elimination rate constant; AUC0-t = area under the octreotide plasma concentration-time curve from 0 to the final time with a concentration <= LOQ; AUCinf = area under the octreotide plasma concentration-time curve from 0 to infinity; Cmax = maximum plasma concentration; GHRH = growth hormone releasing hormone; L/M = lactulose/mannitol; LOQ = limit of quantitation; t½ = elimination half-life; Tlag = absorption lag time; Tmax = time of maximum plasma concentration; Treatment B = Octreolin plus L/M test at 2 hours post Octreolin; Treatment C = Octreolin plus L/M test at 5.5 hours post Octreolin and GHRH-Arginine test.

Study OCT-01

Study design. This was a phase 1, open-label, 4-period crossover, bioavailability evaluation study in 24 healthy subjects. A single 20 mg dose was used in this study. The study aimed to (a) evaluate the effect of a reduced size high fat meal (i.e. snack) post-dose and (b) full standardised meal pre- and post-dose on the absorption of octreotide from Octreolin (oral octreotide acetate) compared to a control fasting condition.

Study results - See **Table 3.3.1.1.4** below.

Study CH-ACM-01 (PK Sub-study)

Study design (see Section 3, clinical efficacy)

A PK sub-study was conducted in 46 patients from selected study sites. The PK profile of MYCAPSSA during chronic treatment was evaluated.

Exposure between healthy volunteers and patients with acromegaly

Exposure between healthy subjects and patients with acromegaly was similar, but a longer half-life in patients with acromegaly than in healthy volunteers was observed.

Table 3.3.1.1.4. Comparison of Octreotide Exposure (mean or mean standard deviation) between Healthy Subjects and Patients with Acromegaly

Source	Population	Dose (mg)	C_{max} (ng/mL)	T_{max} (hr)	AUC[a] (h×ng/mL)	$t_{½}$ (hr)
Octreotide SC						
Novartis PI [c]	HV	0.1	5.20	0.40	10 – 14 [b]	1.7 - 1.9
Study CHI-001 (Single dose)	HV	0.1	3.33 ± 0.91	0.50	10.2 ± 2.32	2.23 ± 0.28
Study CHI-002 (Single dose)	HV	0.1	3.83 ± 0.86	0.50	12.3 ± 1.57	2.27 ± 0.25
Novartis PI	ACM	0.1	2.8	0.7	5.6 [b]	0.83 [d]
Novartis SmPC [e]	- [f]	0.1	- [f]	0.50	- [f]	1.67
Octreotide capsules						

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Study CHI-001 - Treatment D, fasted (Single dose)	HV	20	2.938 ± 2.027	1.67 [0.670 – 4.00]	13.6 ± 11.5	2.45 ± 0.68
Study CHI-002 (Single dose)	HV	20	3.62 ± 1.93	2.50 [0.330 – 4.33]	15.4 ± 8.74	2.66 ± 0.73
Study CHI-004 (Treatment B) (Single dose)	HV	20	3.01 ± 1.44	2.25 (0,33 – 6)	16.9 ± 8.38	1.99 ± 0.15
Study CHI-005 (Single dose)	HV	20	4.35 ± 2.31	2.67	18.5 ± 15.7	2.69 ± 0.80
Study OCT-01 (Single dose)	HV	20	5.91 ± 9.82	3.00	24.4 ± 27.3	2.65 ± 0.85
Study OCT-02 (Single dose)	HV	40	8.21 ± 7.18	3.54	35.3 ± 20.4	3.54 ± 0.88
Study CH-ACM-01 (PK Sub-Study) (Multiple dose)	ACM	20 mg AM/ 20 mg PM	2.51 ± 2.03	1.50	*8.17 ± 8.49* [a]	3.47 ± 1.18
		40 mg AM/ 20 mg PM	3.83 ± 3.18	1.42	*20.3 ± 12.5* [a]	3.19 ± 1.07
		40 mg AM/ 40 mg PM	5.30 ± 4.06	1.00	*19.5 ± 16.3* [a]	4.47 ± 2.02

[a] $AUC_{0\text{-}inf}$ except for study CH-ACM-01 for which AUC represents $AUC_{0\text{-}12}$, the first dosing interval of the day at steady-state when the PK sub-study data is available.

[b] $AUC_{0\text{-}inf}$ estimated from dose (D) and total clearance (CL) Source: Novartis 2012

[c] Source: Novartis 2020c

[d] $t_{½}$: estimated from volume of distribution and total clearance (0.693*(V/CL)

[e] Source: Novartis 2020a

f Not specified

ACM = patients with acromegaly; HV = healthy volunteers; PI = package insert; SmPC = Summary of Product Characteristics

The applicant concluded that the relative bioavailability of oral octreotide compared to sc octreotide was approximately 0.5%. Night dosing may result in decreased exposure (AUC) to octreotide capsules. Octreotide capsules induce an increase in paracellular intestinal permeability measured 2 hours following administration. Within 5.5 hours of administration, intestinal permeability returns to baseline levels.

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The absolute bioavailability of Octreotide capsules 20 mg has not been determined in humans. The applicant performed six studies where bioavailability was analysed in HV (Studies CHI-001, CHI-002, CHI-004, CHI-005, OCT-01 and OCT-02 and in one study in ACM (PK sub-study of Study CH-ACM-01). The sampling time is sufficient to describe bioavailability of both oral and comparator octreotide and AUCinf values.

The applicant claims that study CHI-004 showed that the octreotide capsules formulation increases intestinal absorption of octreotide. The concept is based on applicant's approach to use TPE technology to increase BA of octreotide. The applicant proposes octreotide novel oral formulation that has similar bioavailability as described for subcutaneously injectable somatostatin analogue (2 mg of orally administered octreotide was comparable to subcutaneous injection of 50 micrograms [20 mg would be comparable to 0.5 mg sc] while the proposed novel octreotide capsule (20 mg) was comparable to 0.1 mg octreotide sc in systemic exposure (AUC)). Previous research indicated that absorption of the drug was quite variable between the subjects and the different locations. The dose-corrected systemic availability relative to subcutaneous administration in some studies was 0.28%, but significant plasma octreotide concentrations were achieved even without the TPE technology in the 1986– 1991 period. The then proposed oral formulation managed to lower the mean 24 h growth-hormone concentrations by over 50% in every case (Fuessl et al, 1987; Willimset al, 1986 and Tuvia et al, 2012). The consistent efficiency using TPE technology is not obvious, as seen in high variability in BA and rather limited clinical efficacy in substantial proportion of patients.

Two comparative bioavailability (BA) bridging studies between octreotide capsules and sc Sandostatin IR 0.1-mg single injection were conducted (studies CHI-001 and CHI-002).

The PK of octreotide is linear after single-dose administration of octreotide capsules from 3 mg to 40 mg in healthy subjects under fasted conditions. The median time to maximum plasma concentration (Tmax) after oral administration of octreotide capsules 3 mg to 20 mg ranged from 0.67 to 1.67 hours and was not dose-dependent.

The studies with octreotide capsules 20 mg showed rather broad distribution of both Tmax and C max values. The applicant acknowledges that a capsule containing 20 mg of octreotide (calculated as free base) resulted in a systemic exposure (based on AUC) that was slightly higher than the exposure to a 0.1-mg dose sc Sandostatin IR. The mean time to maximal absorption values ranged from 1.67 to 3.54 hrs for capsules in HV and from 1 to 1.5 hrs in ACM for capsules. The mean time to mean maximal absorption seems clearly numerically longer as compared to ~0.5 hr for mean maximal absorption after SC formulations. However, the mean C max concentrations values were not so different and less numerically different between capsules and SC formulations, i.e., mean C max values after 20 mg were ranging from ~3 till 8.21 ng/mL after oral and ~3.5 ng/ml after SC formulation of 0.1 mg.

After correcting for dose, the octreotide apparent BA from fasted oral administration of octreotide capsules relative to sc Sandostatin IR was calculated as 0.63%.

In patients with acromegaly, there was a dose-related increase in the mean plasma octreotide concentrations after chronic administration of 40 mg (20 mg bid), 60 mg (40 mg morning / 20 mg evening), and 80 mg bid (study CH-ACM-01)

Unprecise calculation of bioavailability. Based on comparable mean Cmax values from studies CHI-001 and CHI-002 the applicant calculated ratio relative to s.c. bioavailability of 0,63%. It was unclear how this BA value was generated as different proportions for different oral dosages were calculated and the applicant was asked to clarify. This calculation does not represent absolute bioavailability and the approach to calculate relative to s.c. bioavailability based on mean Cmax values is unprecise. Based on AUCinf values, it did not seem that 20 mg oral is comparable to 0.1 mg s.c. The number of patients in both cohorts differ more than two times and this is prone to biases. The

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applicant was asked to use bioavailability calculation the AUCinf values from the same patients after both s.c. and oral administration and incorporate these results clearly in SmPC section 5.2. The applicant implemented the requested changes. The agreed wording of section 5.2 of the SmPC states that: "In healthy subjects, systemic exposure, as measured by AUC, of a single oral dose of Mycapssa (20 mg octreotide acetate) was 95% to 100% of that of a single dose of subcutaneous octreotide acetate (0.1 mg octreotide acetate), demonstrating comparable exposure." The issue was considered resolved.

Higher variability in bioavailability after the oral vs s/c administration. Much higher variability was observed in Cmax and AUCinf values after the oral as compared s/c administration, e.g., SD were +/- 50 to 110% vs +/- 10 to 20% for AUC inf mean values for oral vs s/c administration, respectively. This is observed despite higher sample sizes of patients analysed after oral administration as compared to s/c. The consequence of such increased variability on clinical effectiveness has not been provided.

Influence of food

Influence of food (including the size and alcohol) was assessed in several studies, primarily in Study CHI-002, Study OCT-01 and Study OCT-02.

Study CHI-002

The effect of a high-calorie/high-fat meal on the BA of octreotide from octreotide capsules following a single 20-mg dose was assessed in study CHI-002. Mean octreotide plasma concentrations and values for Cmax, AUC(0-t), and AUC(inf) were substantially reduced following fed as compared to fasted Octreolin administration with geometric mean ratios of fed vs. fasted administration ranging from 8.79% to 10.44%. (Table **3.3.1.1.5**).

Table 3.3.1.1.5. Study CHI-002 PK Parameters

Parameter*	20 mg Oral		Subcutaneous
	Fed	Fasted	0.1 mg
Tlag (h)†	1.00 (24) [0.33 – 3.67]	0.330 (24) [0.330 – 1.02]	—‡
Cmax (ng/mL)	0.377 ± 0.261 (24)	3.62 ± 1.93 (24)	3.83 ± 0.86 (14)
Tmax (h)	3.00 (24) [0.670 – 4.67]	2.50 (24) [0.330 – 4.33]	0.50 (14) [0.203 – 4.00]
AUC(0-t) (h×ng/mL)	1.29 ± 0.884 (24)	15.2 ± 8.73 (24)	12.0 ± 1.53 (14)
AUC(inf) (h×ng/mL)	1.45 ± 0.892 (23)	15.4 ± 8.74 (24)	12.3 ± 1.57 (14)
λz (1/h)	0.3309 ± 0.0892 (23)	0.2799 ± 0.0783 (24)	0.3083 ± 0.0331 (14)
t½ (h)	2.28 ± 0.78 (23)	2.66 ± 0.73 (24)	2.27 ± 0.25 (14)

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration LOQ occurred at the first sample time.

‡There was no lag time after SC administration.

Source: Appendix 16.2.6, PK Report Appendix V.

Study OCT-01

Study results: effects of meal size and timing on the BA of octreotide from octreotide capsules were further evaluated in study OCT-01.

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In the Main Study, administration of oral octreotide acetate 1 hour before a full high fat meal, 1 hour after a full high fat meal, or 0.5 hours before a reduced size high fat meal resulted in a substantial decrease in plasma octreotide concentrations by 82% to 92%. (see Table **3.3.1.1.6**).

Table 3.3.1.1.6. Statistical comparison of pharmacokinetic parameters between fed and fasted Test Conditions (Main Study)

Parameter	Geometric Mean*		Geometric Mean Ratio (%)			
	Test	Reference	Estimate	90% Confidence Interval		
1 Hour Before Full High Fat Meal vs. Fasted						
Cmax	0.73	3.45	21.17	13.28	→	33.73
AUC(0-t)	2.31	15.53	14.88	9.79	→	22.62
AUC(inf)	2.48	16.21	15.32	9.94	→	23.61
1 Hour After Full High Fat Meal vs. Fasted						
Cmax	0.27	3.45	7.80	5.00	→	12.16
AUC(0-t)	1.20	15.53	7.71	5.17	→	11.48
AUC(inf)	1.33	16.21	8.22	4.85	→	13.95
0.5 Hour Before Reduced Size High Fat Meal vs. Fasted						
Cmax	0.93	3.45	26.84	17.34	→	41.56
AUC(0-t)	2.83	15.53	18.22	12.30	→	26.98
AUC(inf)	3.31	16.21	20.42	13.50	→	30.90

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†A lag time was not calculated if the first concentration ≤LOQ occurred at the first sample time.

Bioavailability was decreased by approximately 60% when octreotide capsules_were administered 1 hour before a reduced size high fat meal and by approximately 87% (95% CI, from 5 to 40%) when octreotide capsules were administered 2 hours after full high fat meal.

Food, but not the ingested water volume, decreases the absorption of octreotide from octreotide capsules by 90%. Therefore, the octreotide capsules should be administered under fasting conditions (at least 1 hour before and 2 hours after a meal). Bioavailability was decreased by approximately 60% when octreotide capsules were administered 1 hour before a reduced size high fat meal. In the Phase 3 clinical studies in patients with acromegaly, octreotide capsules were effective when administered at least 1 hour prior to a meal and at least 2 hours after a meal. Therefore, applicant states that octreotide capsules should be administered under fasting conditions (at least 1 hour before and 2 hours after a meal). Night dosing may result in decreased exposure (AUC) to octreotide capsules.

Uncertain method of administration. Study OCT-01 showed that bioavailability was decreased by approximately 87% (95% CI, from 5 to 40%) when octreotide capsules were administered 2 hours after full high fat meal. This finding might be the reason for such high variability of BA and thus does not support the proposal made for method administration (Section 4.2 of SmPC). The administration should be limited to administration by 1 hour before the meal. As the administration of octreotide capsules (20 mg) with food results in decreases in the extent of exposure, regardless of meal size or timing (BA was decreased by 60% when octreotide was administered 1 hour before a reduced-size high-fat meal and BA was decreased by 82 – 92% for the other 4 meal size/timing treatments) the applicant was invited to further justify the proposed posology (at least 1 hour before a meal or at least 2 hours after a meal The applicant informed that the instructions regarding administration are the same as those used in all Phase 3 clinical studies, which demonstrated the efficacy of octreotide capsules. However, according to Rapporteurs suggestion, the recommendation for the individual

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patient to standardise intake in relation was added to the SmPC (Section 4.2).). A statement was added to the SmPC section 5.2 that "Full size high fat meals provided 1 hour prior or 2 hours post dose significantly decreased the absorption of Mycapssa".

Distribution

No dedicated distribution studies were performed by the applicant. The applicant addresses distribution data based on originators study results. This information is provided in SmPC Section 5.2. This is acceptable.

Elimination

No dedicated excretion studies were performed by the applicant. Excretion was assessed in view of elimination analysis that was addressed in several studies.

Study CHI-001

Table 3.3.1.1.7 Pharmacokinetics after Oral and Subcutaneous Administration

Parameter*	Octreotide 0.1 mg SC	Octreolin 3 mg PO	Octreolin 10 mg PO	Octreolin 20 mg PO
Tlag (h)†	—‡	0.670 (10) [0.670 – 0.687]	0.670 (4) [0.670 – 0.670]	0.835 (2) [0.670 – 1.00]
Cmax (ng/mL)	3.33 ± 0.91 (12)	0.443 ± 0.256 (12)	1.799 ± 0.995 (12)	2.938 ± 2.027 (9)
Tmax (h)	0.500 (12) [0.167 – 1.00]	0.843 (12) [0.670 – 4.00]	0.670 (12) [0.330 – 4.00]	1.67 (9) [0.670 – 4.00]
AUC(0-t) (h×ng/mL)	10.0 ± 2.23 (12)	1.701 ± 1.194 (12)	5.87 ± 3.16 (12)	13.4 ± 11.6 (9)
AUC(inf) (h×ng/mL)	10.2 ± 2.32 (12)	1.822 ± 1.220 (12)	6.41 ± 3.18 (11)	13.6 ± 11.5 (9)
λz (1/h)	0.3156 ± 0.0371 (12)	0.3778 ± 0.0704 (12)	0.3099 ± 0.0355 (11)	0.3018 ± 0.0776 (9)
t½ (h)	2.23 ± 0.28 (12)	1.90 ± 0.37 (12)	2.26 ± 0.24 (11)	2.45 ± 0.68 (9)

*Mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported

†A lag time was not calculated if the first concentration LOQ occurred at the first sample time

‡There was no lag time after SC administration

LOQ = limit of quantitation; PO = oral administration; SC = subcutaneous

The applicant concluded that there was no effect of route of administration on octreotide elimination, and a comparable mean elimination half-life was obtained following all treatments. Based on data from originator, after iv injection, the elimination is biphasic, with half-lives of 10 and 90 minutes. Most of the peptide is eliminated via the faeces, while approximately 32% is excreted unchanged into the urine.

The applicant also concluded that in patients with acromegaly, elimination after chronic dosing was slightly slower than that seen in healthy volunteers, with mean apparent half-life values at steady state ranging from 3.2–4.5 hours across doses (daily 20 mg, 40 mg, 60 mg, and 80 mg).

Longer half-life as compared to s/c administration. The applicant notes that elimination half-life after sc administration of octreotide is similar to Mycapssa single dose (100 minutes).

No definitive metabolism studies in humans have been performed for octreotide capsules.

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The applicant did not perform dedicated inter-conversion studies.

No definitive metabolism studies in humans have been performed for octreotide capsules. This is acceptable, as there is no data that octreotide metabolism could depend on route of administration.

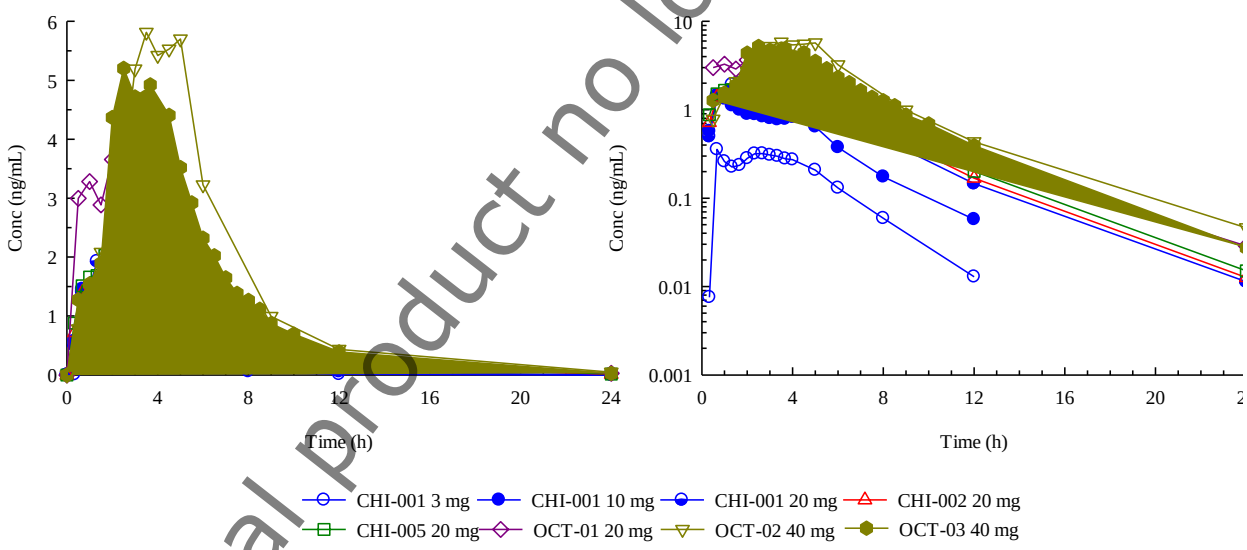
No definitive metabolism studies in humans have been performed for octreotide capsules. This is acceptable, as there is no data that octreotide metabolism could depend on route of administration.

Dose proportionality and time dependencies

Dose proportionality. The dose proportionality was assessed by a power model analysis using the arithmetic mean values from several PK studies. Data were used to assess PK linearity of octreotide after administration of octreotide capsules. Pharmacokinetic parameters included C_{max} and $AUC_{0\text{-}inf}$ following oral administration of single doses to healthy volunteers under fasted conditions.

The applicant notes that although there was variability among the 4 studies with the 20-mg dose, there was a dose-related increase in the mean plasma octreotide concentration after oral administration of single doses of octreotide capsules ranging from 3 mg to 40 mg (see **Figure 3.3.1.1.8** below).

Figure 3.3.1.1.8 Mean plasma concentrations of octreotide after oral administration of single 3 mg to 40 mg doses of octreotide capsules to healthy volunteers under fasted conditions: linear and semi-logarithmic axes



Source: Linearity Assessment Report 95-99-03, Figure 1

Log-log plots (power model assessment) of the mean C_{max} and $AUC_{0\text{-}inf}$ versus dose were linear (Figure **3.3.1.1.9** with mean ± standard error slopes of 1.123 ± 0.098 and 1.136 ± 0.098, respectively. These estimates are close to 1.0, the expected value if the increases are dose-proportional, and 1.0 would be included in a 95% confidence interval, indicating a linear increase in both parameters over doses ranging from 3 mg to 40 mg.

Figure 3.3.1.1.9. Relationship between mean octreotide C_{max} (left panel) and $AUC_{0\text{-}inf}$ (right panel) and dose after oral administration of single 3-mg to 40-mg doses of octreotide capsules to healthy volunteers under fasted conditions

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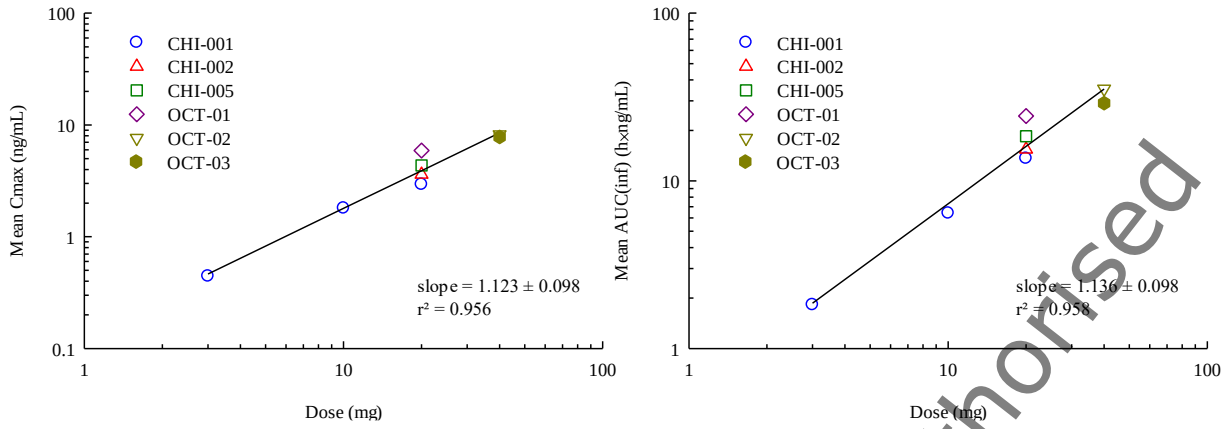

In conclusion, the PK of octreotide is linear after single-dose administration of octreotide capsules from 3 mg to 40 mg. Based on analysis performed by the applicant, the PK of octreotide is linear after single-dose administration of octreotide capsules from 3 mg to 40 mg in healthy subjects under fasted conditions. This is acceptable.

Time dependency. No dedicated studies were performed for time dependence. Based on indirect comparison of the same dosages, mean Cmax levels were not increased and mean half-live values were numerically ~20Ţ higher after multiple dosages for the same dosage administration (20 or 40 mg). This longer elimination is addressed in SmPC section 5.2.

Intra- and inter-subject variability. The Intra- and inter-subject variability was addressed in Study CHI-004 (see study design and above) and several PK parameters. The intra-subject variability was addressed in coefficients of variation and was less than 50% for markers of bioavailability.

Pharmacokinetics in target population. PK of octreotide capsules in patients with acromegaly was addressed in PK sub-study of study CH-ACM-01. There was a dose-related increase in the mean plasma octreotide concentrations after administration of octreotide capsules 40 mg (20 mg bid), 60 mg (40 mg morning / 20 mg evening), and 80 mg bid (40 mg bid). Based on AUC0-t, there is a dose-related and reasonably dose-proportional increase in exposure after the morning dose.

The steady-state mean apparent elimination t½ ranged from 3.19 ± 1.07 (arithmetic mean ± SD, for a dose of 60 mg) to 4.47 ± 2.02 hours (for a dose of 80 mg). The applicant concludes that similar trends in octreotide PK between healthy subjects and patients with acromegaly were seen following oral administration, except for a longer half-life in acromegaly patients than in healthy volunteers.

Study ACM-01 tested PK after the multiple regimen that was assessed after at least two months of receiving the therapeutic dosage regimen (the last month of the Dose Escalation Phase plus the first month of the Fixed Dose Phase. Numerically ~50% longer half-life values were observed in ACM patient's (after the multiple doses) vs healthy volunteers (after single dose administration). The applicant addressed this finding in the SmPC, although the reason for this finding is not explained. This was considered acceptable.

Special populations

Impaired renal function

Impact on PK in patients with impaired renal function was addressed in study CHI-007.

Study CHI-007

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Study design. This was a phase 1, open-label, single dose (**40 mg**) PK and safety study in healthy or with severe renal impairment or with end-stage renal disease on dialysis patients

Study results. The mean plasma octreotide concentrations and PK parameter values in subjects with ESRD on dialysis and their matched controls as well in subjects with severe renal impairment (SRI), i.e., eGFR 15 – 29 mL/min/1.73 m2) and their matched controls were similar (Figure 3.3.1.1.10, Table 3.3.1.1.9). There was a significant increase in octreotide exposure in patients with end stage renal disease (ESRD).

Figure 3.3.1.1.10. Mean (± standard error) plasma concentrations of octreotide following oral administration of a single 40-mg dose of octreotide capsules to subjects with ESRD on dialysis, subjects with SRI, and matched healthy controls: Linear (left panel) and semi-logarithmic (right panel) axes

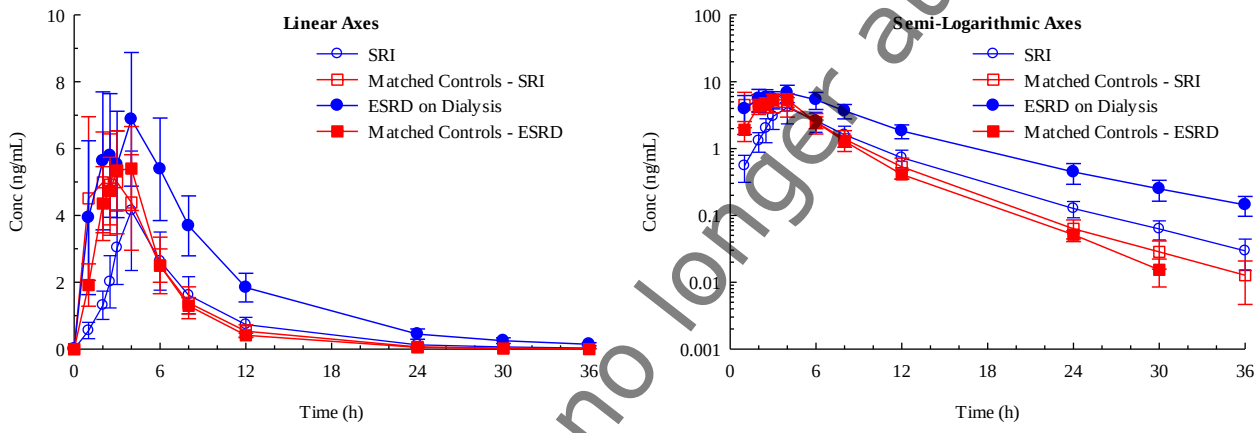

Table 3.3.1.1.8. Summary of pharmacokinetic parameters for octreotide following oral administration of a single 40-mg dose of octreotide capsules to subjects with ESRD on dialysis, subjects with SRI, and matched healthy controls

Parameter*	ESRD on Dialysis		Severe Renal Impairment	
	Subjects (N = 6)	**Matched Healthy Controls (N = 6)**	**Subjects (N = 6)**	**Matched Healthy Controls (N = 6)**
C_{max} (ng/mL)	9.30 ± 5.47	6.13 ± 3.19	4.40 ± 4.17	6.33 ± 5.16
T_{max} (h)	3.00 [1.00 – 8.00]	3.50 [2.00 – 4.00]	4.00 [1.00 – 6.00]	2.00 [1.00 – 3.00]
$AUC_{(0-t)}$ (h×ng/mL)	68.0 ± 37.9	32.2 ± 15.0	28.5 ± 23.8	35.1 ± 29.1
$AUC_{(0-inf)}$ (h×ng/mL)	69.5 ± 38.8	32.4 ± 15.0	29.0 ± 23.9	35.4 ± 29.1
λz (1/h)	0.0999 ± 0.0171	0.1853 ± 0.0333	0.1264 ± 0.0303	0.1521 ± 0.0421

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$t_{1/2}$ (h)	7.09 ± 1.07	3.84 ± 0.67	5.90 ± 2.10	4.95 ± 1.78
CL/F (L/h)	980 ± 912	1460 ± 647	2542 ± 2163	6341 ± 10546
Vz/F(L)	9905 ± 9095	8159 ± 4004	19713 ± 14465	37752 ± 63539

*Mean = standard deviation except Tmax for which the median [Range] is reported.

Source: CSR CHI-007, Appendix 16.2.6, PK Report Amendment I, Table 4

Based on Study CHI-007 results, the SRI function did not affect essentially the mean total exposure (AUC) to octreotide administered following oral administration, whereas numerical ~3x decrease CL/F with only 20% increase in half-life, compared to healthy controls.

In the same study, with octreotide capsules, subjects with ESRD on dialysis had ~2x decrease in CL/F with a corresponding ~2x increase in AUC0-inf and t½ compared to matched healthy subjects. There were minimal changes in Vz/F and Tmax. In both renal populations.

The observed significant increase in octreotide exposure in patients with ESRD is addressed in the SmPC proposing mitigation strategy – to start from 2x smaller dose (20 mg daily) and maintenance dose based on IGF-1 levels, patient's signs and symptoms, and tolerability. The adequacy of this proposal is not tested but seems reasonable, but this is based on small study after single dose administration. The applicant had to address the issue of accumulation during the procedure.

Impaired hepatic function

Impact on PK in patients with impaired hepatic function was addressed in study CHI-PHT-01.

Study CH-PHT-01

Study design. This was a phase 2, open-label, dose escalation, PK, and safety study in **18** patients with impaired liver function liver cirrhosis and portal hypertension patients (Child Pugh A or B).

Study results. Single dose administration of oral octreotide acetate (10 mg or 20 mg) in 18 subjects with cirrhosis and portal hypertension was associated with at least 10% decrease in Hepatic venous pressure gradient (HVPG) or reduction to below 12 mmHg in 61% of subjects. PK analysis indicated a dose-related but greater than dose-proportional increase in the mean plasma octreotide concentrations after administration of 10 mg and 20 mg oral octreotide acetate. PK of oral octreotide acetate in subjects with cirrhosis was determined to be similar to the PK in healthy subjects.

Based on octreotide administered as sc injection data, the elimination capacity may be reduced in patients with liver cirrhosis. In study CH-PHT-01, the PK analysis of octreotide after administration of 10 mg or 20 mg octreotide capsules in subjects with stable cirrhosis and portal hypertension was dose-related but greater than dose-proportional; other mean plasma octreotide concentrations were comparable to the PK in healthy volunteers.

The proposal that no dose adjustment is necessary in patients with Child Pugh A or B is acceptable as there is proposal that the MYCAPSSA dose should be up-titrated based on clinical response.

Lack of studies in patients with Child Pugh C is addressed and the proposal for careful monitoring of these patients initiating treatment with MYCAPSSA is recommended.

Gender. No specific studies were conducted to evaluate the influence of gender on PK/PD. This is acceptable, as no impact from gender is expected.

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Race. No specific studies were conducted to evaluate the influence of race on PK/PD. This is acceptable, as no impact from race is expected.

Weight. No specific studies were conducted to evaluate the influence of weight on PK/PD.

Elderly. No specific studies were conducted in the elderly.

Children. No specific studies were conducted in children.

Octreotide PK following administration of octreotide capsules (10 mg or 20 mg) in subjects with stable cirrhosis and portal hypertension appears to be similar to the PK observed in healthy volunteers from Phase 1 studies.

Renal function (exposure in subjects with severe renal impairment) was lower than in the matched controls, while the patients with ESRD had an increased octreotide exposure).

Specific studies to evaluate the influence of gender, race, and weight were not conducted.

Studies in children and elderly were not conducted.

The PK seems to be sufficiently established in special populations.

Pharmacokinetic interaction studies

The applicant collected data from the SmPc reference drug and indicated that dose adjustments are needed when beta blockers, calcium channel blockers, insulin, antidiabetic drugs, or agents to control fluid and electrolyte balance are used with octreotide. In addition, octreotide reduces the intestinal absorption of ciclosporin, delays it for cimetidine and increases the bioavailability of bromocriptine. Also, somatostatin analogues slows cytochrome P450 enzyme mediated drug metabolism.

Five DDI studies (CHI-005, CHI-006, OCT-02, OCT-03, OCT-04) were conducted to address aspects relating specifically to the octreotide capsules formulation (enhancing intestinal permeability) and route of administration (via the GI tract).

In silico studies were not performed. This is acceptable, as no specific concerns are foreseen regarding oral administration vs injections.

Study CHI-005

Study design. This was a phase 1, open-label, 2-period crossover study in 14 patients that aimed to evaluate the bioavailability and PK changes of octreotide after PPI administration (2 days 20 mg octreotide with 5 days esomeprazole 40 mg). Safety outcomes were also evaluated.

Study results. After 6 days of PPI treatment, there was an approximate 40% decrease in the mean extent of absorption of octreotide. However, this decrease was highly variable among individual subjects, ranging from -1% (minimal or no change) to -86% in 9 of 13 subjects.

Study OCT- 02

Study design. This was a phase 1, single-blind, placebo-controlled, 4-period, 2-sequence crossover study in healthy subjects (N=18) to evaluate the bioavailability (BA), PK, BA dependence on ingested water volume, and safety of Octreotide (capsules 40 mg) used in conjunction with Digoxin (0.5 mg) and Lisinopril (20 mg).

Study results. Water intake did not significantly change the PK parameters of oral octreotide. Concomitant administration of oral octreotide acetate with digoxin does not affect the extent (AUC) of digoxin absorption, but the rate of digoxin absorption was decreased. Cmax decreased by 37% and

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Tmax increased from 1 to 3 hours. Concomitant administration of oral octreotide acetate with lisinopril resulted in an increase in the extent of lisinopril absorption. Cmax increased by 50% and AUC0-12 increased by 40%.

Study CHI-006

Study design. This was a phase 1, single-blind, placebo-controlled, 2- way (males) or 4-way (females) crossover study in healthy subjects (N=20) that aimed to assess the bioavailability (BA), PK, and safety of octreotide used in conjunction with octreotide (capsules 40 mg), warfarin (7.5 mg), HCTZ (25 mg), metformin (850 mg), levonorgestrel/ethinyl estradiol (0.150 mg/0.030 mg (females only)).

Study results. The arithmetic mean plasma concentrations and PK parameters of R-warfarin were comparable after administration with oral octreotide acetate or with placebo. The arithmetic mean plasma concentrations and PK parameters of S-warfarin were comparable after administration with oral octreotide acetate or with placebo. The arithmetic mean plasma concentrations of HCTZ over the initial 5 hours were lower after administration with oral octreotide acetate compared to placebo. The arithmetic and geometric mean values for Cmax and AUC0-5 were lower during concomitant administration. The arithmetic mean plasma concentrations of metformin over the initial 5 hours showed a slower rate of absorption when metformin was administered with oral octreotide acetate. The arithmetic mean plasma concentrations and PK parameters of ethinyl oestradiol were comparable after administration with oral octreotide acetate or with placebo. The arithmetic mean plasma concentrations of levonorgestrel over the initial 3 hours were lower after administration with oral octreotide acetate compared to placebo. The arithmetic and geometric mean values for Cmax and AUC0-5 were lower during concomitant administration.

Study OCT-03

Study design. This was a phase 1, open-label, 5-period, 3-sequence crossover, single dose study designed to evaluate the bioavailability of Octreotide (capsules 40 mg) and PK (accounting for body posture and night-time administration) metoclopramide (20 mg), loperamide (4 mg) in healthy subjects (N=18).

Study results. Administration of oral octreotide acetate in the morning in a standing position resulted in a decrease in the mean plasma concentrations compared to the semi-sitting position. The arithmetic mean values for Cmax, AUC0-t, and AUCinf were also decreased when oral octreotide acetate was administered in a standing position compared to a sitting position. Administration of oral octreotide acetate at night in a semi-sitting position followed by lying resulted in a slower increase in the mean plasma concentrations and lower concentrations compared to the morning administration in the semi-sitting position. The arithmetic mean value for Cmax was reduced after the night administration. Administration of oral octreotide at night in a semi-sitting position followed by lying compared to administration in the morning in a sitting position resulted in a c.a. 20% decrease in AUCinf in 8 of the 14 subjects (57%) completing both treatments, no change (< 20% decrease or increase) in 3 subjects (21%), and a 20% increase in 3 subjects (21%). Administration of oral octreotide acetate 2 hours after a 20 mg oral dose of metoclopramide, a gastroprokinetic agent, resulted in a slight decrease in the mean plasma concentrations of octreotide. The arithmetic mean values for Cmax, AUC0-t, and AUCinf were also decreased when oral octreotide acetate was administered 2 hours after a 20 mg oral dose of metoclopramide. Administration of oral octreotide acetate 2 hours after a 4 mg oral dose of loperamide, an antidiarrheal agent that reduces gastric motility, resulted in minimal differences in the mean plasma concentrations compared to oral octreotide acetate alone. The arithmetic mean value for Cmax was lower, with a GMR of 90.55%.

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Study OCT-04

Study design. This was a phase 1, single-blind, placebo-controlled, 2-period, 2-sequence, single dose crossover study that aimed to assess the bioavailability and PK of Octreotide (capsules 40 mg) when used with cyclosporine (300 mg) and evaluate the safety of such use in healthy subjects (N=18).

Study results. Concomitant administration of cyclosporine and oral octreotide acetate 40 mg (as 2 × 20-mg capsules) results in a 60% decrease in the extent of cyclosporine exposure and a decrease in the rate of cyclosporine absorption. Coadministration of oral octreotide acetate 40 mg (as 2 × 20-mg capsules) and oral cyclosporine 300 mg was safe and well tolerated.

In Study CHI-005 it was shown that administration of octreotide capsules (20 mg) after 6 days of PPI treatment decreases absorption of octreotide, possibly because proton pump inhibitors (PPIs) elevate the gastric pH and impairs the capsule's ability to stay intact until it reaches the small intestine for absorption. Thus, the octreotide capsules dose may need to be increased when PPIs, H2-receptor antagonists, or antacids are given concomitantly. This is addressed in SmPC.

In Study OCT-03 it was shown that motility inducer metoclopramide and the motility inhibitor loperamide does not change the PK of octreotide. In the study OCT-03 interaction with enhancers and inhibitors of gastrointestinal motility was analyzed. The estimates for the Cmax and AUC0-t were about 90%, however the 90% CIs were wide and were not contained within 80-125%.

Three DDI studies (OCT-02, OCT-04, CHI-006) evaluated probe drugs that may be affected by octreotide capsules (HCTZ, and metformin), drugs with a narrow therapeutic window (digoxin, oral contraceptives [ethinyl oestradiol and levonorgestrel], warfarin, and cyclosporine), and low permeability drugs (lisinopril and cyclosporine).

It was revealed that possibly due to the pharmacological GI effects of octreotide capsules may reduce the intestinal absorption of concomitantly administered tested drugs, i.e., cyclosporine, digoxin (rate more than extend), HCTZ, levonorgestrel). The only drug for which a potential **increase** in absorption was noted was lisinopril. There was a 50% increase in Cmax and a 40% increase in AUC when lisinopril was administered concomitantly with octreotide capsules. There is no rationale explaining the increase of lisinopril although the same mechanism on increased bioavailability of octreotide in Mycapssa could play the role. The trends of changes for lisinopril, digoxin and levonorgestrel are addressed properly in SmPC section 4.5. The changes in warfarin, HCTZ, metformin, ethinyl oestradiol, norgestrel, metoclopramide, loperamide were only minimal.

Pharmacokinetics using human biomaterials

Specific pharmacokinetic studies using human biomaterials were not performed. This is acceptable, as no specific PK changes are expected for oral formulation as compared to parenteral one.

2.10.2.2. Pharmacodynamics

Mechanism of action

Based on originator SmPC, in healthy subjects, octreotide inhibits:

• release of GH stimulated by arginine, exercise- and insulin-induced hypoglycaemia

• post-prandial release of insulin, glucagon, gastrin, other peptides of the GEP endocrine system, and arginine-stimulated release of insulin and glucagon

• thyrotropin-releasing hormone (TRH)-stimulated release of thyroid-stimulating hormone (TSH).

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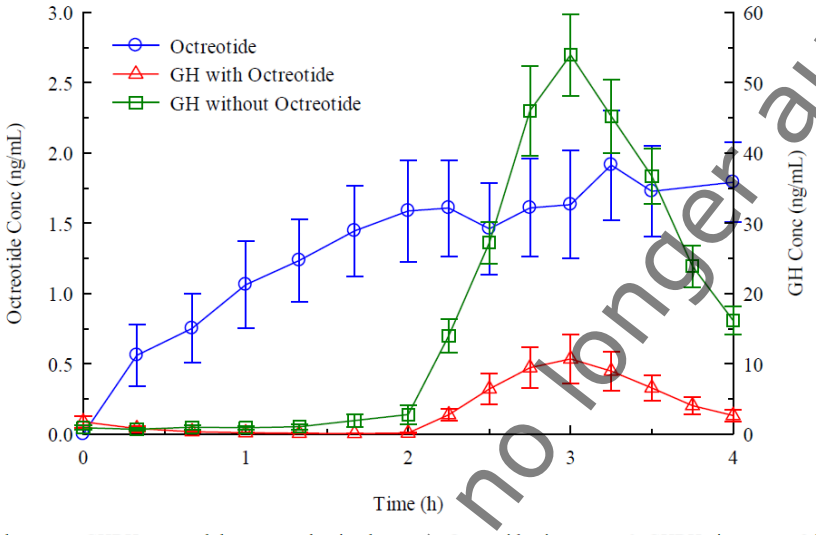
Primary and Secondary pharmacology

For octreotide capsules, a PK/PD study (**CHI-004**) was conducted in 24 volunteers to evaluate the PK of a single 20-mg dose and its effects on GH suppression. Inhibition of GH was recorded in all subjects receiving octreotide capsules. Administration of a single dose 20 mg dose of octreotide capsules results in an approximately 43% decrease in basal GH concentrations as well as an approximately 80% decrease in growth hormone releasing hormone (GHRH)-induced GH concentrations in healthy volunteers. A correlation was noted between octreotide exposure and a decrease in GH.

Figure 3.3.1.2. Mean ± Standard Error Plasma Concentrations of Octreotide and GH After GHRH-Arginine With and Without Octreolin.



GH= growth hormone; GHRH = growth hormone releasing hormone; Octreotide given at t = 0, GHRH given at t = 2 h
Source: Appendix 16.2.6; PK Report, p. 16

The effects of octreotide capsules on IGF-1 and GH levels were determined in study **CH-ACM-01** where the lack of PK/PD correlation was observed and explained by individual tumour characteristics (GH secretion and somatostatin receptors load and sensitivity, somatostatin receptor [SSTR] 2 and 5). In clinical practice, somatostatin analogue doses are not titrated to trough levels but titrated based on the individual response level.

In the Phase 3 studies in patients with acromegaly, octreotide capsules were effective as long-term maintenance therapy [both biochemical (IGF-1 and GH) and symptomatic control] in patients who have responded to and tolerated treatment with parenteral somatostatin analogues.

There does not appear to be an effect of octreotide on ΔQTcF over the range of concentrations observed in this study (Study CH-ACM-01).

Relationship between plasma concentration and effect

Relationship between plasma concentrations and effect was analysed during Studies CHI-004 (in HV) and ACM-01 (in ACM patients).

Study CHI-004

For octreotide capsules, a PK/PD study (CHI-004) was conducted in 24 volunteers to evaluate the PK of a single 20-mg dose and its effects on GH suppression. Inhibition of GH was recorded in all subjects receiving octreotide capsules.

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Administration of a single dose of octreotide capsules (20 mg) resulted in an approximately 44% decrease in basal GH concentrations as well as an approximately 80% decrease in GHRH-induced GH concentrations in healthy volunteers. Although variable, there was a trend toward an increased response, i.e. greater decrease in all GH exposure parameters, as exposure to octreotide increased.

Study CH-ACM-01

Assessments of the Phase 3 study CH-ACM-01 explored the relationship between achieved octreotide concentration (exposure) and therapeutic response (IGF-1 and GH serum levels), and the following observations were made:

• The arithmetic mean ± standard error serum GH concentrations were reasonably constant over the 2.5 to 4 hour period after dosing in all 3 dosing cohorts, with lower concentrations and mean values for average concentration (C_{av}) in the 40-mg cohort than in the 60-mg and 80-mg cohorts.

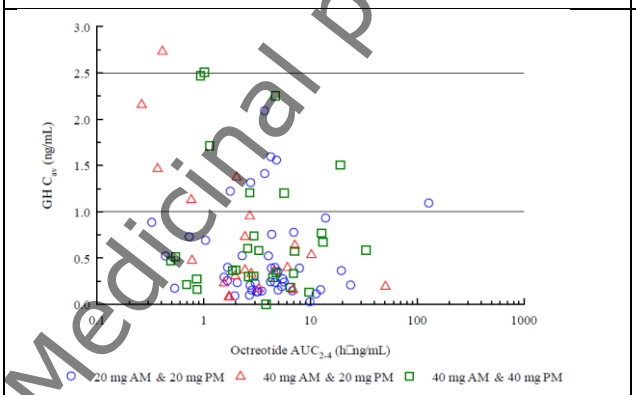
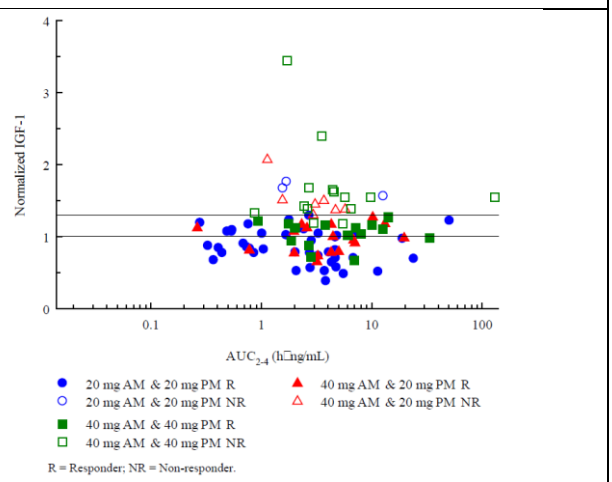
• There does not seem to be a relationship between GH C_{av} and octreotide AUC_{2-4}.

• There was no apparent relationship between normalised IGF-1 levels and octreotide AUC_{2-4} (at Visit TB6 (end of treatment [EOT] in core treatment phase) with almost complete overlap among the 3 cohorts — all evaluable patients, responders, and non-responders. (see Figure 3.3.1.3).

Within the PK substudy population, there were no apparent relationships between normalised IGF-1 levels and octreotide AUC_{0-t}, AUC_{0-4}, or AUC_{2-4} at Visit TB2 (i.e. after at least 2 months of receiving a therapeutic dose of octreotide capsules), with almost complete overlap among the 3 cohorts — all PK substudy population, responders and non-responders.

•The lack of PK/PD correlation is not unexpected, as response to octreotide is known to be correlated to individual tumour characteristics (GH secretion and somatostatin receptors load and sensitivity, somatostatin receptors [SSTR] 2 and 5).

Figure 2.2.7.2: Individual subject normalised IGF-1 levels and GH Cav at EOT (core) versus octreotide AUC2-4 at Visit TB6/EOT/ET after OOC administration of 40 mg as 20 mg BID, 60 mg as 40 mg AM & 20 mg PM, or 80 mg as 40 mg BID to patients with acromegaly

GH Cav	Normalised IGF-1
	

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Missing profiling of PD effect in ACM population. It is noted that the applicant observed a trend towards an increased response (in decrease in all GH exposure parameters) as exposure to octreotide increased in HV and no apparent PK/PD relationships in ACM patients after multiple administration. However, the majority of results were below the cut-off for both IGF-1 and GH markers. The applicant was asked to analyse proportions of factual achievement in pivotal study for both therapeutic PD effect as well as clinical symptoms of the disease, such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia, paraesthesia and reflect that in section 5.1 of SmPC. This issue was addressed by the applicant and was considered resolved.

2.10.3. Discussion on clinical pharmacology

The clinical pharmacology development programme for octreotide capsules consisted of 12 studies (11 clinical pharmacology studies and 1 Phase 3 study.

PK

The absolute bioavailability of Octreotide capsules 20 mg has not been determined in humans.

The applicant performed six studies where bioavailability was analysed in HV (Studies CHI-001, CHI-002, CHI-004, CHI-005, OCT-01 and OCT-02 and in one study in ACM (PK sub-study of Study CH-ACM-01). The sampling time is sufficient to describe bioavailability of both oral and comparator octreotide and AUCinf values.

Two comparative bioavailability (BA) bridging studies between octreotide capsules and sc Sandostatin IR 0.1-mg single injection were conducted (studies CHI-001 and CHI-002).

The PK of octreotide is linear after single-dose administration of octreotide capsules from 3 mg to 40 mg in healthy subjects under fasted conditions. The median time to maximum plasma concentration (Tmax) after oral administration of octreotide capsules 3 mg to 20 mg ranged from 0.67 to 1.67 hours and was not dose-dependent.

The studies with octreotide capsules 20 mg showed rather broad distribution of both Tmax and C max values. The applicant acknowledges that a capsule containing 20 mg of octreotide (calculated as free base) resulted in a systemic exposure (based on AUC) that was slightly higher than the exposure to a 0.1-mg dose sc Sandostatin IR. The mean time to maximal absorption values ranged from 1.67 to 3.54 hrs for capsules in HV and from 1 to 1.5 hrs in ACM for capsules. The mean time to mean maximal absorption seems clearly numerically longer as compared to ~0.5 hr for mean maximal absorption after SC formulations. However, the mean C max concentrations values were not so different and less numerically different between capsules and SC formulations, i.e., mean C max values after 20 mg were ranging from ~3 to 8.21 ng/mL after oral and ~3.5 ng/ml after SC formulation of 0.1 mg.

After correcting for dose, the octreotide apparent BA from fasted oral administration of octreotide capsules relative to sc Sandostatin IR was calculated as 0.63%.

In patients with acromegaly, there was a dose-related increase in the mean plasma octreotide concentrations after chronic administration of 40 mg (20 mg bid), 60 mg (40 mg morning / 20 mg evening), and 80 mg bid (study CH-ACM-01).

Octreotide capsules deliver octreotide to the small intestine and reversibly increase intestinal paracellular absorption without effecting transcellular absorption. The relative bioavailability of oral octreotide compared to sc octreotide was approximately 0.5%.

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Food, but not the ingested water volume, decreases the absorption of octreotide from octreotide capsules by 90%. Therefore, the octreotide capsules should be administered under fasting conditions (at least 1 hour before and 2 hours after a meal). Bioavailability was decreased by approximately 60% when octreotide capsules were administered 1 hour before a reduced size high fat meal. In the Phase 3 clinical studies in patients with acromegaly, octreotide capsules were effective when administered at least 1 hour prior to a meal and at least 2 hours after a meal. Therefore, the applicant proposed that octreotide capsules should be administered under fasting conditions (at least 1 hour before and 2 hours after a meal).

Uncertain method of administration. Study OCT-01 showed that bioavailability was decreased by approximately 87% (95% CI, from 5 to 40%) when octreotide capsules were administered 2 hours after full high fat meal. This finding might be the reason for such high variability of BA and thus does not support the initial proposal made for method administration. It was agreed that the administration should be limited to administration one hour before the meal.

Night dosing may result in decreased exposure (AUC) to octreotide capsules. Food, but not the ingested water volume, decreases the absorption of octreotide from octreotide capsules by 90%, when octreotide capsules were administered 2 hours after full high fat meal.

After sc injection, the volume of distribution of octreotide is 0.27 L/kg and the total body clearance 160 mL/min. Plasma protein binding amounts to 65%. The amount of octreotide bound to blood cells is negligible.

The elimination half-life after sc administration of octreotide is 100 minutes. After iv injection, the elimination is biphasic, with half-lives of 10 and 90 minutes. Most of the peptide is eliminated via the faeces, while approximately 32% is excreted unchanged into the urine. Considering all PK studies the half-life is longer that is consistent with delayed absorption of oral dosage form. The SmPC was amended accordingly.

The PK of octreotide is linear after single-dose administration of octreotide capsules from 3 mg to 40 mg in healthy subjects under fasted conditions.

Several factors were found that influence the PK of octreotide capsules:

(a) meal (high fat/high calorie meal decreases the systemic absorption of octreotide).

(b) body posture (administration of octreotide capsules at night in a semi-sitting position followed by lying resulted in a slower increase in the mean plasma concentrations and lower concentrations compared to the morning administration in the semi sitting position and administration of octreotide capsules in the morning in a standing position resulted in an average 40% decrease in the extent of absorption compared with the sitting position);

(c) interaction with cyclosporine (decreases the cyclosporine exposure and absorption);

(d) PPI treatment (esomeprazole use decreases the absorption of octreotide). Octreotide seems to decrease hydrochlorothiazide exposure, the rate of exposure of digoxin, and increases the exposure of lisinopril;

(e) renal function (exposure in subjects with severe renal impairment was lower than in the matched controls, while the patients with ESRD had an increased octreotide exposure).

Exposure between healthy subjects and patients with acromegaly was similar, but a longer half-life in patients with acromegaly than in healthy volunteers was observed.

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PD and PK/PD

For octreotide capsules, a PK/PD study (CHI-004) was conducted in 24 volunteers to evaluate the PK of a single 20-mg dose and its effects on GH suppression. Inhibition of GH was recorded in all subjects receiving octreotide capsules. Administration of a single dose 20 mg dose of octreotide capsules resulted in an approximately 43% decrease in basal GH concentrations as well as an approximately 80% decrease in growth hormone releasing hormone (GHRH)-induced GH concentrations in healthy volunteers.

The effects of octreotide capsules on IGF-1 and GH levels were determined in study CH-ACM-01 where the lack of PK/PD correlation was observed. In clinical practice, somatostatin analogue doses are not titrated to trough levels but titrated based on the individual response level.

In the Phase 3 studies in patients with acromegaly, octreotide capsules were effective as long-term maintenance therapy [both biochemical (IGF-1 and GH) and symptomatic control] in patients who have responded to and tolerated treatment with parenteral somatostatin analogues.

Assessments of the Phase 3 study CH-ACM-01 explored the relationship between achieved octreotide concentration (exposure) and therapeutic response (IGF-1 and GH serum levels), and the following observations were made:

• The arithmetic mean ± standard error serum GH concentrations were reasonably constant over the 2.5 to 4 hour period after dosing in all 3 dosing cohorts, with lower concentrations and mean values for average concentration (Cav) in the 40-mg cohort than in the 60-mg and 80-mg cohorts

• There does not seem to be a relationship between GH Cav and octreotide AUC2-4.

• There was no apparent relationship between normalised IGF-1 levels and octreotide AUC2-4 (at Visit TB6 (end of treatment [EOT] in core treatment phase) with almost complete overlap among the 3 cohorts — all evaluable patients, responders, and non-responders.

Within the PK sub-study population, there were no apparent relationships between normalised IGF-1 levels and octreotide AUC0-t, AUC0-4, or AUC2-4 at Visit TB2 (i.e. after at least 2 months of receiving a therapeutic dose of octreotide capsules), with almost complete overlap among the 3 cohorts — all PK sub-study population, responders and non-responders.

The lack of PK/PD correlation is not unexpected, as response to octreotide is known to be correlated to individual tumour characteristics (GH secretion and somatostatin receptors load and sensitivity, somatostatin receptors [SSTR] 2 and 5).

The issue of missing profiling of PD effect in ACM population was raised and the applicant was asked to analyse proportions of factual achievement in pivotal study for both therapeutic PD effect as well as clinical symptoms of the disease, such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia, paraesthesia. This was also reflected in section 5.1 of SmPC.

2.10.4. Conclusions on clinical pharmacology

Available data do support certain minimal bioavailability and PD effect to those patients who responded to oral administration after the switch from s.c. formulation. Mycapssa was considered acceptable from clinical pharmacology point of view.

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2.10.5. Clinical efficacy

Three clinical Phase 3 studies in patients with acromegaly contributed to the evaluation of the efficacy of octreotide capsules and those are listed in **Table 3.3.4.**

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Table 3.3.4. Clinical Phase 3 studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
OOC-ACM-302 Phase 3	29 centres in Europe and United States (AU, FR, GE, LI, RU, SB, SP, UK, US)	Randomised, open-label, active-controlled, preceded by a run-in phase, followed by an OLE phase	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)	Efficacy, safety	146 (RCT phase: 92) Octreotide capsules: 55 SRL injections: 37	11 Feb 2016 to 08 Sep 2020 (RCT phase; OLE ongoing)	The mean age at screening was 54.1 years (range: 28 to 73 years), 64.4% of patients were female.	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	Proportion of patients who were biochemically controlled1 throughout the RCT phase: Octreotide capsules: 90.9% SRL injections: 100% Adjusted2 difference in proportions:

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									-9.1 (95% CI: -19.9, 0.5)
OOC-ACM-303 Phase 3	34 centres in Europe, North America, Asia, and Australia/ New Zealand (AU, BU, CA, DE, GE, HU, IS, IT, LA, NE, NZ, PO, SL, SW, TU, UK, US)	Randomised, double-blind, placebo-controlled, followed by an OLE phase	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)	Efficacy, safety	DPC phase: Total: 56 Octreotide capsules: 28 Placebo: 28 OLE phase: 40	30 Aug 2017 to 13 Jun 2019 (DPC phase; OLE ongoing)	The mean age was 55.3 years (range: 30 to 79 years) in the octreotide capsule group and 54.2 years (range: 38 to 73 years) in the placebo group. 16 patients [57.1%] in the octreotide	Acromegaly patients currently receiving injectable somatostatin analogues, who are responders to treatment (IGF-1 ≤ 1 × ULN)	Proportion of patients who maintained their biochemical response (average of last 2 IGF-1 assessments) ≤1 x ULN at the end of the DPC phase: Octreotide capsules: 58.2% Placebo: 19.4% p = 0.0079

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							capsule group and 14 patients [50.0%] in the placebo group were female.		
CH-ACM-01 Phase 3	34 centres in Europe, Israel, and Mexico (GE, HU, IS, IT, LI, ME, NE, PO, RO, SB, SK, SL, UK)	Single-arm, baseline-controlled, followed by an OLE phase	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)	Efficacy, safety	Core treatment phase: Total: 155 Octreotide capsules: 155 OLE phase: 88	13 Mar 2012 to 26 Nov 2013 (core phase; completion of OLE phase: 30 May 2014)	The mean age at screening was 54.2 years (range: 22 to 73 years) and 56.8% of patients were female.	Acromegaly patients currently receiving injectable somatostatin analogues, who are responders to treatment (IGF-1 < 1.3 x ULN and GH < 2.5 ng/mL)	Proportion of responders (IGF-1 <1.3 × ULN and GH <2.5 ng/mL) at the end of the core treatment phase: Octreotide capsules: 64.9% (95% CI: 58.4 - 74.2)

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The applicant performed two concurrently controlled (one with active control and one with placebo control) and one baseline controlled pivotal studies that is in line with ICH E8 provisions and thus it is acceptable.

2.10.5.1. Dose response studies

During the three clinical Phase 3 studies in patients with acromegaly that were designed for the evaluation of the efficacy of octreotide capsules a dose escalation part was an integral part. No formal dose response studies were performed. This is acceptable, considering dose titration approach employed in all three pivotal clinical confirmatory studies.

2.10.5.2. Main studies

Three clinical Phase 3 studies in patients with acromegaly contribute to the evaluation of the efficacy of octreotide capsules: OOC-ACM-302, a randomised, open-label, active-controlled, preceded by a run-in phase, followed by an OLE phase study, OOC-ACM-303, a randomised, double-blind, placebo-controlled, followed by an OLE phase, and CH-ACM-01 a single-arm, baseline-controlled, followed by an OLE phase. Thus, the applicant performed two concurrently controlled (one with active control and one with placebo control) and one baseline controlled pivotal studies that is in line with ICH E8 provisions and thus it is acceptable.

- **Methods**

Study OOC-ACM-302

Design

Study OOC-ACM-302 was a randomised, open-label, active-controlled, multicentre study (Core Study) with two sub-studies (Combination Phase sub-study and Withdrawal Phase sub-study) with Open Label Extension phase, OLE (see Figure 3.3.4.2.1 below). This core study will be discussed as one of main studies for this application and it was designed to evaluate maintenance of response, safety, and PROs in acromegaly patients treated with octreotide capsules and in patients treated with standard of care injectable SRLs, who previously tolerated and demonstrated a biochemical control on both treatments.

Eligible patients had a confirmed diagnosis of acromegaly, had been treated with SRL injections (octreotide 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 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 (see below), 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.

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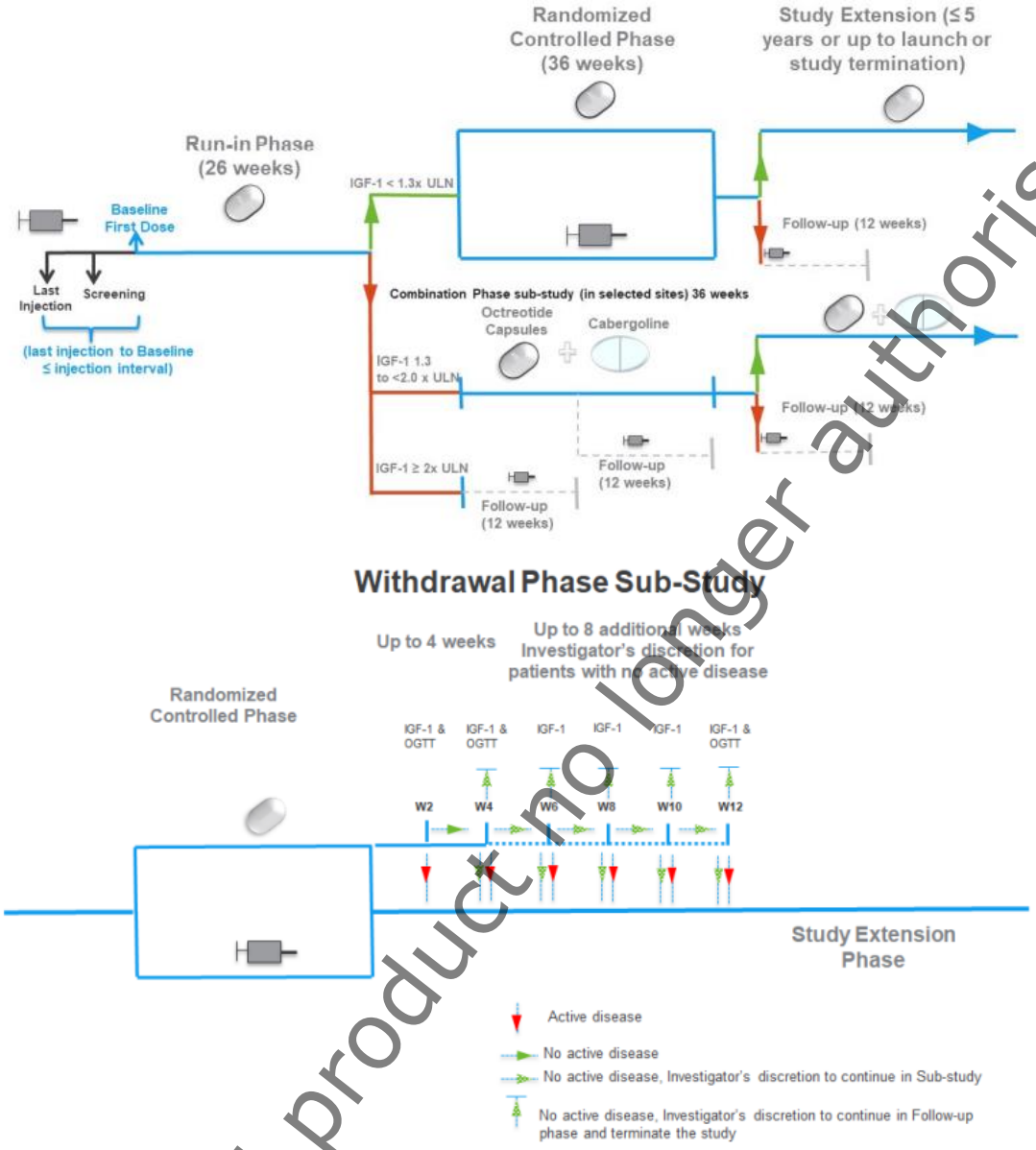
Figure 3.3.4.2.1: Study OOC-ACM-302 overview – Core Study Plus Combination, Follow-up, and Study Extension Phase



Location and settings

Fifty-six study sites were initiated. Twenty-nine study sites in Austria, France, Germany, Hungry, Italy, Lithuania, Russian Federation, Serbia, Spain, and the US enrolled at least 1 patient into the Run-in phase. The trial was conducted in hospitals and university hospitals.

The main pivotal study is based on concurrently controlled with active control arm study (Study 302). The design of this study is enriching the ACM population by excluding non-responders after the switch from parenteral Sandostatin to oral octreotide.

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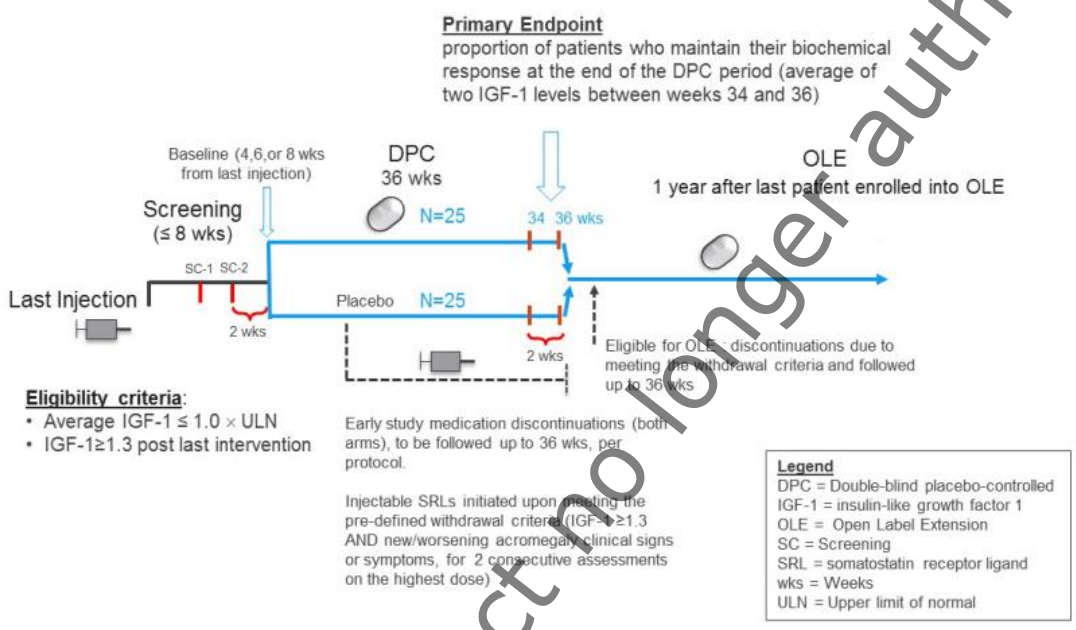
Study OOC-ACM-303

Design

Study OOC-ACM-303 was a phase 3, randomised, double-blind, placebo-controlled (DPC) multicentre study with Open Label Extension phase, OLE (see Figure 3.3.4.2.2) to evaluate the efficacy and safety of octreotide capsules in acromegaly patients who previously tolerated and demonstrated biochemical control on injectable SRL treatment.

Figure 3.3.4.2.2: Study OOC-ACM-303 overview – Core Study Plus Study Open Label Extension Phase



Study CH-ACM-01

Design

The study CH-ACM-01 was a single-arm, open-label, baseline-controlled, multicentre study with 3 (three scenarios for temporal relationships between SRL and Mycapssa (see Figures 3.3.4.2.3 and 3.3.4.2.4). It was designed to evaluate the efficacy and safety of octreotide capsules in patients with acromegaly who responded to and tolerated treatment with somatostatin analogues.

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Figure 3.3.4.2.3: Study OOC-ACM-303 overview – Core Study Plus Study Open label Extension Phase

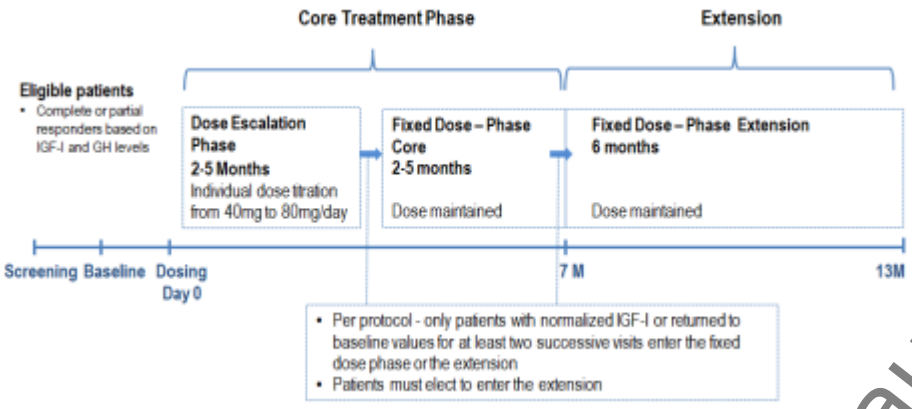
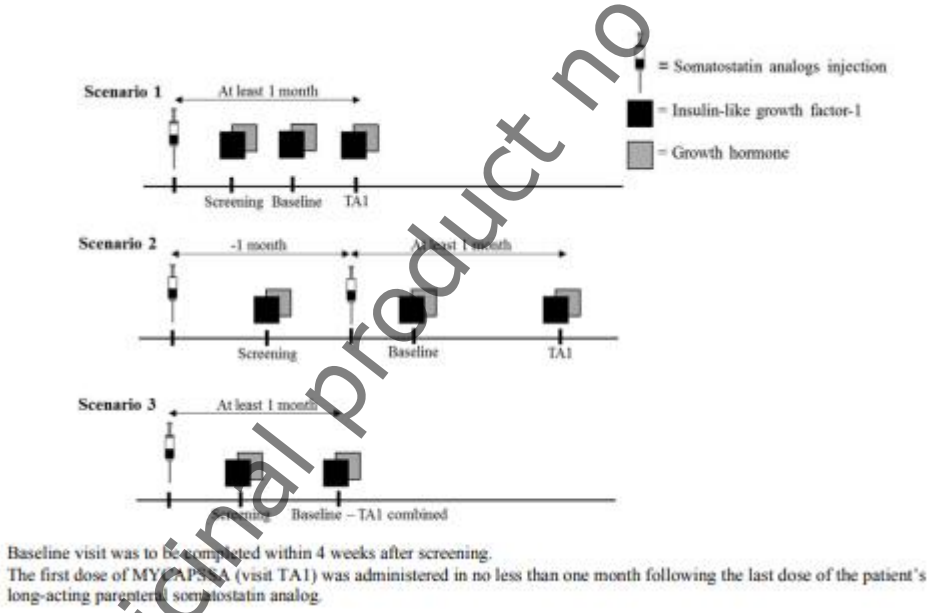


Figure 3.3.4.2.4: Study OOC-ACM-303 overview – Core Study Plus Study Open label Extension Phase



- **Study Participants**

Study OOC-ACM-302

Inclusion/exclusion criteria

Adults 18 to 75 years of age with acromegaly (defined as documented evidence of GH-secreting pituitary tumour that is abnormally responsive to an oral glucose tolerance test or abnormal IGF-1 levels [> 1 times ULN], any time in the past), who were currently receiving parenteral SRLs (octreotide or lanreotide but not pasireotide) for at least 6 months, with a stable dose for at least 4 months, and

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who were biochemically controlled (IGF-1 < 1.3 times ULN and mean integrated GH < 2.5 ng/mL over 2 hours) at screening, were included in this study. Patients were excluded if were taking injections of long-acting SRLs less frequently than once every 8 weeks, or being treated with pegvisomant, dopamine, pasireotide, recent radiotherapy or recent pituitary surgery, with cholelithiasis, high-risk pattern of pituitary tumour location, unstable angina or acute myocardial infarction, other clinically significant uncontrolled disorders (nervous system, GI, renal, pulmonary, diabetes), allergy or hypersensitivity to any of the test compounds or materials.

Study OOC-ACM-303

Inclusion/exclusion criteria

Main inclusion criteria were adults ≥ 18 years of age with active acromegaly (defined as documented evidence of GH-secreting pituitary tumour based on magnetic resonance imaging [MRI]/ pathology report and documented evidence of IGF-1 levels ≥ 1.3 times ULN) who, at screening, were receiving parenteral SRL monotherapy for at least 6 months with a stable dose for at least the last 3 months and who had an average IGF-1 of 2 assessments obtained during the Screening period of ≤ 1 times ULN. Main exclusion criteria: patients taking injections of long-acting SRLs off label (unlabelled doses or dosing interval; e.g., 60 or 90 mg lanreotide every 8 weeks or 30 mg octreotide every 6 or 8 weeks), patients with cholelithiasis, radiotherapy any time in the past, recent pituitary surgery, high-risk pattern of pituitary tumour location, unstable medical condition (acute myocardial infarction, nervous system, GI, renal, pulmonary, or hepatic concomitant disease), known allergy or hypersensitivity to any of the test compounds or materials, or failure to comply.

Study CH-ACM-01

Inclusion/exclusion criteria. Adult patients diagnosed with acromegaly who, at screening, were receiving a stable dose of a parenteral SRL for at least 3 months and who were considered responders to their therapy were eligible for this study. Patients with cholelithiasis, recent pituitary radiotherapy or pituitary surgery, high-risk pattern of pituitary tumour location, tumour with neurologic sequalae, unstable medical condition (renal, hepatic or other, including recent unstable angina or acute myocardial infarction), or otherwise frail and/or non-compliant were excluded from this study.

The populations were defined appropriately to represent controlled stable non-tumour origin acromegaly treatment indication in the maintenance phase. Although patient across all 3 pivotal studies differed as regards previous therapies (radio-, or surgical) in general eligibility criteria represent target population for the proposed indication.

- **Treatments**

Study OOC-ACM-302

Test drug: Octreotide capsules (MYCAPSSA®) were titrated during the Run-in phase from 40 mg (20 mg twice daily; bid) to 60 mg/day (40 mg in the morning and 20 mg in the evening/night) to 80 mg/day (40 mg bid), based on clinical and biochemical response. Octreotide capsules were to be administered bid with a glass of water (240 mL) on an empty stomach (ie, at least 1 hour prior to a meal or at least 2 hours after a meal). Cabergoline (up to 3.5 mg/week per a fixed titration algorithm) was co-administered with octreotide capsules 80 mg in the Combination phase sub-study. Patients participating in the Combination phase sub-study continued to receive cabergoline (up to 3.5 mg/week) with octreotide capsules during the Study Extension phase. Reference drug: standard of care injectable SRL (octreotide long-acting release [LAR] or lanreotide) according to the individual patient use prior to enrolment in the study. The SRLs were provided as injectable suspension.

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Study OOC-ACM-303

Test drug: Mycapssa (octreotide capsule). During the DPC period, octreotide treatment was started at a total dose of 40 mg per day (for patients randomised to the octreotide capsule group); it was taken orally in 2 doses: one 20 mg capsule in the morning and one 20 mg capsule in the evening/night. Dose escalation was based on measurement of the patient's circulating IGF-1 levels and acromegaly-related symptoms. Dose escalation was performed in a stepwise manner from 1 capsule twice daily (bid; equivalent to 40 mg/day), to 2 capsules in the morning and 1 capsule in the evening/night (equivalent to 60 mg/day), to 2 capsules bid (equivalent to 80 mg/day). Patients were instructed to take the study drug with a glass of water (240 mL) on an empty stomach (ie, at least 1 hour prior to a meal or at least 2 hours after a meal).

Study CH-ACM-01

Test drug: Oral octreotide acetate, 20 mg, in an enteric-coated capsule (MYCAPSSA). Oral octreotide treatment was started at a total dose of 40 mg per day; it was to be taken by mouth in two doses: 20 mg in the morning and 20 mg in the evening/night. Patients were instructed to take the study medication at least 1 hour prior to a meal and at least 1 to 2 hours after a meal.

In all 3 studies starting dose was the same (40 mg) with somewhat different instruction for method of administration - patients were instructed to take the study drug with a glass of water (240 mL) on an empty stomach i.e., at least 1 hour prior to a meal or at least 2 hours after meal in Studies 302 and 303 and (as it is proposed in MAA) whereas "at least 1 hour prior to a meal and at least 1 to 2 hours after a meal". This is acceptable as far, as for main studies that are Studies 302 and 303. Study ACM-01 contributes as exploratory study only.

- **Objectives**

Study OOC-ACM-302. 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 Randomised, Controlled Treatment (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).

Study OOC-ACM-303. The primary objective of this study was to assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly who previously demonstrated biochemical control on SRLs.

Study CH-ACM-01. The main objective of this study was to evaluate the efficacy and safety of MYCAPSSA as maintenance therapy in patients with acromegaly who were responders to a stable dose of a parenteral SRLs. Additional objectives were to assess treatment satisfaction with parenteral somatostatin analogues vs. oral therapy and to determine the PK profile of MYCAPSSA during chronic treatment.

The objectives of the Studies are focused on assessment of comparative maintenance of biochemical control (in studies 302 and 303) vs baseline maintenance. Study 302 objective does comply with EMA SA given to the applicant and thus is acceptable for confirmatory purpose.

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- **Outcomes/endpoints**

Study OOC-ACM-302

The primary efficacy endpoint (in line with EMA SA) was the proportion of patients who were biochemically controlled throughout the RCT phase. A patient was considered biochemically controlled if his or her IGF-1 time weighted average (TWA) during the RCT phase was < 1.3 times ULN.

The use of TWA response over time is a simple longitudinal data analysis approach intended to minimise the number of missing patients from a primary effectiveness analysis and to account for natural variation among the measure of interest that may be observed over the time period of monitoring. The TWA response over the treatment period represents an integrated measure of efficacy across time. It is derived as the area under the curve (AUC) divided by the total amount of time under observation between the first and last IGF-1 value.

The applicant also included additional primary endpoints for in line with the request from the FDA (hereinafter referred to as exploratory landmark analyses) those were as follows:

• Run-in phase – Proportion of patients biochemically controlled at the end of the Run-in phase, defined as IGF-1 < 1.3 times ULN (based on the average of week 24 and week 26)

• RCT phase – Proportion of patients on octreotide capsules who were biochemically controlled at the end of the RCT phase, defined as IGF-1 < 1.3 times ULN (based on the average of week 62 and week 58).

Secondary Efficacy Endpoints

The secondary efficacy endpoints were as follows:

1. The proportion of patients who were biochemically controlled throughout the RCT phase (IGF-1 TWA during the RCT phase was < 1.3 times ULN);
2. Proportion of patients with clinical and biochemical response at the end of the RCT phase (week 62/EOT). Patients were considered controlled if they met both of the following criteria: a) Biochemically controlled if their IGF-1 TWA during the RCT phase was < 1.3 times ULN; b) Clinically controlled if their AIS score at week 62/EOT was maintained or reduced compared to week 26 (start of RCT phase);
3. Proportion of patients who maintained or reduced the overall number of active acromegaly symptoms at the end of the RCT phase (week 62/EOT) compared to week 26 (start of RCT phase);
4. Proportion of patients who maintained or improved their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least 1 point in the AIS score), compared to week 26 (start of RCT phase);
5. Change from baseline (week 36) in Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ) scale scores at the end of the RCT phase;
6. Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country) who entered the Study Extension phase, overall and by treatment group;
7. Change in IGF-1 from the start of the RCT phase (week 26) through the end of the RCT phase (week 62);
8. Change in mean integrated GH from the start of the RCT phase (week 26) to end of the RCT phase (week 62);

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9. Shift in response categories at the end of the RCT phase (week 62/EOT) compared to week 26 (start of RCT phase).

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.

Several PRO questionnaires were used as well: Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ); EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L) and The Work productivity questionnaire (WPAI).

Study OOC-ACM-303

The primary efficacy endpoint was the proportion of patients who maintained their biochemical response at the end of the DPC phase. Maintenance of response was defined by using the average IGF-1 level of the last 2 available assessments (analysed centrally) between Weeks 34 and 36 in the DPC phase. If the average IGF-1 was ≤1 x ULN, a patient was classified as a responder (i.e. maintained their biochemical response). If the average IGF-1 was >1 x ULN, a patient was classified as a non-responder. Patients who discontinued study drug during the DPC phase for any reason were classified as non-responders for the primary analysis, regardless of their IGF-1 values.

Study CH-ACM-01

The primary efficacy endpoint was: Concentrations of IGF-1 and mean GH over 2 hours at the end of the Core Treatment Period as a measure of response in the modified Intention-to-Treat (mITT) Population. Response was defined as IGF-1 < 1.3 times ULN adjusted for age and an integrated GH levels over 2 hours < 2.5 ng/mL.

The chosen primary endpoints are clinically meaningful, in line with EMA SA given for pivotal confirmatory purpose in the planned indication (in Study 302) and are therefore endorsed.

- **Sample size**

Study OOC-ACM-302. The sample size was determined based on the CHMP advice to include 150 patients to be enrolled into the Run-in phase of the study to ensure a minimum of 80 patients would enter the RCT phase, with approximately 48 patients assigned to octreotide capsule arm and 32 patients assigned to SRL injection arm. The CHMP also recommended an unbalanced randomisation (3:2) to maximise data collected from treatment with octreotide capsules in the comparative setting and enhance the octreotide capsule treatment safety database. An assessment of non-inferiority (NI) was made by comparing the lower bound of the 2-sided 95% CI for the difference in biochemical control (octreotide capsules - SRL) to a NI margin of -20%, based on prior studies with SRLs that showed maintenance of response between 80-90% as well as on information provided in the Cerdelga® European Public Assessment Report (EPAR) where the EMA accepted a -20% NI margin for Cerdelga, an oral drug, compared to an injectable drug in an orphan population (Gaucher disease).

Study OOC-ACM-303. The *ex-ante* power was determined based on an assumed sample of 50 patients, with 25 in each arm. Power was determined to be at least 80% even under conservative assumptions of a 10% false-response and 50% true response rate (lower than even in the initial trials). The final study sample was a bit larger with 56 total. An assessment of superiority was made using an exact logistic regression model, with covariates for treatment, baseline SRL dose (low vs mid or high) and baseline IGF-1 level (<median vs ≥median).

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Study CH-ACM-01. This was an open-label study control used to establish the safety profile and maintenance profile of the drug. A total of 155 patients were enrolled. Experts in the field determined that the response rate of 50% would be reasonable, and statistical calculations bore out that this size would exhibit sufficient power. At least 150 evaluable patients were to be enrolled in this study.

The approaches used for determining sample size in the OOC-ACM-302, OOC-ACM-303, CH-ACM-01 study were appropriate given the information at the time and are endorsed.

- **Randomisation and Blinding (masking)**

Study OOC-ACM-302. Patients using SRLs who completed the 6-months run-in phase (116 [79,5%]) were randomised into the treatment group. 30 patients (20.5%) discontinued. Most frequent reasons for discontinuation during the run in phase were treatment failure (5.5%) and adverse events (9.6%; mostly mild to moderate gastrointestinal events). The odds of being randomised decreased with increasing IGF-1 level. The CHMP recommended an unbalanced 3:2 randomisation as well. The study utilised a centralised stratified randomisation based on the following variables on week 24 of the Run-in phase: (1) IGF-1 ≤ 1 times ULN vs IGF-1 > 1 times ULN to < 1.3 times ULN and (2) Octreotide capsule treatment dose at week 24 (40 mg vs 60 mg or 80 mg). This was an open-Label study.

Study OOC-ACM-303. Patients were randomised in a 1:1 ratio across all centres. Patients were stratified by previous treatment dosing level (low or mid/high). This was a double-blind, placebo-controlled study. Treatment allocation was not revealed before database lock, after the last patient had completed the DPC period.

Study CH-ACM-01 Randomisation was not appropriate for the study objective, which was to demonstrate long-term safety and maintenance characteristics of the treatment. This was an open-Label study.

The randomisation methods in the two pivotal trials (Study 302 and 303) were appropriate given their different objectives (active comparison, causality and efficacy, safety and maintenance). The approaches are endorsed. The blinding, where it was applied, was done so appropriately.

- **Statistical methods**

Study OOC-ACM-302

This study was an actively controlled multi-centre RCT for patients with acromegaly between 18 and 75 years of age, who were biochemically controlled under SRL exhibiting an IGF-1 < 1.3 ULN and GH < 2.5 ng/mL over 2 hours. 135 patients entered in the run-in phase, 81 remained in the RCT phase, with 34 in the control group, and 47 in the treatment group. Additional subgroup analysis was performed for gender, region, age, baseline characteristics.

The primary endpoint was the proportion of patients who were biochemically controlled; this mirrors the common practice of monitoring patients' IGF using SRL.

The test of the primary end-point was non-inferiority margin at the 20% level at 95% confidence, adjusted for baseline values using the Miettinen & Nurminen method.

No interim analyses of efficacy were planned, but there were interim safety analyses done to comply with FDA practices.

The population, surrogate endpoint under active control, and NI inferiority level are appropriately chosen. The statistical approach for study OOC-ACM-302 is endorsed.

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Study OOC-ACM-303. This study looks at whether the proportion of patients in the treatment group maintaining biochemical response differs from the placebo control. Given baseline differences in IGF-1 and response, the proportions of where adjusted using logistic regression. The study uses Newcombe's proportion test to determine the adjusted proportions.

The population, placebo control, and endpoint measurement are appropriately chosen. While the covariate adjustment using logistic regression (rather than sufficiently sized subgroups) is less than ideal, it is statistically reasonable. The statistical approach for study OOC-ACM-303 is acceptable for showing clinical efficacy in maintenance.

Study CH-ACM-01. This study looks at the proportion of responders at end of treatment. Subgroup analysis included age, gender, and renal function, which was appropriate given safety as a primary motivation for the study.

Worth noting are the number of patients withdrawing and resuming their baseline treatment. The sponsor was requested to specify the proportion test or method of constructing the confidence intervals used to assess the primary endpoint in CH-ACM-01. The Clopper-Pearson (Exact) method was used to estimate the 95% confidence intervals for the primary endpoint in study CH-ACM-01. This was considered acceptable.

The statistical approaches were endorsed.

Results

- **Participant flow**

Study OOC-ACM-302

From the 146 patients enrolled into the 26-week Run-in phase (see Table 3.3.4.2.1 and Figure 3.3.4.2.4) and who received at least 1 dose of study drug (octreotide capsules), a total of 116 patients (79.5%) completed the Run-in phase and 30 patients (20.5%) discontinued the Run-in phase. Reasons for discontinuation were TEAE (14 patients [9.6%]); treatment failure (8 patients [5.5%]), 3 of whom entered the Combination phase; withdrawal by patient (6 patients [4.1%]); Investigator request (1 patient, 0.7%]); and protocol deviation (1 patient, 0.7%]).

Of the 116 patients who completed the Run-in phase, 92 patients (79.3%) entered the RCT phase, 11 (9.4%) entered the Combination phase, and 13 (11.2%) did not continue treatment. Eleven of the 13 patients who did not continue treatment were ineligible for the RCT phase or Combination phase.

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Table 3.3.4.2.1. Patient Disposition During the OOC-ACM-302 Core Study

	Octreotide Capsule Treatment (Final Dose)			
	40 mg (N = 53) n (%)	60 mg (N = 34) n (%)	80 mg (N = 59) n (%)	Overall (N = 146) n (%)
Enrolled in Run-in phase	53	34	59	146
Discontinued from Run-in phase	12 (22.6)	6 (17.6)	12 (20.3)	30 (20.5)
Reason for discontinuation				
Adverse event	11 (20.8)	3 (8.8)	0	14 (9.6)
Investigator request	0	0	1 (1.7)	1 (0.7)
Withdrawal by patient	1 (1.9)	2 (5.9)	3 (5.1)	6 (4.1)
Treatment failure	0	0	8 (13.6)	8 (5.5)
Entered the Combination phase	0	0	3 (5.1)	3 (2.1)
Discontinued study	0	0	5 (8.5)	5 (3.4)
Protocol deviation	0	1 (2.9)	0	1 (0.7)
Completed Run-in phase	41 (77.4)	28 (82.4)	47 (79.7)	116 (79.5)
Entered RCT phase	39 (73.6)	25 (73.5)	28 (47.5)	92 (63.0)
Entered Combination phase	0	0	11 (18.6)	11 (7.5)
Did not continue treatment	2 (3.8)	3 (8.8)	8 (13.6)	13 (8.9)
Not eligible for RCT phase and eligible to Combination phase	0	0	0	0
Eligible for RCT phase	1 (1.9)	1 (2.9)	0	2 (1.4)
Not eligible for RCT phase or Combination phase	0	1 (2.9)	4 (6.8)	5 (3.4)
Not eligible for RCT phase and Combination phase not applicable	1 (1.9)	1 (2.9)	4 (6.8)	6 (4.1)
Entered Follow-up	14 (26.4)	9 (26.5)	17 (28.8)	40 (27.4)
Due to treatment discontinuation	12 (22.6)	6 (17.6)	9 (15.3)	27 (18.5)
Completed Run-in and did not continue into RCT or Combination phase	2 (3.8)	3 (8.8)	8 (13.6)	13 (8.9)
Completed Follow-up	9 (17.0)	6 (17.6)	13 (22.0)	28 (19.2)
Discontinued Follow-up	5 (9.4)	3 (8.8)	4 (6.8)	12 (8.2)

Percentages were based on the number of enrolled patients.
If insulin-like growth factor 1 (IGF-1) was < 1.3 times the upper limit of normal and mean growth hormone (GH) was < 2.5 ng/mL, then the patient was eligible for the RCT phase. If (2 ≥ IGF-1 ≥ 1.3) or (< IGF-1 < 1.3 and mean GH ≥ 2.5) then the patient was eligible for the Combination phase. Other patients who completed the Run-in phase and did not meet IGF-1 and mean GH criteria were not eligible for the RCT and Combination phases.
EAS = Enrolled Analysis Set; RCT = Randomized, Controlled Treatment
Source: Post-text Table 14.1.1.2 and Listing 16.2.1.2

Of the 55 patients assigned to the octreotide capsule group, 54 patients (98.2%) completed the RCT phase and 1 patient (1.8%) discontinued treatment due to a TEAE. 34 patients (63.0%) elected to continue into the Study Extension phase. Of the 37 patients assigned to the SRL injection group, 35 patients (94.6%) completed the RCT phase. Two patients chose to withdraw from the study during the RCT phase for personal reasons.

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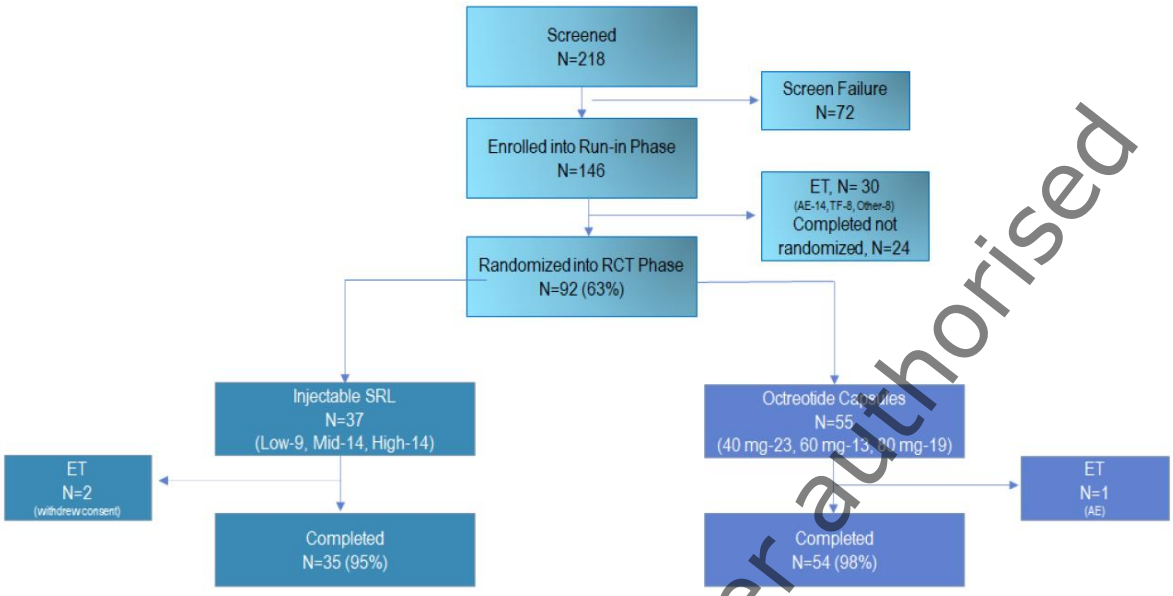
Figure 3.3.4.2.5. Patient Disposition During the OOC-ACM-302 Core Study

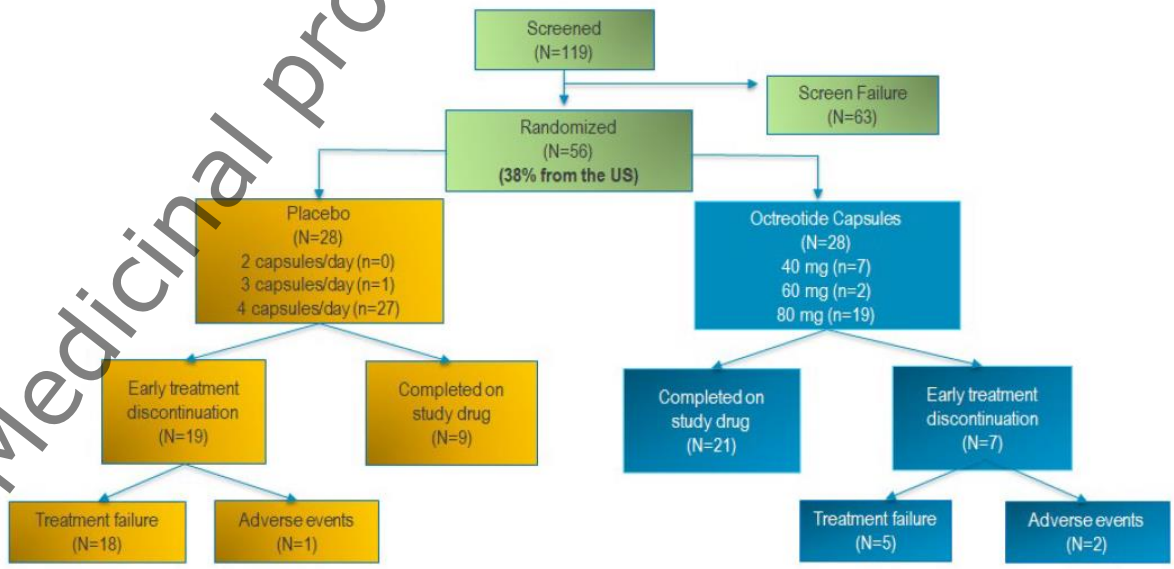


AE = adverse event; ET = early termination; RCT = randomized, controlled treatment; SRL = somatostatin receptor ligand; TF = treatment failure

Study OOC-ACM-303

A total of 119 patients were screened for this study (see Figure 3.3.4.2.6.). Fifty-six patients (47.1%) completed the screening; 28 were randomly assigned to the octreotide capsule group and 28 were randomly assigned to the placebo group. All 56 enrolled patients completed the DPC period. Thirty patients completed the DPC period on study drug (21 patients [75.0%] in the octreotide capsule group and 9 patients [32.1%] in the placebo group). Overall, 26 patients discontinued study drug treatment during the DPC and required rescue medication (7 patients [25.0%] in the octreotide capsule group and 19 patients [67.9%] in the placebo group).

Figure 3.3.4.2.6 Patient Disposition During the Core Study OOC-ACM-303



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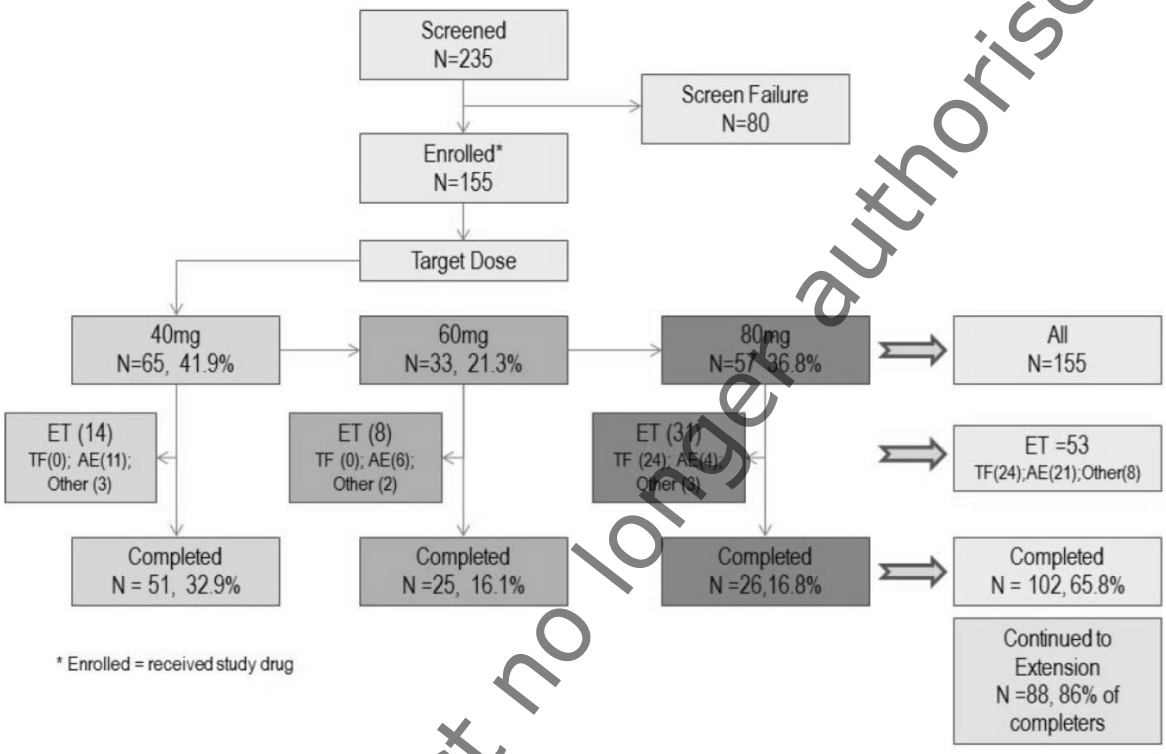
Study CH-ACM-01

Two hundred and thirty-five patients were screened for this study (see Figure 3.3.4.2.7); of these patients, 155 were enrolled for participation.

Figure 3.3.4.2.7. Patient Disposition During the Core Treatment Period Study CH-ACM-01



AE = adverse event; ET = End of Core Treatment; TF = treatment failure
Source: Post-text Tables 14.1.1, 14.1.2, 14.1.3, 14.1.8

Patients were involved into the core studies as per sample size required in all three pivotal studies. Participant flows shows consistent high treatment discontinuation rate across all three trials due to treatment inefficacy and adverse events.

1. In the study OOC-ACM-302 a total of 116 patients (79.5%) completed the Run-in phase and 30 patients (20.5%) discontinued the Run-in phase. Reasons for discontinuation were TEAE (14 patients [9.6%]); treatment failure (8 patients [5.5%]). Of the 55 patients assigned to the octreotide capsule group, 54 patients (98.2%) completed the RCT phase and 1 patient (1.8%) discontinued treatment due to a TEAE.

2. In the study OOC-ACM-303 twenty-six patients discontinued study drug treatment during the DPC period and required rescue medication (7 patients [25.0%] in the octreotide capsule group and 19 patients [67.9%] in the placebo group).

3. In the study CH-ACM-01, sixteen patients discontinued early during the Dose Escalation Phase due to adverse events; 10 of those early terminations were due to GI side effects.

Unknown real failure rate after switching in study 302. The enrichment design applied to RCT Phase from Run-in Phase (EAS) excluded 8 Mycapssa treatment failures and unknown number of treatment failures from the 14 patients withdrawn due to ADR and 24 patients who completed Run-in

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Phase but were excluded from RCT phase and entered into combination phase. The individual IGF-1 and GH test results could not initially be retrieved from the application. The applicant has provided the requested data. The data from the Run-in phase suggest that ~64% to 78% of patients will respond to treatment with octreotide capsules.

Possibly too low comparative efficacy due to high withdrawal rate during switch (run-in) period. One fifth of patients (30/116) discontinued from the switch period of Study 302. More than half of discontinued patients were due to TEAE (14 patients) or treatment failures (8 patients). Although primary analysis is performed from all of the 55 patients assigned to the octreotide capsule group, this approach is not representative to future clinical use, where efficacy should be known before switching to alternative treatment. The applicant is asked to address the issue of limited efficacy after the switch. About 30-40% of patients switching from SRL to Mycapssa loose biochemical control and are considered to be non-responders. The applicant was requested to justify the acceptability of this responder rate and to analyse whether non-responders can be identified based on their demographic/disease characteristics in order to refine the target population to avoid futile switches. This issue was addressed by the applicant and is currently considered as resolved. This medicinal product can be beneficial for patients who respond to octreotide capsules and reduce the need for injections and associated inconveniences. The patients that fail the oral therapy trial can be reverted to injectable treatment options.

- **Recruitment**

Study OOC-ACM-302. Initiation Date: 11 February 2016 (first site initiated); Completion Date: 08 September 2020 (core study);

Study OOC-ACM-303. Initiation Date: 30 August 2017 (first site initiated); Completion Date: 13 June 2019 (core study);

Study CH-ACM-01. Initiation Date: 13 March 2012; Completion Date: 30 May 2014.

All recruitments were initiated after the major amendments were performed and thus, acceptable.

- **Conduct of the study**

Study OOC-ACM-302

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Table 3.3.4.2.2. Changes in the Conduct of the Study 302

Protocol Version	Protocol Date	Major Change(s)
Original Protocol, Version 1.0	25 August 2015	Not distributed; changes were made to Version 1.0 prior to implementation in response to suggestions from the Scientific Advice Working Party (SAWP) of the European Medicines Agency (EMA).
Version 2.0 (Amendment 1.0)	30 November 2015	Changed the primary efficacy endpoint to reflect a time-weighted average (TWA) biochemical response; modified the eligibility criteria; extended the duration of the RCT phase; added predefined stopping rules
Version 3.0 (Amendment 2.0)	01 July 2016	Updated the ACRO-TSQ and added visit-specific forms
Version 4.0 (Amendment 3.0)	04 March 2018	Additional year open-label extension (OLE)
Version 5.0 (Amendment 4.0)	25 January 2019	Additional year OLE
Version 6.0 (Amendment 5.0)	16 January 2020	Additional 2 years OLE; new corporate address; updated patient exposure numbers; updated benefit and risk sections; added Phase 3 study OOC-ACM-303 information
US country-specific amendment Version 6.1 (Amendment 6.0)	09 March 2020	Allowed eligible patients who completed study OOC-ACM-303 OLE to enroll into the OOC-ACM-302 Study Extension phase

Changes in the Planned Analyses

Table 3.3.4.2.3. SAP Changes

SAP Version	Summary of Changes
27 September 2016	Original
09 April 2018	1. Extend the duration of the Study Extension phase from 1 year to 2 years, as originally planned in the study protocol v3.0 2. Addition of a voluntary Withdrawal phase sub-study to assess evidence of active disease and the requirement for chronic treatment in patients previously treated with octreotide capsules in the Randomized Controlled Treatment (RCT) phase 3. Additional endpoints relating to biochemical control on octreotide capsules, to satisfy FDA requirements 4. Clarify timing of database lock for the core study
06 May 2019	1. Added the ACRO-TSQ analyses following evaluation of the measurement properties, responsiveness to change, and minimum important difference using data from the Run-in phase 2. Clarified the definition of treatment-emergent adverse events 3. Removed Appendix 14.2 (schedule of activities) as these were old versions and the updated versions are contained within the protocol 4. Corrected grammar and spelling mistakes

Changes to the planned analyses outlined in the SAP

1. The primary analysis specified the adjusted 95% CIs would be obtained using the stratified Newcombe method but the stratified Miettinen & Nurminen method using Cochran–Mantel–Haenszel (CMH) weights was used instead because the results of the study did not allow the Miettinen & Nurminen method to be used due to the presence of 0's in some strata.

2. Sensitivity analyses were conducted for the primary and secondary endpoints (e.g. Patients were randomised at week 26 (Baseline of the RCT phase) based on IGF-1 and GH values collected at week 24. Analyses were conducted using a subset of the FAS that only included patients who met the IGF-1

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and GH inclusion criteria using week 26 values (Baseline of the RCT phase). These analyses were referred to as Week 26 Responders).

Study OOC-ACM-303. The study was initiated with Protocol Version 4. The protocol subsequently was amended twice. The amendments changed the order of the secondary objectives and secondary efficacy endpoints; added an exploratory endpoint (i.e., proportion of patients who require rescue medication [e.g., re-initiate SRL treatment]), modified the definition of the FAS.

Study CH-ACM-01. During protocol amendments pituitary MRI versus brain MRI was specified, additional testing planned (e.g. anti-octreotide antibodies), new secondary efficacy endpoint of proportion of patients with both normalised IGF-1 levels (adjusted for age) and mean integrated GH over 2 hours < 2.5 ng/mL was added, 6-month Extension Treatment Period was added. Some endpoints were modified after interaction with regulatory agencies.

The changes to the planed analyses do not seem to impair the overall validity of the clinical trial.

- **Baseline data**

Study OOC-ACM-302

Patients' mean age at screening for the run-in phase for study OOC-ACM-302 was 54.1 years. Most patients were Caucasian (91.1%), and about two thirds were female (64.4%). The demographic characteristics of patients in the RCT phase were similar to those in the run-in phase. Also, the demographic characteristics were well balanced between the octreotide capsules group and the SRL injections group. (See Table 3.3.4.2.4)

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Table 3.3.4.2.4. Demographic characteristics in the run-in and RCT phases of study 302 (EAS, FAS)

	Run-in phase	RCT phase		
	Octreotide capsules (N = 146)	Octreotide capsules (N = 55)	SRL injections (N = 37)	Overall (N = 92)
Gender (n [%])				
Male	52 (35.6)	20 (36.4)	11 (29.7)	31 (33.7)
Female	94 (64.4)	35 (63.6)	26 (70.3)	61 (66.3)
Race (n [%])				
Asian	1 (0.7)	0	0	0
Black/African or African American	3 (2.1)	2 (3.6)	0	2 (2.2)
White/Caucasian	133 (91.1)	49 (89.1)	35 (94.6)	84 (91.3)
Other	9 (6.2)	4 (7.3)	2 (5.4)	6 (6.5)
Region (n [%]) [1]				
Eastern Europe	84 (57.5)	30 (54.5)	22 (59.5)	52 (56.5)
Western Europe	25 (17.1)	11 (20.0)	5 (13.5)	16 (17.4)
North America	37 (25.3)	14 (25.5)	10 (27.0)	24 (26.1)
Age (years) at screening				
Mean (SD)	54.1 (10.50)	54.1 (10.88)	55.2 (8.78)	54.5 (10.05)
Age (categorical) (n [%])				
< 65 years old	124 (84.9)	46 (83.6)	32 (86.5)	78 (84.8)
≥ 65 years old	22 (15.1)	9 (16.4)	5 (13.5)	14 (15.2)
Body mass index (kg/m^2) at screening				
Mean (SD)	29.4 (4.68)	28.8 (4.75)	28.5 (4.50)	28.7 (4.63)

[1] Eastern Europe: Hungary, Lithuania, Russia, and Serbia; Western Europe: Austria, France, Germany, Italy, Spain, and United Kingdom; North America: United States

Source: CSR OOC-ACM-302, Tables 14.1.3.2, 14.1.3.3, and 14.1.4.2

Acromegaly baseline characteristics: Patients enrolled into study OOC-ACM-302 had documented evidence of a GH secreting pituitary tumour (see Table 3.3.4.2.5). Per the protocol-defined criteria, all eligible patients were to be biochemically controlled on their parenteral SRL treatment at screening (defined as IGF-1 <1.3 x ULN and mean integrated GH <2.5 ng/mL).

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Table 3.3.4.2.5 Acromegaly baseline characteristics in the run-in and RCT phases of study 302 (EAS, FAS)

	Run-in phase	RCT phase		
	Octreotide capsules (N = 146)	Octreotide capsules (N = 55)	SRL injections (N = 37)	Overall (N=92)
Pituitary tumour (n [%]) [1]				
Microadenoma	35 (24.0)	13 (23.6)	11 (29.7)	
Macroadenoma	107 (73.3)	40 (72.7)	26 (70.3)	
Other	3 (2.1)	2 (3.6)	0	
Missing	1 (0.7)	0	0	
Duration of acromegaly (n [%])				
<10 years	78 (53.4)	22 (40.0)	23 (62.2)	45 (48.9)
10 to <20 years	50 (34.2)	26 (47.3)	10 (27.0)	36 (39.1)
≥20 years	18 (12.3)	7 (12.7)	4 (10.8)	11 (12.0)
Previous treatments for acromegaly (n [%])				
Surgery only	95 (65.1)	35 (63.6)	25 (67.6)	60 (65.2)
Radiotherapy only	3 (2.1)	1 (1.8)	0	1 (1.1)
Surgery and radiotherapy	21 (14.4)	10 (18.2)	7 (18.9)	17 (18.5)
Neither surgery nor radiotherapy	27 (18.5)	9 (16.4)	5 (13.5)	14 (15.2)
Residual tumour size (n [%])				
No remnants	69 (47.3)	24 (43.6)	21 (56.8)	45 (48.9)
<5 mm	122 (83.6)	12 (21.8)	8 (21.6)	20 (21.7)
5-10 mm	94 (64.4)	13 (23.6)	3 (8.1)	16 (17.4)
>10 mm	130 (89.0)	6 (10.9)	5 (13.5)	11 (12.0)
AIS score at baseline [1]				
Mean (SD)	4.8 (3.10)	4.2 (2.92)	5.0 (2.98)	4.5 (2.96)
Symptom burden at baseline (n [%]) [2]				
≥1	130 (89.0)	48 (87.3)	34 (91.9)	82 (89.1)
≥2	122 (83.6)	41 (74.5)	34 (91.9)	75 (81.5)
≥3	94 (64.4)	31 (56.4)	24 (64.9)	55 (59.8)
Baseline IGF-1 (ULN)				
Mean (SD)	0.9 (0.27)	0.8 (0.25)	0.8 (0.24)	0.8 (0.25)
≤1 x ULN (n [%])	98 (67.1)	43 (78.2)	28 (75.7)	71 (77.2)
>1 to <1.3 x ULN (n [%])	38 (26.0)	11 (20.0)	8 (21.6)	19 (20.7)
≥1.3 x ULN (n [%])	10 (6.8)	1 (1.8)	1 (2.7)	2 (2.2)
RCT Baseline IGF-1 (ULN)				
Mean (SD)	-	0.9 (0.35)	0.8 (0.21)	0.9 (0.30)
≤1 x ULN (n [%])	-	37 (67.3)	29 (78.4)	66 (71.7)
>1 to <1.3 x ULN (n [%])	-	12 (21.8)	8 (21.6)	20 (21.7)
≥1.3 x ULN (n [%])	-	6 (10.9)	0	6 (6.5)
Baseline GH (ng/mL)				
Mean (SD)	0.88 (0.818)	0.77 (0.601)	0.79 (0.757)	0.78 (0.664)
≤1 ng/mL (n [%])	95 (65.1)	38 (69.1)	25 (67.6)	63 (68.5)
>1 to <2.5 ng/mL (n [%])	45 (30.8)	16 (29.1)	10 (27.0)	26 (28.3)
≥2.5 ng/mL (n [%])	6 (4.1)	1 (1.8)	2 (5.4)	3 (3.3)

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Table 3.3.4.2.5 Acromegaly baseline characteristics in the run-in and RCT phases of study 302 (EAS, FAS)

	Run-in phase	RCT phase		
	Octreotide capsules (N = 146)	Octreotide capsules (N = 55)	SRL injections (N = 37)	Overall (N=92)
RCT Baseline GH (ng/mL)				
Mean (SD)	-	0.55 (0.54)	0.62 (0.63)	0.58 (0.58)
≤1 ng/mL (n [%])	-	44 (80.0)	28 (75.7)	72 (78.3)
>1 to <2.5 ng/mL (n [%])	-	10 (18.2)	8 (21.6)	18 (19.6)
≥2.5 ng/mL (n [%])	-	1 (1.8)	1 (2.7)	2 (2.2)
Prior injectable somatostatin analogue treatment [3]				
Low dose	30 (20.5)	10 (18.2)	9 (24.3)	19 (20.7)
Middle dose	55 (37.7)	19 (34.5)	14 (37.8)	33 (35.9)
High dose	61 (41.8)	26 (47.3)	14 (37.8)	40 (43.5)

[1] Calculated as the unweighted sum of 5 acromegaly signs/symptoms (joint pain, fatigue, perspiration, swelling of extremities, and headache. Score ranges from 0 (all signs/symptoms absent) to 15 (all signs/symptoms) rates as severe.

[2] Number of active acromegaly symptoms

[3] Low dose: any octreotide dose <20 mg total/month or lanreotide < 90 mg total/month. Middle dose: any octreotide dose <30 mg total/month or lanreotide <120 mg total/month. High dose: any octreotide dose ≥30 mg total/month or lanreotide ≥120 mg total/month.

Source: CSR OOC-ACM-302, Tables 14.1.4.1 and 14.1.4.2

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The demographic data were balanced between the octreotide capsules group and the placebo group (see **Table 3.3.4.2.6**.

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Table 3.3.4.2.6. Demographic characteristics in the DPC phase of study ACM-303 (FAS)

	Octreotide capsules (N = 28)	Placebo (N = 28)	Overall (N = 56)
Gender (n [%])			
Male	12 (42.9)	14 (50.0)	26 (46.4)
Female	16 (57.1)	14 (50.0)	30 (53.6)
Race (n [%]) [1]			
Asian	1 (3.6)	2 (7.1)	3 (5.4)
Black/African or African American	0	1 (3.6)	1 (1.8)
White/Caucasian	27 (96.4)	24 (85.7)	51 (91.1)
Other	0	1 (3.6)	1 (1.8)
Region [2]			
Europe	14 (50.0)	8 (28.6)	22 (39.3)
Outside Europe	14 (50.0)	20 (71.4)	34 (60.7)
Age (years) at screening			
Mean (SD)	55.3 (11.89)	54.3 (10.93)	54.8 (11.33)
Age (categorical) (n [%])			
< 65 years old	21 (75.0)	22 (78.6)	43 (76.8)
≥ 65 years old	7 (25.0)	6 (21.4)	13 (23.2)
Body mass index (kg/m^2) at screening			
Mean (SD)	29.1 (6.26)	31.0 (5.58)	30.0 (5.96)

[1] Patients could have selected multiple race categories.

[2] Europe includes Bulgaria, Denmark, Germany, Hungary, Italy, Latvia, Netherlands, Poland, Slovenia, Sweden, UK. Outside Europe includes Australia, Canada, Israel, New Zealand, Turkey, US. Information on patient numbers derived from patient tracker.

Source: CSR OOC-ACM-303, Table 14.1.3.1

Acromegaly baseline characteristics: Patients enrolled into study OOC-ACM-303 had documented evidence of a GH secreting pituitary tumour (see **Table 3.3.4.2.7**). The acromegaly baseline characteristics were fairly balanced between the octreotide capsules group and the placebo group.

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Table 3.3.4.2.7 Acromegaly baseline characteristics in the DPC phase of study ACM-303 (FAS)

	Octreotide capsules (N = 28)	Placebo (N = 28)	Overall (N = 56)
Duration of acromegaly (n [%])			
<10 years	15 (53.6)	20 (71.4)	35 (62.5)
10 to <20 years	8 (28.6)	5 (17.9)	13 (23.2)
≥20 years	5 (17.9)	3 (10.7)	8 (14.3)
Previous treatments for acromegaly (n [%]) [1]			
Octreotide daily injection	0	3 (10.7)	3 (5.4)
Octreotide long acting	21 (75.0)	18 (64.3)	39 (69.6)
Lanreotide	9 (32.1)	12 (42.9)	21 (37.5)
Pasireotide	0	4 (14.3)	4 (7.1)
Bromocriptine	3 (10.7)	3 (10.7)	6 (10.7)
Cabergoline	7 (25.0)	3 (10.7)	10 (17.9)
GH receptor antagonist – pegvisomant	0	2 (7.1)	2 (3.6)
SRLs plus dopamine agonists	4 (14.3)	1 (3.6)	5 (8.9)
SRLs plus pegvisomant	0	1 (3.6)	1 (1.8)
Prior acromegaly surgery			
Yes	25 (89.3)	24 (85.7)	49 (87.5)
No	3 (10.7)	4 (14.3)	7 (12.5)
Symptom burden [2]			
≥1	23 (82.1)	24 (85.7)	47 (83.9)
≥2	18 (64.3)	19 (67.9)	37 (66.1)
≥3	10 (35.7)	14 (50.0)	24 (42.9)
Baseline IGF-1 (ULN) [3]			
Mean (SD)	0.80 (0.157)	0.84 (0.210)	0.82 (0.185)
Baseline IGF-1 (categorical) (n [%]) [3]			
≤1 x ULN	27 (96.4)	23 (82.1)	50 (89.3)
>1 to <1.3 x ULN	1 (3.6)	5 (17.9)	6 (10.7)
≥1.3 x ULN	0	0	0
Baseline GH (ng/mL)			
Mean (SD)	0.66 (0.745)	0.90 (1.009)	0.78 (0.887)
Baseline GH (categorical) (n [%])			
≤1 ng/mL	23 (82.1)	21 (75.0)	44 (78.6)
>1 to <2.5 ng/mL	4 (14.3)	4 (14.3)	8 (14.3)
≥2.5 ng/mL	1 (3.6)	3 (10.7)	4 (7.1)
Prior injectable treatment overall (n [%]) [4]			
Low	6 (21.4)	5 (17.9)	11 (19.6)
Medium	8 (28.6)	11 (39.3)	19 (33.9)
High	14 (50.0)	12 (42.9)	26 (46.4)

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[1] Previous treatment anytime in the past. Patients could have had multiple previous treatments for acromegaly.
[2] Symptom burden reflects the number of ongoing acromegaly symptoms at Screening on the acromegaly history form.
[3] Based on the average of the 2 assessments within 2 weeks prior to randomisation.
[4] Low dose: octreotide 10 mg every 4 weeks; lanreotide 60 mg every 4 weeks or 120 mg every 8 weeks. Medium dose: octreotide 20 mg every 4 weeks; lanreotide 90 mg every 4 weeks or 120 mg every 6 weeks. High dose: octreotide 30 mg every 4 weeks; lanreotide 120 mg every 4 weeks.

Source: CSR OOC-ACM-303, Tables 14.1.4.1 and 14.1.4.4.1

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Demographic characteristics: The mean age of patients at screening was 54.2 years. Most patients were white/Caucasian (88.4%), and about half were female (56.8%). Of the 155 patients in the ITT population, 28 patients (18.1%) were older than 65 years, and 127 patients (81.9%) were 65 years or younger. Most patients (122 of 155; 78.7%) were recruited in Europe.

Acromegaly baseline characteristics: Relevant acromegaly baseline characteristics are presented for the mITT population and the FD responders in (see **Table 3.3.4.2.8)**.

Table 3.3.4.2.8). Acromegaly baseline characteristics in the core treatment phase of study CH-ACM-01 (mITT and FD responders)

	Octreotide capsules	
	mITT population (N = 151)	FD responders (N = 91)
Duration of acromegaly (n [%])		
<10 years	72 (47.7)	39 (42.9)
10 to <20 years	51 (33.8)	34 (37.4)
≥20 years	28 (18.5)	18 (19.8)
Prior treatment for acromegaly (n [%]) [1]		
Surgery	117 (77.5)	73 (80.2)
Medication other than somatostatin analogues	60 (39.7)	35 (38.5)
Radiation	13 (8.6)	8 (8.8)
Surgery followed by radiation	8 (5.3)	4 (4.4)
Radiation followed by surgery	1 (0.7)	1 (1.1)
Prior injectable treatment (n [%]) [2]		
Octreotide LAR	93 (61.6)	49 (53.8)
Low	12 (7.9)	9 (9.9)
Middle	49 (32.5)	26 (28.6)
High	32 (21.2)	14 (15.4)
Lanreotide	58 (38.4)	42 (46.2)
Low	11 (7.3)	10 (11.0)
Middle	13 (8.6)	11 (12.1)
High	34 (22.5)	21 (23.1)

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Symptom burden (n [%]) [3]		
≥1	122 (80.8)	69 (75.8)
≥2	92 (60.9)	56 (61.5)
≥3	65 (43.0)	38 (41.8)
IGF-1 (ULN)		
Mean (SD)	0.9 (0.25)	0.8 (0.19)
2-hour GH (ng/mL)		
Mean (SD)	0.9 (0.71)	0.9 (0.65)

[1] Prior treatment at any time in the past. Patients could appear in more than 1 category.

[2] Low dose: any octreotide dose <20 mg total/month or lanreotide <90 mg total/month. Middle dose: octreotide <30 mg total/month or lanreotide <120 mg total/month or lanreotide 120 mg every 6 weeks. High dose: octreotide ≥30 mg total/month or lanreotide ≥120 mg total/month.

[3] Number of acromegaly symptoms based on the AIS

Source: Supplementary Analyses, CH-ACM-01 Tables 1 and 2

- **Treatment compliance**

Study OOC-ACM-302. Mean octreotide capsule compliance was 96.3% during the Run-in phase. Across dose groups, 95.9% of patients were 75-100% compliant with their study medication. Drug compliance during the RCT phase was similar between the octreotide capsule group (98.5%) and the SRL injection group (98.3%).

Study OOC-ACM-303. In both treatment groups patients were ⩾ 75% compliant with the study drug dosing regimen. Thirty patients completed the DPC period on study drug (21 patients [75.0%] in the octreotide capsule group and 9 patients [32.1%] in the placebo group). Twenty-six patients discontinued study drug treatment during the DPC period and required rescue medication (7 patients [25.0%] in the octreotide capsule group and 19 patients [67.9%] in the placebo group).

Study CH-ACM-01

In study patients >95% of patients were ⩾ 75% compliant with the study drug dosing regimen.

Baseline demographic and clinical characteristics data do not indicate any asymmetry in characteristics across treatment arms. The study population reflects the intended indication well.

Across trials the study compliance was good.

- **Numbers analysed**

Study OOC-ACM-302

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Table 3.3.4.2.9. Patient Disposition for the RCT Phase (All Randomised Patients)

	Octreotide Capsule All Doses[1] (N = 55) n (%)	SRL Injection All Doses[2] (N = 37) n (%)	Overall (N = 92) n (%)
Randomized into RCT phase	55	37	92
Discontinued from RCT phase	1 (1.8)	2 (5.4)	3 (3.3)
Reason for discontinuation			
Adverse event	1 (1.8)	0	1 (1.1)
Withdrawal by patient	0	2 (5.4)	2 (2.2)
Discontinued RCT phase and entered Follow-up	1 (1.8)	2 (5.4)	3 (3.3)
Discontinued RCT phase and completed Follow-up	0	0	0
Completed RCT phase	54 (98.2)	35 (94.6)	89 (96.7)
Entered Study Extension phase	34 (61.8)	18 (48.6)	52 (56.5)
Did not enter Study Extension phase[3]	20 (36.4)	17 (45.9)	37 (40.2)
Entered Follow-up	16 (29.1)	15 (40.5)	31 (33.7)
Completed Follow-up	14 (25.5)	14 (37.8)	28 (30.4)
Discontinued Follow-up	2 (3.6)	1 (2.7)	3 (3.3)

Percentages were based on the number of randomized patients.
[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] Six patients completed the RCT phase and met the eligibility criteria for the Study Extension phase but did not enter the Study Extension phase.
RCT = randomized, controlled treatment; SRL = somatostatin receptor ligand
Source: Post-text Table 14.1.1.3 and Listing 16.2.1.3

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Study OOC-ACM-303

Table 3.3.4.2.10. Patient Disposition for the DPC Period (Full Analysis Set)

	Octreotide Capsule Treatment Group (Final Dose in DPC Period)					
Parameter	**40 mg (N = 7) n (%)**	**60 mg (N = 2) n (%)**	**80 mg (N = 19) n (%)**	**Total (N = 28) n (%)**	**Placebo (N = 28) n (%)**	**Overall (N = 56) n (%)**
Enrolled in DPC Period (ie, randomized)	7 (100.0)	2 (100.0)	19 (100.0)	28 (100.0)	28 (100.0)	56 (100.0)
Completed the DPC Period	7 (100.0)	2 (100.0)	19 (100.0)	28 (100.0)	28 (100.0)	56 (100.0)
Discontinued Study Drug Treatment and Completed the DPC	1 (14.3)	0	6 (31.6)	7 (25.0)	19 (67.9)	26 (46.4)
Completed on SRL	1 (14.3)	0	6 (31.6)	7 (25.0)	19 (67.9)	26 (46.4)
Completed on no treatment	0	0	0	0	0	0
Completed on other treatment	0	0	0	0	0	0
Reasons for Discontinuation of Study Drug Treatment and Completed the DPC						
Treatment failure	0	0	5 (26.3)	5 (17.9)	18 (64.3)	23 (41.1)
Met the predefined withdrawal criteria	0	0	3 (15.8)	3 (10.7)	18 (64.3)	21 (37.5)
Did not meet the predefined withdrawal criteria	0	0	2 (10.5)	2 (7.1)	0	2 (3.6)
Treatment failure reason:						
IGF-1 > 1 ULN but < 1.3 ULN [1]	0	0	1 (5.3)	1 (3.6)	0	1 (1.8)
IGF-1 ≥ 1.3 ULN without exacerbation of acromegaly signs/symptoms	0	0	1 (5.3)	1 (3.6)	0	1 (1.8)
IGF-1 ≥ 1.3 ULN for a single assessment	0	0	0	0	0	0
Exacerbation of acromegaly signs/symptoms	0	0	0	0	0	0
Adverse event	1 (14.3)	0	1 (5.3)	2 (7.1)	1 (3.6)	3 (5.4)
Patient withdrew consent	0	0	0	0	0	0
Investigator request	0	0	0	0	0	0
Sponsor request	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Other	0	0	0	0	0	0
Discontinued Study Drug Treatment and Did Not Complete the DPC	0	0	0	0	0	0
Completed the DPC Period on Study Drug	6 (85.7)	2 (100.0)	13 (68.4)	21 (75.0)	9 (32.1)	30 (53.6)
Entered the OLE	6 (85.7)	1 (50.0)	12 (63.2)	19 (67.9)	9 (32.1)	28 (50.0)
Did not enter the OLE	0	1 (50.0)	1 (5.3)	2 (7.1)	0	2 (3.6)

	Octreotide Capsule Treatment Group (Final Dose in DPC Period)					
Parameter	**40 mg (N = 7) n (%)**	**60 mg (N = 2) n (%)**	**80 mg (N = 19) n (%)**	**Total (N = 28) n (%)**	**Placebo (N = 28) n (%)**	**Overall (N = 56) n (%)**
Completed the DPC Period Not on Study Drug After Meeting the Predefined Withdrawal Criteria in the DPC	0	0	3 (15.8)	3 (10.7)	18 (64.3)	21 (37.5)
Entered the OLE	0	0	1 (5.3)	1 (3.6)	11 (39.3)	12 (21.4)
Did not enter the OLE	0	0	2 (10.5)	2 (7.1)	7 (25.0)	9 (16.1)

[1] One patient with IGF-1 > 1 but < 1.3 also experienced exacerbation of acromegaly signs/symptoms.
DPC = double-blind, placebo-controlled; IGF-1 = insulin-like growth factor-1; OLE = open-label extension; ULN = upper limit of normal
Source: Post-text Table 14.1.1.2

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Table 3.3.4.2.11. Patient Disposition at the End of Screening and End of Core Treatment Period – All Study Patients – Core Treatment Period

Category	Total n (%)
Screened	**235**
Failed Screening [1]	**80 (34.0)**
Did not meet inclusion/exclusion criteria	69 (29.4)
Patient request	8 (3.4)
Non-compliance with protocol requirements	1 (0.4)
Sponsor request	1 (0.4)
Other	1 (0.4)
Enrolled [2]	**155**
Competed Core Treatment Period [3]	**102 (65.8)**
Early terminated during the Core Treatment Period [3]	**53 (34.2)**
Treatment failure	24 (15.5)
Adverse event	21 (13.5)
Patient request	5 (3.2)
Lost to follow-up	2 (1.3)
Sponsor request	1 (0.6)
Terminated prior to entry into Fixed Dose Phase [3]	**45 (29.0)**
Treatment failure	21 (13.5)
Adverse event	16 (10.3)
Patient request	5 (3.2)
Lost to follow-up	2 (1.3)
Sponsor request	1 (0.6)
Terminated during the Fixed Dose Phase [3]	**8 (5.2)**
Adverse event	5 (3.2)
Treatment failure	3 (1.9)

[1] Percentage of screen failures, including reasons for screen failure, was based on the total number of patients screened.
[2] A patient was considered enrolled in the study if the patient completed visit TA1 (see Table 3).
[3] Percentage of patients completed and early terminated (other than prior to screening) was based on the total number of patients enrolled.
Source: Post-text Table 14.1.1

Across trials there was a high treatment discontinuation rate across trials due to treatment inefficacy and adverse events (see comments in section Participant flow above).

The applicant was invited to discuss reasons for the high discontinuation rate in CH-ACM-01, including differences in populations of the three clinical studies. The applicant clarified that the higher discontinuation rates in study CH-ACM-01 (34%), compared to Studies OOC-ACM-303 and OOC-ACM-3032 (25% and 20.5%) was mainly related to GI AEs. The applicant's response is acceptable.

- **Outcomes and estimation**

Study OOC-ACM-302

Primary endpoint results
The primary efficacy endpoint was the proportion of patients who were biochemically controlled throughout the RCT phase. A patient was considered biochemically controlled if his or her IGF-1 TWA during the RCT phase was <1.3 x ULN.

Overall, 90.9% of patients in the octreotide capsules group maintained biochemical control (95% CI 80.0, 97.0) compared to 100% of patients in the SRL injections group (95% CI 90.5, 100). The lower bound of the 2-sided 95% CI for the adjusted difference (octreotide capsules minus SRL injections) in

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proportions between the 2 treatment groups achieved the prespecified NI criterion of -20% (95% CI 19.9, 0.5), see Table **3.3.4.2.12.**

Table 3.3.4.2.12. Proportion of patients who were biochemically controlled throughout the RCT phase 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 **(%)**	23 (100)	11 (84.6)	16 (84.2)	**50 (90.9)**	9 (100)	14 (100)	14 (100)	**37 (100)**
95% CI for responder [3]				(80.0, 97.0)				(90.5, 100)
Non-responder	0	2 (15.4)	3 (15.8)	5 (9.1)	0	0	0	0
Difference in unadjusted proportions				-9.1				
95% CI [4]				(-19.6, 0.8)				
Difference in adjusted proportions [5]				-9.1				
95% CI [5]				**(-19.9, 0.5)**				

A patient was considered biochemically controlled if his or her IGF-1 TWA during the RCT phase was <1.3 x ULN.

[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).

Source: CSR OOC-ACM-302, Table 14.2.1.1

Secondary endpoint results

65.5% of patients in the octreotide capsules group and 73.0% of patients in the SRL injections group were clinically and biochemically controlled at the end of the RCT phase (adjusted treatment difference: -6.8%; 95% CI -25.3, 13.2).

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).

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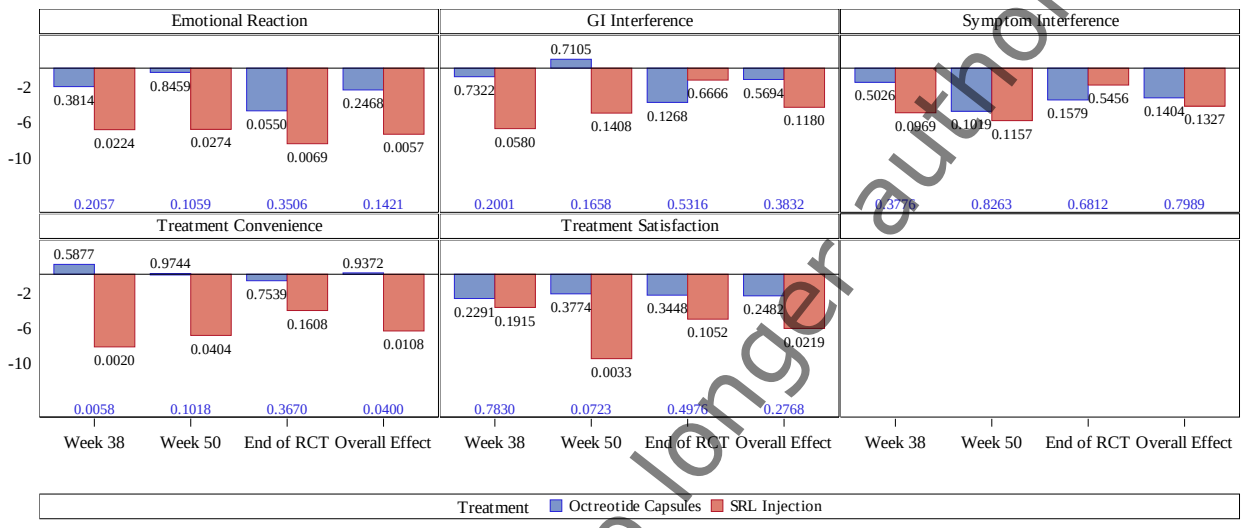
Mean Acromegaly Treatment Satisfaction Questionnaire ACRO-TSQ scales during RCT phase were generally comparable between the 2 treatment groups. However, numerical changes in Emotional Reaction, Treatment Convenience, and Treatment Satisfaction consistently favoured octreotide capsules. A significant 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 3.3.4.2.8.)

Figure 3.3.4.2.8. ACRO-TSQ scales change during the RCT phase of study OOC-ACM-302 by treatment group and visit (FAS)



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.

Study OOC-ACM-303

The primary efficacy endpoint of study OOC-ACM-303 was the proportion of patients who maintained their biochemical response at the end of the DPC phase. Maintaining biochemical response was defined as having an average IGF-1 ≤1 x ULN.

Overall, 58.2% of the patients in the octreotide capsules group vs 19.4% of the patients in the placebo group maintained their biochemical response at the end of the DPC phase; the difference between the 2 groups was statistically significant (p = 0.0079), with an odds ratio of 5.77 in favour of octreotide capsules.

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Table 3.3.2.6.2. Proportion of patients who maintained their biochemical response at the end of the DPC phase in study OOC-ACM-303 (FAS)

	Octreotide capsules (Final dose in DPC phase)				
	40 mg (N = 7)	60 mg (N = 2)	80 mg (N = 19)	Total (N = 28)	Placebo (N = 28)
Unadjusted proportions (n[%])					
Responder	5 (71.4)	1 (50.0)	10 (52.6)	**16 (57.1)**	**5 (17.9)**
Non-responder	2 (28.6)	1 (50.0)	9 (47.4)	12 (42.9)	23 (82.1)
Observed	1 (14.3)	1 (50.0)	3 (15.8)	5 (17.9)	4 (14.3)
Early withdrawal [1]	1 (14.3)		6 (31.6)	7 (25.0)	19 (67.9)
Adjusted proportions [2]					
Responder				**58.16**	19.42
Non-responder				41.84	80.58
Difference in adjusted proportions [2]				**38.74**	
95% CI				**(10.68, 59.90)**	
P-value				0.0079	
Odds ratio (octreotide capsules/placebo) [2]				5.7674	
95% CI				(1.4440, 28.2115)	

[1] Patients who discontinued study drug during the DPC phase for any reason were classified as non-responders.

[2] Adjusted proportions and odds ratios were obtained from an exact logistic regression model including covariates for treatment group, baseline SRL dose (low versus medium or high) and baseline IGF-1 level (< median, ⩾ median). CI for difference in adjusted proportions used Newcombe method.

The applicant was asked to discuss reasons for differences in the percentage of patients who maintained their biochemical response between studies 302 and 303. The applicant responded that generally, maintenance of response in patients responding to octreotide capsules as well as initial response to octreotide capsules following switch from iSRLs were comparable between studies OOC-ACM-302 and OOC-ACM-303. Observed differences were mainly related to the differences in numbers of discontinuations from both studies. The applicant's response is acceptable.

Study CH-ACM-01

The primary efficacy endpoint was the proportion of responders (IGF-1 <1.3 × ULN and GH <2.5 ng/mL) at the end of the core treatment phase. Of the 151 patients in the mITT population, 64.9% were responders at the end of the core treatment phase. See **Table 3.3.2.6.3.)**

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Table 3.3.2.6.3. Responders at the end of the core treatment phase of study ACM-01 (mITT, LOCF)

	Octreotide capsules (Dose at end of treatment)			
	40 mg (N = 61)	60 mg (N = 33)	80 mg (N = 57)	Total (N = 151)
Responders [1]				
n	53	22	23	98
%	**86.9**	**66.7**	**40.4**	**64.9**
Exact 95% CI for %	83.0 – 98.1	48.2 – 82.0	**27.6** – 54.2	58.4 – 74.2

[1] Response was defined as IGF 1 < 1.3 times ULN (adjusted for age and sex) and 2-hour integrated GH < 2.5 ng/mL

Source: CSR CH-ACM-01, Table 14.2.1

Primary analysis of pivotal studies show that the capsules exert certain efficacy in maintaining biochemical control in some ACM patients and for those, in whom maintenance is achieved this can have a non-inferior effect to the injectable formulation.

The individual test results for primary endpoints of the pivotal study could not be retrieved from submission dossier. The applicant did not comply with the advice from CHMP to use full normalisation of IGF-1 for primary endpoint analysis. The applicant was asked to present all test results for primary and co-primary analyses for Study 302. The applicant has provided the requested data. The applicant did not perform additional analysis that would duplicate the already conducted analyses. The applicant conducted an analysis to show the results under full normalisation of IGF-1. This was considered acceptable.

Unjustified robustness of statistical significance of NI. NI of 20% was shown with 95% CI (M&N) of (-19.9, 0.5), Table 21 of Study 302 CSR, p. 112. Three patients were withdrawn from RCT – one in Mycapssa arm (due to ADR) and two in SRL arm (patient decision on Day 379 and Day 253). The individual primary efficacy data are not retrieved from the application. The applicant was asked:

a) To provide case report forms for all three withdrawn patients from both Mycapssa and SRL arms.

b) To provide individual primary endpoint related test results for all participated in RCT phase in excel format;

c) To reanalyze primary endpoint considering three scenarios and two cut-off values: (1) SRL arm adjusted for both excluded patients from SRL arm to be treated as responders (using BOCF analysis) and Mycapssa arm remains as it is; (2) Mycapssa arm adjusted for excluded patient form Mycapssa arm (due to ADR) to be treated based on LOCF analysis and SRL arm remains as it is; and (3) both arms are adjusted in the same manner as it is proposed in (1) and (2). These calculations were performed, and these issues were addressed by the applicant and are considered resolved.

- **Ancillary analyses**

Study OOC-ACM-302

The results of the sensitivity analyses in Week 26 responders, PP, FAS (ET-TF) populations assessed the robustness of the primary analysis to show similar non-inferiority of primary endpoint (above -20%).

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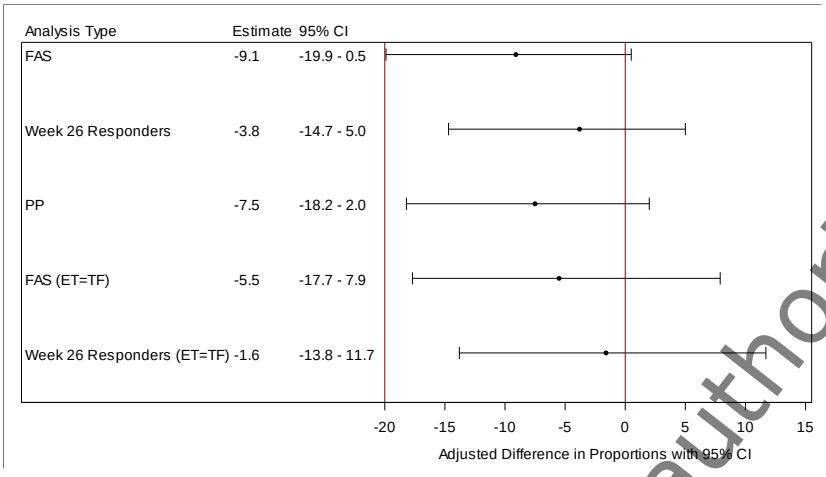
Figure 3.3.2.6.4. Forest plot of treatment difference in proportions and 95% CI for the primary efficacy endpoint and all sensitivity analyses



FAS: full analysis set; Week 26 responders: Patients in the FAS who were biochemically controlled at RCT baseline (Week 26); PP: per-protocol set; FAS (ET=EF): Patients in the FAS where any patient who discontinued treatment early was imputed to be a non-responder; Week 26 (ET=EF): Week 26 responders where any patient who discontinued treatment early was imputed to be a non-responder.

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

Source: CSR OOC-ACM-302, Figure 14.2.1.2

CH-ACM-01

The sensitivity analysis using the Markov Chain Monte Carlo method to impute missing data showed a 66.5% response, consistent with the primary LOCF analysis (CSR CH-ACM-01).

Sensitivity analyses showed results, consistent to the primary effect.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

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Table 3.4.1. Summary of efficacy for trial OOC-ACM-302 Phase 3

Title: A Phase 3, Randomized, Open-Label, Active Controlled, Multicenter Study to Evaluate Maintenance of Response, Safety, and Patient Reported Outcomes in Acromegaly Patients Treated with Octreotide Capsules, and in Patients Treated with Standard of Care Parenteral Somatostatin Receptor Ligands, who Previously Tolerated and Demonstrated a Biochemical Control on Both Treatments			
Study identifier	OOC-ACM-302 Phase 3 US IND Number: 108,163 EudraCT Number: 2015-002854-11 Protocol Number: OOC-ACM-302		
Design	Randomised, open-label, active-controlled, preceded by a run-in phase, followed by an open-label extension (OLE) phase		
	Duration of main phase: Duration of Run-in phase:		36 weeks 26 weeks
	Duration of Extension phase:		up to 5 years or until product marketing or termination of the study by the Sponsor. Withdrawal phase sub-study and the Study Extension phase were followed-up for 12 weeks.
Hypothesis	Non-inferiority: an assessment of non-inferiority (NI) was made by comparing the lower bound of the 2-sided 95% CI for the difference in biochemical control (octreotide capsules - SRL) to a NI margin of -20%, based on prior studies with SRLs that showed maintenance of response between 80-90%.		
Treatments groups	Oral Octreotide group (Test group)		Octreotide capsules were titrated up to 80 mg/day (40 mg bid), based on clinical and biochemical response, 36 weeks, 55 patients.
	Reference Therapy group: Injectable Somatostatin Receptor Ligands (reference group)		Standard of care injectable SRL (octreotide long-acting release [LAR] or lanreotide), 36 weeks, 37 patients.
	Combination phase sub-study (conducted in non-EU sites)		Octreotide capsules + cabergoline, for patients failing to respond to octreotide capsules, 36 weeks (in parallel to the RCT duration), 14 patients.
Endpoints and definitions	Primary endpoint	NORM IGF-1	Proportion of patients who were biochemically controlled throughout the RCT phase. Patients were considered biochemically controlled if their IGF-1-time weighted average (TWA) during the RCT phase was < 1.3 times ULN.
	Co-Primary endpoint	Run-in IGF-1	Run-in phase – Proportion of patients who were biochemically controlled at the end of the Run-in phase, defined as IGF-1 < 1.3 times ULN (based on the average of week 24 and week 26)
	Co-Primary endpoint	AVG NORM IGF-1	RCT phase – Proportion of patients on octreotide capsules who were biochemically controlled at the end of the RCT phase, defined as IGF-1 < 1.3 times ULN (based on the average of week 62 and week 58)

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Title: A Phase 3, Randomized, Open-Label, Active Controlled, Multicenter Study to Evaluate Maintenance of Response, Safety, and Patient Reported Outcomes in Acromegaly Patients Treated with Octreotide Capsules, and in Patients Treated with Standard of Care Parenteral Somatostatin Receptor Ligands, who Previously Tolerated and Demonstrated a Biochemical Control on Both Treatments			
Study identifier	OOC-ACM-302 Phase 3 US IND Number: 108,163 EudraCT Number: 2015-002854-11 Protocol Number: OOC-ACM-302		
	Secondary efficacy endpoint	n/a	Proportion of patients who maintained or reduced the overall number of active acromegaly symptoms at the end of the RCT phase (week 62/EOT) compared to week 26 (start of RCT phase)
	Secondary efficacy endpoint	n/a	Proportion of patients who maintained or improved their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least 1 point in the AIS score) compared to week 26 (start of RCT phase)
	Secondary efficacy endpoint	n/a	Change from baseline (week 26) in Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ) scale scores to the end of the RCT phase
	Secondary efficacy endpoint	n/a	Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country), who entered the Study Extension phase, overall and by treatment group
	Secondary efficacy endpoint	n/a	Change in IGF-1 from the start of the RCT phase (week 26) through the end of the RCT phase (week 62)
	Secondary efficacy endpoint	n/a	Change in mean integrated GH from the start of the RCT phase (week 26) to the end of the RCT phase (week 62)
	Secondary efficacy endpoint	n/a	Shift in response categories at the end of the RCT phase (week 62/EOT) compared to week 26 (start of RCT phase)
Database lock	22 October 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS)		
		Octreotide Capsule Treatment	**SRL Injection (Dose)**

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Title: A Phase 3, Randomized, Open-Label, Active Controlled, Multicenter Study to Evaluate Maintenance of Response, Safety, and Patient Reported Outcomes in Acromegaly Patients Treated with Octreotide Capsules, and in Patients Treated with Standard of Care Parenteral Somatostatin Receptor Ligands, who Previously Tolerated and Demonstrated a Biochemical Control on Both Treatments								
Study identifier	OOC-ACM-302 Phase 3 US IND Number: 108,163 EudraCT Number: 2015-002854-11 Protocol Number: OOC-ACM-302							
Descriptive statistics and estimate variability	90.9% of patients in the octreotide capsule group maintained biochemical control (95% CI: 80.0, 97.0) compared to 100% of patients in the SRL injection group (95% CI: 90.5, 100). The lower bound of the 2-sided 95% CI for the adjusted difference (octreotide capsules minus SRLs) in proportions between the 2 treatment groups achieved the prespecified NI criterion of -20% (95% CI: -19.9, 0.5).							
	Treatment group	40 mg	60 mg	80 mg	Total	**Low**	Middle	High	Total
	Number of subjects	23	13	19	55	**9**	14	14	37
	Responder (absolute number)	23 (100)	11 (84.6)	16 (84.2)	50 (90.9)	9 (100)	14 (100)	14 (100)	37 (100)
	95% CI for Responder (Clopper-Pearson)				(80.0, 97.0)				(90.5, 100)
	Unadjusted difference in proportions				-9.1				
	95% CI (Newcombe)				(-19.6, 1.6)				
	Unadjusted difference in proportions				-9.1				
	95% CI (M&N)				(-19.6, 0.8)				
	Adjusted difference in proportions				NE				
	95% CI (Newcombe)				NE				
	Adjusted difference in proportions				-9.1				
	95% CI (M&N)				(-19.9, 0.5)				

Title: A Phase 3, Randomized, Open-Label, Active Controlled, Multicenter Study to Evaluate Maintenance of Response, Safety, and Patient Reported Outcomes in Acromegaly Patients Treated with Octreotide Capsules, and in Patients Treated with Standard of Care Parenteral Somatostatin Receptor Ligands, who Previously Tolerated and Demonstrated a Biochemical Control on Both Treatments									
Study identifier	OOC-ACM-302 Phase 3 US IND Number: 108,163 EudraCT Number: 2015-002854-11 Protocol Number: OOC-ACM-302								
Co-Primary endpoints		Octreotide Capsule Treatment				SRL Injection (Dose)			
		40 mg	60 mg	80 mg	Total	**Low**	Middle	High	Total
	Number of subjects	23	13	19	55	9	14	14	37
Proportion of Patients Biochemically Controlled at End of RCT Phase (FAS)	Responders (percentage)	23 (100)	12 (92.3)	14 (73.7)	49 (89.1)	9 (100)	14 (100)	12 (85.7)	35 (94.6)
	95% CI for Responder4	(85.2, 100)	(64.0, 99.8)	(48.8, 90.9)	(77.8, 95.9)	(66.4, 100)	(76.8, 100)	(57.2, 98.2)	(81.8, 99.3)
Notes									
Analysis description	**Secondary analyses**								
Number of active acromegaly symptoms reduction	Proportion of patients who maintained or reduced the overall number of active acromegaly symptoms at the end of the RCT phase (week 62/EOT) compared to week 26 (start of RCT phase) 74.5% (41/55) of patients in the octreotide capsule group (95% CI: 61.0, 85.3) and 70.3% (26/37) of patients in the SRL injection group (95% CI: 53.0, 84.1) 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 for the adjusted difference in proportions: -13.6, 23.9).								
Maintained or improved their overall AIS score	Proportion of patients who maintained or improved their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least 1 point in the AIS score) compared to week 26 (start of RCT phase) 72.7% of patients in the octreotide capsule group (95% CI: 59.0, 83.9) and 67.6% of patients in the SRL injection group (95% CI: 50.2, 82.0) 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 for the adjusted difference in proportions: -13.2, 25.2). Additionally, 19 of 55 patients (34.5%) receiving octreotide capsules reported that their symptoms did not worsen before their next dose was due, compared to 8 of 37 patients (21.6%) receiving SRL injections.								

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Title: A Phase 3, Randomized, Open-Label, Active Controlled, Multicenter Study to Evaluate Maintenance of Response, Safety, and Patient Reported Outcomes in Acromegaly Patients Treated with Octreotide Capsules, and in Patients Treated with Standard of Care Parenteral Somatostatin Receptor Ligands, who Previously Tolerated and Demonstrated a Biochemical Control on Both Treatments	
Study identifier	OOC-ACM-302 Phase 3 US IND Number: 108,163 EudraCT Number: 2015-002854-11 Protocol Number: OOC-ACM-302
ACRO-TSQ scale scores	Change from baseline (week 26) in Acromegaly Treatment Satisfaction Questionnaire (ACRO-TSQ) scale scores to the end of the RCT phase ACRO-TSQ scale scores were generally comparable between treatment groups at the End of the RCT phase: 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 noted were statistically significant.
Study Extension phase entering subjects	Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country), who entered the Study Extension phase, overall and by treatment group. 63.0% of patients in the octreotide capsule group and 51.4% of patients in the SRL injection group entered the Study Extension phase.
IGF-1 change	Change in IGF-1 from the start of the RCT phase (week 26) through the end of the RCT phase (week 62) the least-squares mean (LSM) estimate of the IGF-1 TWA during the RCT phase was 0.87 (95% CI: 0.83, 0.91) for the octreotide capsule group and 0.82 (95% CI: 0.77, 0.87) for the SRL injection group. The geometric LSM ratio (octreotide capsule/SRL injection) was 1.06 (95% CI: 0.98, 1.15),
Change in mean integrated GH	Change in mean integrated GH from the start of the RCT phase (week 26) to the end of the RCT phase (week 62) the LSM change in GH from the start of the RCT phase to the end of the RCT phase was -0.03 (95% CI: -0.24, 0.19) for the octreotide capsule group, suggesting no change, and 0.29 (95% CI: 0.02, 0.55) for the SRL injection group, suggesting an increase in GH levels. The LSM treatment difference (octreotide capsule – SRL injection) was -0.31 (95% CI: -0.66, 0.03).
Shift in response categories	Shift in response categories at the end of the RCT phase (week 62/EOT) compared to week 26 (start of RCT phase) Forty-six patients (83.6%) in the octreotide capsule group and 32 patients (86.5%) in the SRL injection group maintained or improved their IGF-1 category from week 26 to week 62/EOT of the RCT phase. Forty-nine patients (89.1%) in the octreotide capsule group and 30 patients (81.1%) in the SRL injection group maintained or improved their GH category from week 26 to week 62/EOT of the RCT phase.

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Table 3.4.2. Summary of efficacy for trial OOC-ACM-303

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy and Safety of Octreotide Capsules in Patients Who Previously Tolerated and Demonstrated Biochemical Control on Injectable Somatostatin Receptor Ligands (SRL) Treatment			
Study identifier	OOC-ACM-303 Phase 3		
Design	Randomised, double-blind, placebo-controlled, followed by an OLE phase		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Study Period: Approximately 11 months (core study) Initiation Date: 30 August 2017 (first site initiated) Completion Date: 13 June 2019 (core study) Screening period: Up to 8 weeks. DPC period: 36 weeks. OLE: At least 1 year. Follow-up period: For patients who discontinued study medication early during the DCP period: through week 36 of the DPC period.
Hypothesis	Superiority assessment was made by comparing the octreotide capsule group with the placebo group using the primary endpoint.		
Treatments groups	Oral octreotide		During the DPC period, octreotide treatment was started at a total dose of 40 mg per day and titrated up to 80 mg/day in accordance with the clinical response. During the OLE, the initial octreotide dose was 60 mg (3 capsules) for all patients. 28 patients were randomly assigned to the octreotide capsule group.
	Placebo		Placebo capsules, which were identical in appearance to the octreotide capsules. 28 patients were randomly assigned to the placebo group.
Endpoints and definitions	Primary endpoint	PROP	Proportion of patients who maintained their biochemical response (average of last 2 IGF-1 assessments) ⩽1 x ULN at the end of the DPC phase.
	Secondary efficacy endpoint	GH response	Proportion of patients who maintained GH response (ie, GH < 2.5 ng/mL) at week 36, out of those who were responders (ie, GH < 2.5 ng/mL) on SRL injections at screening.
	Secondary efficacy endpoint	IGF-1 > 1 times ULN	Time to loss of response, IGF-1 > 1 times ULN
	Secondary efficacy endpoint	GF-1 > 1.3 times ULN	Time to loss of response, IGF-1 > 1.3 times ULN
	Secondary efficacy endpoint	Rescue treatment	Proportion of patients who began rescue treatment prior to and including week 36
	Secondary efficacy endpoint	Change in mean GH.	Change from Baseline (screening assessment) to end of treatment in mean GH.

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Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy and Safety of Octreotide Capsules in Patients Who Previously Tolerated and Demonstrated Biochemical Control on Injectable Somatostatin Receptor Ligands (SRL) Treatment			
Study identifier	OOC-ACM-303 Phase 3		
	Secondary efficacy endpoint	Change in IGF-1.	Change from Baseline (average of 2 assessments within 2 weeks prior to randomisation) to end of treatment in IGF-1.
Database lock	Not provided clearly.		

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population and time point description	Full Analysis Set (FAS)					
		Octreotide Capsule Treatment				**Placebo**
Descriptive statistics and estimate variability	Treatment group	40 mg	60 mg	80 mg	Total	**Placebo**
	Number of subjects	7	2	19	28	28
	Responder (absolute number)	5 (71.4)	1 (50.0)	10 (52.6)	16 (57.1)	5 (17.9)
	Adjusted proportions (Responder)				58.16	19.42
	Difference in adjusted proportions				38.74	
	95% CI for Responder difference				(10.68, 59.90)	
	P value				0.0079	
	Odds ratio				5.7674	
	95% CI				(1.4440, 28.2115)	
Notes	Database lock date should be provided clearly.					
Analysis description	**Secondary analyses**					

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Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy and Safety of Octreotide Capsules in Patients Who Previously Tolerated and Demonstrated Biochemical Control on Injectable Somatostatin Receptor Ligands (SRL) Treatment	
Study identifier	OOC-ACM-303 Phase 3
GH response	Proportion of patients who maintained GH response (ie, GH < 2.5 ng/mL) at week 36, out of those who were responders (ie, GH < 2.5 ng/mL) on SRL injections at screening. Seventy-eight percent (77.7%) of patients treated with octreotide capsules maintained their GH levels below 2.5 ng/mL at the end of the DPC period vs 30.4% on placebo (p = 0.0007)
IGF-1 > 1 times ULN	Time to loss of response, IGF-1 > 1 times ULN. The time to loss of response (IGF-1 > 1 times ULN) was significantly greater in the octreotide capsule group (median > 36 weeks) vs the placebo group (median = 16 weeks) (p < 0.0001).
IGF-1 > 1.3 times ULN	Time to loss of response, IGF-1 > 1.3 times ULN. The time to loss of response (IGF-1 ⩾ 1.3 times ULN) was significantly greater in the octreotide capsule group (median > 36 weeks) vs the placebo group (median = 16 weeks) (p < 0.0001).
Rescue treatment	Proportion of patients who began rescue treatment prior to and including week 36. Seventy-five percent (75%) of patients treated with octreotide capsules did not require rescue medication with injectable SRLs (octreotide LAR or lanreotide depot) anytime throughout the core study vs 32.1% of patients treated with placebo (p = 0.0029).
Change in mean GH.	Change from Baseline (screening assessment) to end of treatment in mean GH. The observed mean change from Baseline (Screening assessment) in GH level, including data on rescue medications, was -0.03 ng/mL in the octreotide capsule group and 0.18 ng/mL in the placebo group. The median change in both groups was zero from Screening to end of study. The mean GH of all patients treated with octreotide capsules (both responders and non-responders) at the end of treatment was maintained below 1 ng/mL (mean = 0.60 ng/mL) while it was > 2.5 ng/mL in the placebo group (mean = 2.57 ng/mL).
Change in IGF-1.	Change from Baseline (average of 2 assessments within 2 weeks prior to randomisation) to end of treatment in IGF-1. The observed IGF-1 mean change from Baseline to the end of study, including data on rescue medications, was 0.13 times ULN in the octreotide capsule group and 0.13 times ULN in the placebo group. The median change from Baseline to end of study in the octreotide capsule group and placebo group was 0.0 and 0.1 times ULN, respectively.

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Table 3.4.3. Summary of efficacy for Phase 3 trial CH-ACM-01

Title: Efficacy and Safety of Oral Octreolin™ in Patients with Acromegaly Who Are Currently Receiving Parenteral Somatostatin Analogs			
Study identifier	CH-ACM-01 Phase 3		
Design	Single-arm, baseline-controlled, followed by an OLE phase		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Study Period: Approximately 26 months Initiation Date: 13 March 2012 Completion Date: 30 May 2014 Screening Period: Up to 4 weeks; Baseline Period: Up to 4 weeks; Core Treatment Period: At least 7 months (this included a Dose Escalation Phase of ⩾ 2 months and a Fixed Dose Phase (Core) of 2 to 5 months); Voluntary Extension Treatment Period/Fixed Dose Phase (Extension): At least 6 months; and 5. Follow-up Period: 2 weeks.
Hypothesis	The primary efficacy analysis was descriptive and presented the proportion of responders in the mITT Population at the End of Treatment with an exact 95% CI. Response was defined as IGF-1 < 1.3 times the ULN adjusted for age and an integrated GH level over 2 hours < 2.5 ng/mL.		
Treatments groups	Oral octreotide		Oral octreotide treatment was started at a total dose of 40 mg per day and up titrated up to 80 mg/day based on IGF-1 levels.
	Reference Therapy		Patients currently maintained on a stable dose of an injectable SRL were switched from their ongoing therapy to MYCAPSSA.
Endpoints and definitions	Primary endpoint	n/a	Concentrations of IGF-1 and mean GH over 2 hours at the end of the Core Treatment Period as a measure of response in the modified Intention-to-Treat (mITT) Population. Response was defined as IGF-1 < 1.3 times ULN adjusted for age and an integrated GH level over 2 hours < 2.5 ng/mL.
	Co-Primary endpoint	n/a	Proportion of patients with the following IGF-1 and GH values at baseline and at the end of the Core Treatment Period.
	Co-Primary endpoint	n/a	Maintenance of IGF-1 response during the Fixed Dose Phase (Core) - Proportion of patients with IGF-1 levels (adjusted for age) < 1.3 times ULN at the end of the Core Treatment Period who also had IGF 1 levels (adjusted for age) < 1.3 times ULN at the first assessment in the Fixed Dose Phase
	Secondary efficacy endpoint	n/a	Maintenance of IGF-1 and GH response during the Fixed Dose Phase (Core) - Proportion of responders (IGF 1 levels [adjusted for age] < 1.3 times ULN and integrated GH < 2.5 ng/mL) at the end of the Core Treatment Period who also had IGF 1 levels (adjusted for age) < 1.3 times ULN and GH < 2.5 ng/mL at the first assessment in the Fixed Dose Phase

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Title: Efficacy and Safety of Oral Octreolin™ in Patients with Acromegaly Who Are Currently Receiving Parenteral Somatostatin Analogs					
Study identifier	CH-ACM-01 Phase 3				
Database lock	Not provided clearly.				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	mITT Population				
Descriptive statistics and estimate variability Descriptive statistics and estimate variability	Responders				
	Percentage	64.9%			
	95% CI	(58.4 – 74.2)			
	LOCF (last observation carried forward) Imputation	Summary of Responders at the End of Treatment (Octreotide (OCT) Capsule Treatment)			
	Treatment group, mITT Population	OCT 20 + 20	OCT 40 + 20	OCT 40 + 40	Total
	Number of subjects	61	33	57	151
	Responders	53	22	23	98
	Percentage	86.9	66.7	40.4	64.9
	95% CI for percentage	83.0 – 98.1	48.2 – 82.0	27.6 – 54.2	58.4 – 74.2
	Worst Case Imputation, ITT/Safety Population	Summary of Responders at the End of Treatment			
	Number of subjects	65	33	57	155
	Responders	48	19	15	82
	Percentage	73.8	57.6	26.3	52.9
	Exact 95% CI for percentage	61.5 – 84.0	39.2 – 74.5	15.5 – 39.7	44.7 – 61.0
Notes	Database lock date should be provided clearly.				
Analysis description	**Secondary analyses**				

Title: Efficacy and Safety of Oral Octreolin™ in Patients with Acromegaly Who Are Currently Receiving Parenteral Somatostatin Analogs		
Study identifier	CH-ACM-01 Phase 3	
IGF-1 and GH value stratified response, Core Treatment Period.		
mITT Population (N=151)	Baseline n (%)	End of Treatment n (%)
IGF-1 < 1.3 times ULN and GH < 5.0 ng/mL	138 (91.4)	99 (65.6)
IGF-1 < 1.3 times ULN and GH < 1.0 ng/mL	95 (62.9)	80 (53.0)
IGF-1 ⩽ 1.0 times ULN and GH < 5.0 ng/mL	96 (63.6)	54 (35.8)
IGF-1 ⩽ 1.0 times ULN and GH < 2.5 ng/mL	93 (61.6)	54 (35.8)
IGF-1 ⩽ 1.0 times ULN and GH < 1.0 ng/mL	65 (43.0)	48 (31.8)
IGF-1 < 1.3 times ULN	138 (91.4)	101 (66.9)
IGF-1 ⩽ 1.0 times ULN	96 (63.6)	56 (37.1)
GH < 5.0 ng/mL	151 (100.0)	147 (97.4)
GH < 2.5 ng/mL	145 (96.0)	143 (94.7)
GH < 1.0 ng/mL	100 (66.2)	117 (77.5)
IGF-1 ⩾ 1.3 times ULN and GH < 2.5 ng/mL	11 (7.3)	45 (29.8)
IGF-1 < 1.3 times ULN and GH ⩾ 2.5 ng/mL	4 (2.6)	1 (0.7)
IGF-1 ⩾ 1.3 times ULN and GH ⩾ 2.5 ng/mL	2 (1.3)	3 (2.0)
	First Assessment in Fixed Dose Phase n (%)	End of Treatment n (%)
FD Population (N=110)		
IGF-1 < 1.3 times ULN and GH < 5.0 ng/mL	91 (82.7)	88 (80.0)
IGF-1 < 1.3 times ULN and GH < 1.0 ng/mL	82 (74.5)	72 (65.5)
IGF-1 ⩽ 1.0 times ULN and GH < 5.0 ng/mL	59 (53.6)	51 (46.4)
IGF-1 ⩽ 1.0 times ULN and GH < 2.5 ng/mL	59 (53.6)	51 (46.4)

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Title: Efficacy and Safety of Oral Octreolin™ in Patients with Acromegaly Who Are Currently Receiving Parenteral Somatostatin Analogs		
Study identifier	CH-ACM-01 Phase 3	
IGF-1 ⩽ 1.0 times ULN and GH < 1.0 ng/mL	53 (48.2)	45 (40.9)
IGF-1 < 1.3 times ULN	91 (82.7)	88 (80.0)
IGF-1 ⩽ 1.0 times ULN	59 (53.6)	51 (46.4)
GH < 5.0 ng/mL	109 (99.1)	110 (100.0)
GH < 2.5 ng/mL	109 (99.1)	108 (98.2)
GH < 1.0 ng/mL	97 (88.2)	90 (81.8)
IGF-1 ⩾ 1.3 times ULN and GH < 2.5 ng/mL	18 (16.4)	21 (19.1)
IGF-1 < 1.3 times ULN and GH ⩾ 2.5 ng/mL	0 (0.0)	1 (0.9)
IGF-1 ⩾ 1.3 times ULN and GH ⩾ 2.5 ng/mL	1 (0.9)	1 (0.9)

Fixed Dose responders		
Responders and IGF-1 Response Status		
Response Cohort	Beginning of Fixed Dose Phase n (%)	End of Fixed Dose Phase n (%)
Responders at First Assessment of the Fixed Dose Phase (N)		91
Response	91 (100.0)	82 (90.1)
Patients with IGF-1 < 1.3 times ULN at First Assessment in the Fixed Dose Phase (N)		91
IGF-1 < 1.3 times ULN	91 (100.0)	83 (91.2)

Maintenance of IGF-1 response during the Fixed Dose Phase (Core).	Of the 110 patients in the FD Population, 87 (79.1%) were responders at the End of Treatment (Core) based on the LOCF imputation method. Response rates for the 40 mg was 94.2% and for 60 mg - 76.0%, while for the 80 mg dose group the response was 57.6%.Of the 91 patients who entered the Fixed Dose Phase as responders (defined as IGF-1 < 1.3 times ULN adjusted for age and an integrated GH over 2 hours < 2.5 ng/mL), 82 patients (90.1% [95% CI: 82.1 – 95.4]) maintained their response at the End of Treatment (Core) based on the LOCF imputation method.

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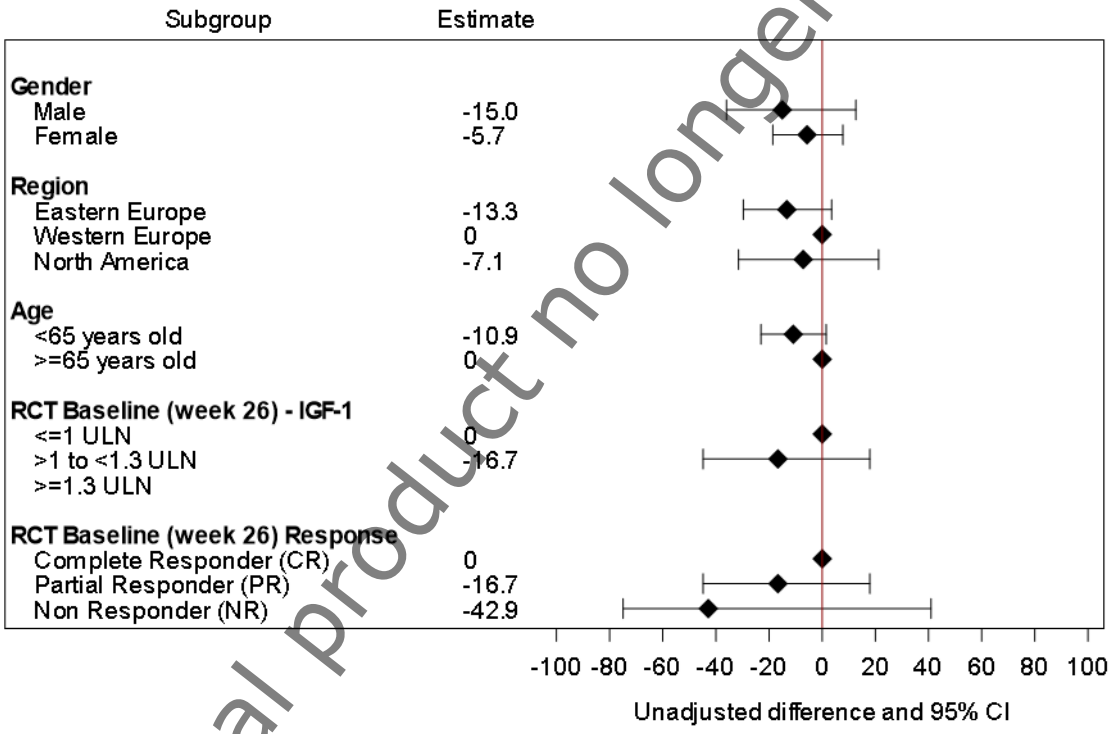
2.10.5.3. Clinical studies in special populations

Designated clinical studies were not conducted in special populations.

Efficacy in subpopulations of study OOC-ACM-302

Subgroup analyses were performed for the primary efficacy endpoint (proportion of patients who were biochemically controlled throughout the RCT phase) based on the patient's age, gender, region, RCT baseline IGF-1, and RCT baseline response. The primary endpoint results were similar in subgroups based on gender, region, and age (Figure 3.3.4.4.1.). Note that no patients 75 years of age or older were enrolled into the RCT phase.

Figure 3.3.4.4.1. Forest plot of treatment difference in proportion of patients who were biochemically controlled throughout the RCT phase by subgroup in study OOC-ACM-302 (FAS)



Source: CSR OOC-ACM-302, Figure 14.2.1.1

The applicant performed efficacy assessments in male/females and several different age groups. These analyses did not reveal essential differences in efficacy. There is no proposal for special dosage in the elderly population. The SmPC of Sandostatin states that "*There is no evidence of reduced tolerability or altered dosage requirements in elderly patients treated with Sandostatin*." The applicability of this recommendation to Mycapssa was confirmed by the applicant during the procedure.

2.10.5.4. In vitro biomarker test for patient selection for efficacy

N/A

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2.10.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Phase 3 studies met their primary endpoints. There were differences in the definition of the efficacy endpoints of the Phase 3 studies.

Table 3.3.4.6. Maintenance of response and symptom improvement results of the Phase 3 studies

	OOC-ACM-302	OOC-ACM-303	CH-ACM-01
Maintenance of response to octreotide capsules	90.9% [1]	91.7% [2]	90.1% [3]
Symptom improvement based on AIS	Significant reduction in number of patients with swelling of extremities (p = 0.011) and fatigue (p = 0.031); borderline significance for joint pain (p = 0.096) [4]	- [5]	Significant reduction in symptom scores for swelling of extremities (p = 0.0070), fatigue (p = 0.0151), and joint pain (p = 0.0146) [6]

Maintenance of response in phase 3 studies was presented in Table 3.3.4.6.

No pooled analyses or meta-analysis as performed, assumingly due to differences in the definition of the efficacy endpoints. This was considered acceptable.

2.10.5.6. Supportive studies

OOC-ACM-302 additional sub studies.

Study Extension Phase. 34 of the 54 patients who completed the RCT phase (63.0%) from the octreotide capsule group elected to continue into the Study Extension phase for an additional 12 months. Of the 35 patients who completed the RCT phase after switching from injectable SRLs to octreotide capsules on Baseline and then switching back to injectable SRLs at the beginning of the RCT, 18 patients (51.4%) elected to switch again from injectable SRLs to octreotide capsules and entered the Study Extension phase.

Combination Phase Sub-study. Cabergoline (up to 3.5 mg/week per a fixed titration algorithm) was co-administered with octreotide capsules 80 mg in the Combination phase sub-study. All 8 patients (100%) who completed the Combination phase maintained or improved their IGF-1 category from Combination Phase Baseline to the end of the Combination phase.

OOC-ACM-303 OLE Study

This clinical study report addendum summarises the data from the first 48 weeks of the open-label extension (OLE) of study OOC-ACM-303. Forty patients (20 from each treatment group in the double-blind, placebo-controlled [DPC] period) were enrolled into the OLE. As of the 12 May 2020 data cut-off date, all ongoing patients completed 48 weeks of the OLE.

• 90% of patients enrolled into the OLE who were treated with octreotide capsules during the DPC period (n = 20) completed 48 weeks in the OLE.

• Patients who completed the DPC period on octreotide capsules maintained their insulin-like growth factor 1 (IGF-1) level at the end of the 48 weeks OLE (0.91 times upper limit of normal [ULN] at baseline and 0.90 times ULN at 48 weeks).

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FU study CH-ACM-01

This study was a follow-up, retrospective, non-interventional study in patients with acromegaly who previously participated in and completed the Chiasma CH-ACM-01 study. No study drug was administered.

Two groups were recruited: (1) patients who had not restarted acromegaly therapy and patients whose data are missing regarding treatment initiation at the end of the 2- week follow-up period; (2) all MYCAPSSA responders who restarted acromegaly therapy after completing the CH-ACM-01 study. Of the 155 patients who participated in CH-ACM-01, 149 patients (96.2%) have restarted acromegaly treatment, 3 patients (1.9%) have not re-initiated treatment, and no data are available for the remaining 3 patients (1.9%): 2 patients died, and 1 patient refused to sign an informed consent. Analysis of retained follow-up serum samples Twenty-four of the 51 patients (with evaluable samples, who had not re-initiated medical treatment with SRLs before the follow-up serum sample was collected), had IGF-1 ≥ 1.3 times ULN from the retained serum sample collected during the approximate 2-week follow-up period. Thus, overall, 36 (24+2+10) of 51 patients (70.6%) lost IGF-1 control within 2 weeks following cessation of treatment

2.10.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy data was collected from 3 trials: (1) OOC-ACM-302 a Phase 3 Randomised, open-label, active-controlled, preceded by a run-in phase, followed by an OLE phase trial, (2) OOC-ACM-303 a Phase 3 Randomised, double-blind, placebo-controlled, followed by an OLE phase, and (3) CH-ACM-01 Phase 3 Single-arm, baseline-controlled, followed by an OLE phase. The design of the studies was adequate and the populations were adequately selected. The active control trial used an appropriate comparator, i.e. the same active substance administered s/c that can be regarded as standard of care.

Efficacy data and additional analyses

The main issue during the assessment that constituted an overarching major objection was connected to the points noted in the clinical pharmacology section and in the efficacy section: the applicant proposes a novel oral formulation of octreotide that has similar bioavailability as described for subcutaneously injectable somatostatin analogue (2 mg of octreotide orally administered was comparable to subcutaneous injection of 50 micrograms [20 mg would be comparable to 0.5 mg sc] while the proposed octreotide capsule 20 mg was comparable to 0.1 mg octreotide sc in systemic exposure [AUC]). Due to quite variable bioavailability the octreotide does not seem constantly reaching therapeutical values in all populations and that is why a substantial number of switched ACM patients do not maintain efficacy and withdraw due to failure. Due to possibly too low comparative efficacy likely related to high withdrawal rate during switch (run-in) period, one major objection was raised. This major objection was addressed by the applicant and is currently considered to be resolved (see below).

Mycapssa showed NI against standard of care (SRL inj) by primary Biochemical control in 50/55 [90,9%] vs 37/37 [100%] of patients with a difference [95%CI] of -9.1% [-19.9, 0.5], measured by IGF-1 <1.3xULN TWA during the RCT phase in Study 302. This primary effect was supported by a number of secondary endpoints: Proportion of ACM patients with Clinical control (measured by AIS score) as well as with co-secondary Clinical and Biochemical control effects with difference [95%CI] between Mycapssa and SRL inj of 5.4% [-13.2, 25.2] and -6.8% [-25.3, 13.2], respectively. The primary efficacy analysis was supported also by clinical superiority effect over placebo shown in

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another pivotal Study 303 in measuring responder analyses maintaining average IGF-1 1xULN with difference [95%CI] of 38.74% [10.68, 59.90].

The primary effect observed in Study 302 was considered as clinically relevant, because the NI with margin of 20% was not exceeded.

Major issues raised was the risk of possibly too low comparative efficacy due to high withdrawal rate during switch (run-in) period.

It was noted that 30-40% of patients switching from SRL to Mycapssa do not benefit from the switch. The applicant was requested to provide the reasons for discontinuation or decision not to randomise these patients (AEs, loss of effect) and to justify the acceptability of the observed responder rate and demographics and complementing characteristics.

The applicant clarified that the majority of patients responded to octreotide capsules at the end of the Run-in phase (64-78%) and only 5.5% discontinued treatment during the Run-in phase due to loss of efficacy (treatment failure). The applicant also believes that: a) the observed response rate is in line with maintenance of response rates in prior clinical trials with injectable somatostatin analogues; b) patients that respond to octreotide capsules maintain their response for long term.

The provided data show that Mycapssa can be beneficial for patients that respond to octreotide capsules and reduce the need for injections and associated inconveniences. The patients that fail the oral therapy trial can be reverted to injectable treatment options.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

N/A

2.10.7. Conclusions on clinical efficacy

During the assessment a major objection was raised due to limited efficacy: it was noted that 30-40% of patients switching from SRL to Mycapssa do not benefit from the switch. The applicant was requested to provide the reasons for discontinuation or decision not to randomise these patients (AEs, loss of effect) and to justify the acceptability of the observed responder rate and demographics and complementing characteristics. The provided data show that Mycapssa can be beneficial for patients that respond to octreotide capsules and reduce the need for injections and associated inconveniences. The patients that fail the oral therapy trial can be reverted to injectable treatment options.

2.10.8. Clinical safety

2.10.8.1. Patient exposure

During the clinical development programme, 571 human subjects received at least 1 dose of octreotide capsules. In the 11 clinical pharmacology studies, a total of 214 subjects were exposed to octreotide capsules for 1 to 6 days.

In the 3 Phase 3 studies, a total of 349 patients with acromegaly were exposed to octreotide capsules (146 in study OOC-ACM-302, 48 in study OOC-ACM-303, and 155 in study CH-ACM-01). The overall

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exposure to octreotide capsules monotherapy in these studies was 390.2 patient years (192.7 patient years in study OOC-ACM-302, 71.6 patient years in study OOC-ACM-303, and 125.9 patient years in study CH-ACM-01).

Overall, 154 patients were treated for up to 1 year, 137 patients for between 1 and 2 years, and 58 patients for more than 2 years.

Extent of exposure in the clinical pharmacology studies

For the 214 subjects who were exposed in the 11 clinical pharmacology studies (184 healthy volunteers, 18 subjects with hepatic impairment, 6 subjects with severe renal impairment, and 6 subjects with end-stage renal disease [ESRD] on dialysis), drug exposure was typically 1 day and not more than 6 days.

Baseline characteristics for Study 302 are provided in Table 3.3.2.4.2. (Section efficacy) and amended safety characteristics for Studies 303 and ACM-01 in this section below.

Table 3.3.7.1. Acromegaly baseline characteristics of patients in studies OOC-ACM-303 and CH-ACM-01 (Safety set)

	OOC-ACM-303			**CH-ACM-01**	
	Core treatment phase		OLE phase	Core treatment phase	OLE phase
	Octreotide capsules (N = 28)	Placebo (N = 28)	Octreotide capsules (N = 40)	Octreotide capsules (N = 155)	Octreotide capsules (N = 88)
Pituitary tumour (n [%])					
Microadenoma	10 (35.7)	9 (32.1)	13 (32.5)	52 (33.5)	32 (36.4)
Macroadenoma	6 (21.4)	5 (17.9)	6 (15.0)	98 (63.2)	53 (60.2)
Other	12 (42.9)	14 (50.0)	21 (52.5)	5 (3.2)	3 (3.4)
Duration of acromegaly (n [%])					
<10 years	15 (53.6)	20 (71.4)	23 (57.5)	74 (47.7)	43 (48.9)
10 to <20 years	8 (28.6)	5 (17.9)	11 (27.5)	53 (34.2)	28 (31.8)
≥20 years	5 (17.9)	3 (10.7)	6 (15.0)	28 (18.1)	17 (19.3)
Baseline IGF-1 (ULN)					
Mean (SD)	0.8 (0.16)	0.8 (0.21)	0.8 (0.19)	0.9 (0.25)	0.9 (0.21)
Baseline IGF-1 (categorical) (n [%])					
≤ 1 x ULN	27 (96.4)	23 (82.1)	35 (87.5)	99 (63.9)	69 (78.4)

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> 1 to < 1.3 x ULN	1 (3.6)	5 (17.9)	5 (12.5)	43 (27.7)	17 (19.3)
≥ 1.3 x ULN	0	0	0	13 (8.4)	2 (2.3)
Baseline GH (ULN)					
Mean (SD)	0.7 (0.75)	0.9 (1.01)	0.7 (0.83)	0.9 (0.72)	1.0 (0.69)
Baseline GH (categorical) (n [%])					
<2.5 ng/mL	27 (96.4)	25 (89.3)	38 (95.0)	148 (95.5)	85 (96.6)
≥2.5 ng/mL	1 (3.6)	3 (10.7)	2 (5.0)	7 (4.5)	3 (3.4)

Overall, 154 patients were treated for up to 1 year, 137 patients for between 1 and 2 years, and 58 patients for more than 2 years.

Across all the 3 Phase 3 studies of octreotide, subjects have been exposed to octreotide at total daily doses ranging from 40 to 80 mg, which is consistent with the applied octreotide capsules doses.

The demographic characteristics were very similar across the Phase 3 studies. Patients were predominantly White/Caucasian (only few subjects were Asian and Black) with a mean age of 54 years, about 20% were elderly, and about 60% were females. The demographic data were well balanced between the octreotide capsules and control groups.

The acromegaly baseline characteristics of patients were similar across the Phase 3 studies. About half of the enrolled patients had an acromegaly duration of <10 years. Mean baseline IGF-1 levels were 0.8 - 0.9 x upper limit of normal (ULN); mean baseline GH levels ranged between 0.7 and 0.9 ng/mL.

For the 214 subjects who were exposed in the 11 clinical pharmacology studies (184 healthy volunteers, 18 subjects with hepatic impairment, 6 subjects with severe renal impairment, and 6 subjects with end-stage renal disease [ESRD] on dialysis), drug exposure period was very short: it was typically 1 day and not more than 6 days.

The safety size was considered sufficient for long-term exposure assessment.

2.10.8.2. Adverse events

Adverse events in the Phase 3 studies

The applicant presented the data that the most commonly reported AEs across the 3 Phase 3 studies with octreotide capsules were belonged to the System Organ Class (SOC) gastrointestinal disorders, nervous system disorders, musculoskeletal and connective tissue disorders, general disorders and administration site conditions, infections and infestations, skin and subcutaneous disorders, and investigations.

RCT Phase of Study OOC-ACM-302

19 patients (34.5%) in the octreotide capsule group and 15 patients (40.5%) in the SRL injection group experienced a TEAE that was considered related to study drug. Five patients (9.1%) in the octreotide capsule group and 4 patients (10.8%) in the SRL injection group experienced 1 or more severe TEAEs. The incidence of the following common TEAEs (reported by ≥ 3% of patients in either treatment group) was higher in the octreotide capsule group than in the SRL injection group: flatulence

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(25.5% vs 21.6%), nausea (20.0% vs 8.1%), abdominal pain (9.1% vs 8.1%), nasopharyngitis (9.1% vs 0%), headache (9.1% vs 2.7%), arthralgia (9.1% vs 5.4%), influenza (3.6% vs 2.7%), acute sinusitis (3.6% vs 0%), urinary tract infection (3.6% vs 0%), peripheral swelling (5.5% vs 0%), osteoarthritis (5.5% vs 0%), and cough (3.6% vs 2.7%).

Table 3.3.7.2.1 Overview of adverse events in study OOC-ACM-302

	Run-in phase	RCT phase		OLE phase
	Octreotide capsules (N = 146) n (%)	Octreotide capsules (N = 55) n (%)	SRL injections (N = 37) n (%)	Octreotide capsules (N = 57) n (%)
Patients with at least 1 AE	106 (72.6)	39 (70.9)	26 (70.3)	27 (47.4)
Patients with at least 1 SAE	6 (4.1)	3 (5.5)	3 (8.1)	4 (7.0)
Patients with at least 1 moderate AE	48 (32.9)	16 (29.1)	8 (21.6)	14 (24.6)
Patients with at least 1 severe AE	19 (13.0)	5 (9.1)	4 (10.8)	7 (12.3)
Patients with a treatment-related AE	79 (54.1)	19 (34.5)	15 (40.5)	10 (17.5)
Patients with an AE leading to study drug discontinuation	14 (9.6)	1 (1.8)	0	1 (1.8)
Deaths	0	1 (1.8)	0	0

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Table 3.3.7.2.2 Overview of adverse events in studies OOC-ACM-303 and CH-ACM-01 (Safety set)

	OOC-ACM-303			CH-ACM-01	
	Core treatment phase		OLE phase	Core treatment phase	OLE phase
	Octreotide capsules (N = 28) n (%)	Placebo (N = 28) n (%)	Octreotide capsules (N = 40) n (%)	Octreotide capsules (N = 155) n (%)	Octreotide capsules (N = 88) n (%)
Patients with at least 1 AE	28 (100)	27 (96.4)	36 (90.0)	134 (86.5)	58 (65.9)
Patients with at least 1 SAE	2 (7.1)	1 (3.6)	6 (15.0)	17 (11.0)	6 (6.8)
Patients with at least 1 moderate AE	14 (50.0)	12 (42.9)	12 (30.0)	60 (38.7)	16 (18.2)
Patients with at least 1 severe AE	3 (10.7)	7 (25.0)	8 (20.0)	42 (27.1)	14 (15.9)
Patients with a **treatment-related AE**	18 (64.3)	15 (**53.6**)	20 (50.0)	89 (57.4)	21 (23.9)
Patients with an AE leading to study drug discontinuation	2 (7.1)	1 (3.6)	1 (2.5)	22 (14.2)	1 (1.1)
Patients who died due to an AE	0	0	0	2 (1.3)	0

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Table 3.3.7.2.3. Adverse events reported for >5% of patients in any phase of study OOC-ACM-302 by SOC and PT

SOC PT	Run-in phase Octreotide capsules (N = 146)	RCT phase Octreotide capsules (N = 55)	RCT phase SRL injections (N = 37)	OLE phase Octreotide capsules (N = 57)
Patients with at least 1 AE	106 (72.6)	39 (70.9)	26 (70.3)	27 (47.4)
Gastrointestinal disorders	72 (49.3)	23 (41.8)	13 (35.1)	15 (26.3)
Abdominal pain	13 (8.9)	5 (9.1)	3 (8.1)	2 (3.5)
Abdominal pain upper	8 (5.5)	0	0	2 (3.5)
Constipation	5 (3.4)	3 (5.5)	5 (13.5)	2 (3.5)
Diarrhoea	22 (15.1)	6 (10.9)	5 (13.5)	5 (8.8)
Flatulence	14 (9.6)	14 (25.5)	8 (21.6)	1 (1.8)
Nausea	32 (21.9)	11 (20.0)	3 (8.1)	3 (5.3)
Vomiting	5 (3.4)	0	2 (5.4)	3 (5.3)
General disorders and administration site conditions	21 (14.4)	4 (7.3)	9 (24.3)	6 (10.5)
Fatigue	9 (6.2)	1 (1.8)	1 (2.7)	1 (1.8)
Injection site nodule	1 (0.7)	0	5 (13.5)	0
Injection site pain	1 (0.7)	0	3 (8.1)	0
Pain	0	0	2 (5.4)	0
Peripheral swelling	7 (4.8)	3 (5.5)	0	0
Infections and infestations	39 (26.7)	15 (27.3)	6 (16.2)	8 (14.0)
Nasopharyngitis	9 (6.2)	5 (9.1)	0	4 (7.0)
Urinary tract infection	8 (5.5)	2 (3.6)	0	2 (3.5)
Musculoskeletal and connective tissue disorders	22 (15.1)	9 (16.4)	3 (8.1)	9 (15.8)
Arthralgia	6 (4.1)	5 (9.1)	2 (5.4)	3 (5.3)
Back pain	5 (3.4)	0	1 (2.7)	3 (5.3)
Osteoarthritis	0	3 (5.5)	0	1 (1.8)
Nervous system disorders	27 (18.5)	6 (10.9)	7 (18.9)	5 (8.8)
Dizziness	9 (6.2)	0	3 (8.1)	1 (1.8)
Headache	18 (12.3)	5 (9.1)	1 (2.7)	0
Skin and subcutaneous tissue disorders	6 (4.1)	2 (3.6)	4 (10.8)	1 (1.8)
Erythema	0	0	4 (10.8)	0

Table 3.3.7.2.4 Treatment-related adverse events reported for at least 3% of patients on PT level in any treatment group/phase of study OOC-ACM-302, by SOC and PT

SOC PT	Run-in phase Octreotide capsules (N = 146)	RCT phase Octreotide capsules (N = 55)	RCT phase SRL injections (N = 37)	OLE phase Octreotide capsules (N = 57)
Patients with at least 1 treatment-related AE	79 (54.1)	19 (34.5)	15 (40.5)	10 (17.5)
Gastrointestinal disorders	68 (**46.6**)	17 (30.9)	9 (24.3)	8 (14.0)
Abdominal distension	5 (3.4)	0	1 (2.7)	0
Abdominal pain	12 (8.2)	3 (5.5)	2 (5.4)	0
Abdominal pain upper	7 (4.8)	0	0	0

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Constipation	3 (2.1)	1 (1.8)	3 (8.1)	0
Diarrhoea	20 (13.7)	4 (7.3)	5 (13.5)	3 (5.3)
Dyspepsia	5 (3.4)	1 (1.8)	0	2 (3.5)
Flatulence	12 (8.2)	10 (18.2)	6 (16.2)	1 (1.8)
Nausea	31 (21.2)	9 (16.4)	1 (2.7)	2 (3.5)
General disorders and administration site conditions	5 (3.4)	0	8 (21.6)	1 (1.8)
Injection site nodule	1 (0.7)	0	5 (13.5)	0
Injection site pain	1 (0.7)	0	3 (8.1)	0
Pain	0	0	2 (5.4)	0
Nervous system disorders	9 (6.2)	1 (1.8)	0	0
Headache	7 (4.8)	1 (1.8)	0	0
Skin and subcutaneous tissue disorders	1 (0.7)	0	4 (10.8)	0
Erythema	0	0	4 (10.8)	0

Table 3.3.7.2.5 Adverse events reported for at least 5% of patients on PT level in studies OOC-ACM-303 and CH-ACM-01, by SOC and PT (Safety set)

	OOC-ACM-303			**CH-ACM-01**	
	Core treatment phase		OLE phase	Core treatment phase	OLE phase
SOC PT	Octreotide capsules (N = 28)	Placebo (N = 28)	Octreotide capsules (N = 40)	Octreotide capsules (N = 155)	Octreotide capsules (N = 88)
Patients with at least 1 AE	28 (100)	27 (96.4)	36 (90.0)	134 (86.5)	58 (65.9)
Gastrointestinal disorders	19 (67.9)	17 (60.7)	21 (52.5)	89 (57.4)	17 (19.3)
Nausea	6 (21.4)	3 (10.7)	8 (20.0)	46 (29.7)	0
Diarrhoea	8 (28.6)	6 (21.4)	5 (12.5)	28 (18.1)	5 (5.7)
Dyspepsia	3 (10.7)	1 (3.6)	0	13 (8.4)	2 (2.3)
Flatulence	1 (3.6)	2 (7.1)	2 (5.0)	9 (5.8)	1 (1.1)
Abdominal distension	1 (3.6)	1 (3.6)	3 (7.5)	10 (6.5)	1 (1.1)
Abdominal pain upper	1 (3.6)	3 (10.7)	3 (7.5)	12 (7.7)	3 (3.4)
Abdominal pain	2 (7.1)	2 (7.1)	3 (7.5)	8 (5.2)	4 (4.5)
Vomiting	4 (14.3)	0	5 (12.5)	9 (5.8)	1 (1.1)
Abdominal discomfort	4 (14.3)	3 (10.7)	1 (2.5)	4 (2.6)	0
Large intestine polyp	2 (7.1)	0	0	1 (0.6)	0
Nervous system disorders	10 (35.7)	13 (46.4)	14 (35.0)	61 (39.4)	18 (20.5)
Headache	4 (14.3)	9 (32.1)	4 (10.0)	51 (32.9)	13 (14.8)
Dizziness	1 (3.6)	0	4 (10.0)	8 (5.2)	1 (1.1)
Paraesthesia	0	2 (7.1)	4 (10.0)	3 (1.9)	2 (2.3)
Hypoaesthesia	0	2 (7.1)	2 (5.0)	2 (1.3)	0
Carpal tunnel syndrome	4 (14.3)	4 (14.3)	5 (12.5)	1 (0.6)	0
Tremor	0	0	2 (5.0)	1 (0.6)	0
Musculoskeletal and connective tissue disorders	11 (39.3)	21 (75.0)	18 (45.0)	57 (36.8)	13 (14.8)
Arthralgia	9 (32.1)	16 (57.1)	8 (20.0)	40 (25.8)	11 (12.5)
Back pain	2 (7.1)	4 (14.3)	2 (5.0)	9 (5.8)	1 (1.1)
Pain in extremity	0	3 (10.7)	2 (5.0)	2 (1.3)	0

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SOC PT	OOC-ACM-303 Core treatment phase Octreotide capsules (N = 28)	 Placebo (N = 28)	 OLE phase Octreotide capsules (N = 40)	CH-ACM-01 Core treatment phase Octreotide capsules (N = 155)	 OLE phase Octreotide capsules (N = 88)
Joint swelling	1 (3.6)	0	3 (7.5)	1 (0.6)	0
Muscular weakness	0	0	2 (5.0)	0	0
Osteoarthritis	3 (10.7)	0	1 (2.5)	0	1 (1.1)
Soft tissue swelling	1 (3.6)	3 (10.7)	3 (7.5)	0	0
General disorders and administration site conditions	10 (35.7)	15 (53.6)	18 (45.0)	53 (34.2)	15 (17.0)
Asthenia	0	1 (3.6)	2 (5.0)	34 (21.9)	9 (10.2)
Peripheral swelling	3 (10.7)	4 (14.3)	4 (10.0)	24 (15.5)	3 (3.4)
Fatigue	2 (7.1)	7 (25.0)	4 (10.0)	8 (5.2)	2 (2.3)
Oedema peripheral	2 (7.1)	3 (10.7)	2 (5.0)	2 (1.3)	0
Influenza like illness	0	2 (7.1)	4 (10.0)	2 (1.3)	0
Pain	2 (7.1)	0	1 (2.5)	0	0
Infections and infestations	13 (46.4)	8 (28.6)	18 (45.0)	52 (33.5)	19 (21.6)
Nasopharyngitis	3 (10.7)	4 (14.3)	7 (17.5)	11 (7.1)	2 (2.3)
Influenza	0	0	0	10 (6.5)	2 (2.3)
Upper respiratory tract infection	1 (3.6)	2 (7.1)	4 (10.0)	8 (5.2)	3 (3.4)
Urinary tract infection	2 (7.1)	1 (3.6)	5 (12.5)	5 (3.2)	2 (2.3)
Sinusitis	3 (10.7)	0	3 (7.5)	3 (1.9)	0
Viral upper respiratory tract infection	1 (3.6)	0	2 (5.0)	0	0
Skin and subcutaneous tissue disorders	8 (28.6)	11 (39.3)	13 (32.5)	41 (26.5)	11 (12.5)
Hyperhidrosis	6 (21.4)	7 (25.0)	5 (12.5)	33 (21.3)	9 (10.2)
Night sweats	1 (3.6)	2 (7.1)	2 (5.0)	2 (1.3)	0
Investigations	9 (32.1)	10 (35.7)	14 (35.0)	23 (14.8)	12 (13.6)
Blood glucose increased	3 (10.7)	1 (3.6)	6 (15.0)	5 (3.2)	0
Blood creatine phosphokinase increased	0	1 (3.6)	2 (5.0)	4 (2.6)	1 (1.1)
Aspartate aminotransferase increased	0	0	2 (5.0)	1 (0.6)	1 (1.1)
Insulin-like growth factor increased	0	2 (7.1)	2 (5.0)	1 (0.6)	2 (2.3)
Blood pressure increased	0	1 (3.6)	2 (5.0)	0	0
Hepatic enzyme increased	0	0	2 (5.0)	0	1 (1.1)
Metabolism and nutrition disorders	3 (10.7)	4 (14.3)	7 (17.5)	21 (13.5)	3 (3.4)
Decreased appetite	0	1 (3.6)	2 (5.0)	4 (2.6)	0
Hyperglycaemia	0	1 (3.6)	3 (7.5)	2 (1.3)	1 (1.1)
Vascular disorders	1 (3.6)	1 (3.6)	3 (7.5)	13 (8.4)	6 (6.8)
Hypertension	0	1 (3.6)	0	8 (5.2)	3 (3.4)
Respiratory, thoracic and mediastinal disorders	1 (3.6)	2 (7.1)	8 (20.0)	11 (7.1)	6 (6.8)
Oropharyngeal pain	1 (3.6)	1 (3.6)	3 (7.5)	1 (0.6)	0
Hepatobiliary disorders	3 (10.7)	3 (10.7)	4 (10.0)	11 (7.1)	8 (9.1)

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SOC PT	OOC-ACM-303			CH-ACM-01	
	Core treatment phase		OLE phase	Core treatment phase	OLE phase
	Octreotide capsules (N = 28)	Placebo (N = 28)	Octreotide capsules (N = 40)	Octreotide capsules (N = 155)	Octreotide capsules (N = 88)
Cholelithiasis	2 (7.1)	1 (3.6)	0	6 (3.9)	6 (6.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.6)	1 (3.6)	2 (5.0)	9 (5.8)	1 (1.1)
Haemangioma of liver	0	0	2 (5.0)	1 (0.6)	1 (1.1)

Adverse events by dose level

The applicant presented data that no dose-dependent safety signals were noted for octreotide capsules in the Phase 3 studies.

In the run-in phase of study OOC-ACM-302, AEs were reported for 64.2%, 85.3%, and 72.9% of patients receiving 40 mg, 60 mg, or 80 mg as final dose, respectively. Treatment-related AES were reported for 50.9%, 67.6%, and 49.2% of patients, respectively.
During the study OOC-ACM-302 run-in phase 72.6% of patients experienced at least 1 AE, 54.1% of patients have treatment related AEs. The most commonly (46.6%) reported TEAEs were belonged to the SOC gastrointestinal (GIT) disorders: nausea, diarrhoea, flatulence, abdominal pain, abdominal upper pain, diarrhoea and dyspepsia have been reported.

In the RCT phase, AEs were reported for 69.6%, 84.6%, and 63.2% of patients in the octreotide capsules group at the 40 mg, 60 mg, or 80 mg dose levels, respectively; drug-related AEs were reported for 26.1%, 53.8%, and 31.6% of patients. In the SRL injections group, AEs were reported for 55.6%, 64.3%, and 85.7% of patients treated with low, middle, and high doses, respectively; drug-related AEs were reported for 22.2%, 28.6%, and 64.3% of patients with low, middle, and high doses, respectively.

The applicant presented safety profiling in SmPC section 4.8 of octreotide capsules where the spectrum and frequency of AEs for Mycapssa and sc Sandostatin AEs are mostly comparable.

In study OOC-ACM-303, the AE incidence was 100% for all octreotide capsules dose levels (40 mg, 60 mg, and 80 mg) and 96.4% for placebo. Treatment-related AEs were reported for 28.6%, 100.0%, and 73.7% of patients receiving octreotide capsules 40 mg, 60 mg, or 80 mg, respectively, while 53.6% of patients in the placebo-group were reported with drug-related AEs.

In the core treatment phase of study CH-ACM-01, the incidences of AEs in patients treated with octreotide capsules at 40 mg, 60 mg, and 80 mg were 74.8%, 67.8%, and 66.7%, respectively. Drug-related AEs were reported for 45.8%, 33.3%, and 31.6% of patients, respectively. No dose-related AE patterns were noted.

Conclusions regarding adverse events

From the data provided it seems that rates of patients experienced AEs/ADRs in general are comparable to SRL inj (70.9% / 34.5% vs 70.3% / 40.5% for Mycapssa AEs/ADRs vs SRL inj AEs/ADRs, respectively) and comparable to SRL inj ADRs in the enriched population (34.5 .1% vs 40.5% for Mycapssa vs SRL inj) and only 2x numerically higher proportions of patients experienced ADRs over placebo (7.1% vs 3.6% for Mycapssa vs Pbo, respectively.

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TEAE were comparable between the octreotide capsules group and the SRL injection group and also between the octreotide capsules group and the placebo group.

In all Phase 3 studies, the most frequently reported AEs were GI events and headache. The argumentation of the applicant, that the spectrum and frequency of GI AEs for oral octreotide and iSRLs are mostly comparable, was considered acceptable. The argumentation of the applicant, that manifestation of headache in patients using oral octreotide and iSRL is comparable, was also considered acceptable.

2.10.8.3. Serious adverse event/deaths/other significant events

Study OOC-ACM-302

The applicant states that the serious adverse event (SAE) pattern in the Phase 3 studies was in line with the disease characteristics of acromegaly and with the known safety profile of octreotide. In the RCT phase of study OOC-ACM-302, the SAE incidence was similar in the octreotide capsules and SRL injection groups (5.5% vs. 8.1%).

None of the individual PTs was reported for more than 1 patient, and none was considered related to study drug by the investigator.

In the core treatment phase of study OOC-ACM-303, 2 patients (7.1%) in the octreotide capsules group and 1 patient (3.6%) in the placebo group reported SAEs. In the OLE phase, 6 patients (15.0%) reported SAEs. None of these events was considered to be related to the study drug by the investigator.

Malignancies. The reported malignancies during treatment with octreotide capsules are in line with published information the disease burden of patients with acromegaly.

Deaths

A total of 4 deaths were reported in the clinical study programme of octreotide capsules. Two of the deaths were reported in study OOC-ACM-302. None of the deaths were considered related to study drug.

Relationship of adverse events to dose and treatment duration

In all Phase 3 studies, treatment with octreotide capsules was started at 40 mg daily and escalated to 60 mg or 80 mg, as needed to obtain biochemical control. No dose-dependent safety signals were noted.

The serious adverse event (SAE) pattern in the Phase 3 studies was in line with the disease characteristics of acromegaly and with the known safety profile of octreotide. In the run-in and OLE phases of Phase 3 studies hepatobiliary SAEs (acute cholescystitis, post cholecystectomy syndrome, bile duct obstruction, cholelithiasis, transaminase increased) and acute pancreatitis were SAEs considered related to study drug. All these AEs have been included in SmPC. The applicant states that other SAEs were not considered related to study drug.

The applicant was presented information that cardiac SAEs (bradycardia, acute myocardial infarction, cardiac failure) are not related to octreotide. Cardiac SAEs have been reconsidered and bradycardia as AE was included in SmPC section 4.8.

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The applicant states that there was no suggestion of an increased risk of AEs over time with octreotide capsules and no dose-dependent safety signals were noted. The mentioned applicant's conclusion is acceptable.

The reported low number cases of malignancies during treatment with octreotide capsules are in line with published information the disease burden of patients with acromegaly. The applicant's conclusion on the deaths cases to be not related to study drug octreotide were considered acceptable.

2.10.8.4. Laboratory findings

Clinical laboratory evaluations during studies of octreotide included haematology, chemistry, urinalysis.

Glucose dysregulation tests

Glucose-associated AEs reported during the run-in phase of *Study OOC-ACM-302* were hyperglycaemia (3.4% of patients), hypoglycaemia (1.4%), diabetes mellitus (0.7%), Type 2 diabetes mellitus (0.7%), and blood glucose increased (0.7%).

In the core treatment phase of *study OOC-ACM-303*, an AE of blood glucose increased was reported for 10.7% of patients in the octreotide capsules group, and diabetes mellitus and hypoglycaemia were reported for 3.6% each. In the placebo group, AEs of hyperglycaemia and HbA_{1c} increased were reported for 3.6% of patients each. None of these events was serious. Regarded as related to study drug were 1 event of blood glucose increased and 1 event of diabetes mellitus in the octreotide capsules group.

Thyroid dysfunction tests

Hypothyroidism and thyroid disorder (e.g. decreased thyroid stimulating hormone [TSH], decreased total thyroxin [T4], and decreased free T4) are commonly reported adverse reactions of sc Sandostatin IR.

During study OOC-ACM-302 one patient (1.8%) in the octreotide capsules group experienced a thyroid-associated AE (secondary hypothyroidism), which was assessed by the investigator as mild in intensity and unrelated to study drug. In study OOC-ACM-303, biochemical hypothyroidism was not reported. In study CH-ACM-01, in the core treatment phase, the following AEs were reported for 1 patient (0.6%) each: hypothyroidism, thyroid neoplasm, blood TSH increased, blood TSH decreased, free T4 increased, and free T4 decreased.

Haematological tests

There were no significant differences in haematologic shifts between treatment groups (CSR OOC-ACM-302).

The applicant states that the findings of the laboratory evaluations in the Phase 3 studies were in line with the safety profile of octreotide and the disease burden of acromegaly. This is acceptable.

Hypoglycaemia. Because of its inhibitory action on growth hormone, glucagon, and insulin, octreotide may affect glucose regulation. The applicant states that the serious hypoglycaemia event in the core treatment phase of study CH-ACM-01 was considered not related to study drug. The applicant agrees that hypoglycaemia may be associated with SRLs, and it is listed as an ADR in the SmPC of Mycapssa.

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2.10.8.5. Safety in special populations

Elderly

The percentages of patients by age group who experienced AEs in each category were generally similar, except for Musculoskeletal pain (9% in patients ≥65 years vs. 2% in patients <65 years), Nervous system disorders (41.5% in patients ≥65 years vs. 34.5% in patients <65 years); Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures (20.0% in patients ≥65 years vs. 11.3% in patients <65 years). These AEs can be explained as an effect of concomitant diseases. Only one patient >75 years of age was enrolled in the octreotide capsules programme with multiple AEs. The investigator considered all of the events to be grade 1 and not related to the study drug.

Gender

There were no meaningful differences in the proportions of male and female patients with AEs, SAEs, and AEs leading to study drug discontinuation. The AE patterns were consistent for male and female patients.

Race

Most patients in the Phase 3 studies (about 90% in all studies) were Caucasian. The low number of patients of other races did not allow to perform a meaningful assessment of the AE profile of octreotide capsules by race.

Renal impairment

Study CHI-007 investigated PK and safety of octreotide capsules in subjects with severe renal impairment (SRI defined as eGFR 15 – 29 mL/min/1.73 m2), subjects with ESRD on dialysis, and matched healthy controls. The study showed that the safety profile of octreotide capsules was similar between renally impaired subjects and healthy controls, and that octreotide capsules were safe and well tolerated in subjects with renal impairment.

The applicant states, that that octreotide capsules were safe and well tolerated in subjects with renal impairment. The applicant states, that no dose adjustment is necessary in patients with mild, moderate, or severe renal impairment. There is a significant increase in octreotide exposure in patients with end stage renal disease (ESRD). Therefore, applicant proposes different posology recommendations only for patients with ESRD. They should start taking MYCAPSSA 20 mg daily.

Hepatic impairment

PK and safety of octreotide capsules were also investigated in subjects with stable cirrhosis and portal hypertension (Child Pugh A or B; study CH-PHT-01). Both octreotide doses tested (10 mg and 20 mg) appeared to be safe and well tolerated.

The applicant states, that octreotide capsules were safe and well tolerated in subjects with stable cirrhosis and portal hypertension. Patients with Child Pugh C have not been studied; careful monitoring of these patients initiating treatment with MYCAPSSA is recommended.

The Study CH-PHT-01 was performed only with single dose octreotide capsules and limited number (18) of participants. It should be taken into account. On the other hand, SmPC section 4.2 states that in patients with Child Pugh A or B; the MYCAPSSA dose should be up-titrated based on clinical response.

The conclusions of the applicant were endorsed by the CHMP.

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Pregnancy and lactation

No pregnant or breastfeeding women have been exposed to octreotide capsules in the clinical development programme.

2.10.8.6. Immunological events

Not applicable.

2.10.8.7. Safety related to drug-drug interactions and other interactions

Study CHI-002: Food effect

Systemic exposure to octreotide was substantially reduced following fed as compared to fasted administration of octreotide capsules. Adverse events were reported for 76.0% of the subjects who received octreotide capsules while fed, 70.8% of the subjects who received octreotide capsules while fasted. The AEs considered related to study treatment were consistent with the known safety profile of octreotide and were independent of fasting status.

Study OCT-01: Food effect

Oral administration of octreotide capsules 20 mg with food resulted in decreases in the extent of exposure, regardless of meal size or timing. The incidence of AEs was slightly higher with octreotide capsules 20 mg given 1 hour after full test meal (8 subjects reported AEs) and octreotide capsules 20 mg in fasted condition (7 subjects) than with the other test conditions (octreotide capsules given 1 h prior to full test meal or 30 mg prior to light test meal; 2-5 subjects). There were no observable AE patterns attributable to type of diet or timing of octreotide capsules intake.

Study CH-005: PPI (esomeprazole)

The safety profile of octreotide capsules plus esomeprazole was acceptable and was comparable to that following octreotide capsules alone, although there were more drug-related AEs following co-administration of both drugs.

Study CH-006: Warfarin, HCTZ, metformin, oestradiol

Octreotide capsules plus the probe substrates had higher numbers of subjects reporting AEs than placebo plus the probe substrates. The AEs tending to be more frequent with octreotide capsules plus levonorgestrel/ethinyl oestradiol versus placebo plus levonorgestrel/ethinyl oestradiol were dizziness and headache. The AEs tending to be more frequent with octreotide capsules plus warfarin, HCTZ, and metformin versus placebo plus warfarin, HCTZ, and metformin were headache, nausea, dizziness, vomiting, and abdominal pain. Overall, co-administration of octreotide capsules and the probe substrates was well tolerated.

Study OCT-03: Metoclopramide and loperamide

The number of subjects with AEs was similar across the test conditions in this study. Octreotide capsules 40 mg were safe and well tolerated, regardless of administration with metoclopramide or loperamide.

Medicinal product no longer authorised

Study OCT-02: Digoxin and lisinopril

The proportion of subjects with AEs was similar for octreotide capsules plus digoxin and lisinopril (52.9%) and placebo plus digoxin and lisinopril (47.1%). Co-administration of octreotide capsules with digoxin and lisinopril was safe and well tolerated.

Study OCT-04: Cyclosporine

The proportion of subjects experiencing an AE was substantially higher with placebo plus cyclosporin than for octreotide capsules plus cyclosporin (47.1% vs. 18.8%). Co-administration of octreotide capsules and oral cyclosporine was safe and well tolerated.

Several food effect and DDI studies were conducted with octreotide capsules due to their novel formulation and route of administration. In these studies, the AE profile of octreotide capsules co-administered with warfarin, HCTZ, metformin, levonorgestrel/ ethinyl oestradiol or digoxin and lisinopril was consistent with the known safety profile of octreotide or each of the probe drugs, and the safety profile of octreotide capsules co-administered with PPI was well tolerated.

The DDI safety information presented in the SmPC of octreotide capsules is in line with the reference medicinal product Sandostatin.

Risk of changes in absorption of concomitant medicinal products. The effects of this oral octreotide formulation on the absorption of other co-medicated medicines, varying from a 3-fold decrease in bioavailability of ciclosporin to a 1.4-fold increase in absorption of lisinoprol, is of concern. The interactions could be due to octreotide, effects on the gastrointestinal tract and the excipients. The applicant was requested to discuss the effects of this octreotide formulation on the absorption of other co-administered medicines and the mechanism behind these interactions and to discuss which medicines (e.g., good soluble poor permeable compounds, poor aqueous soluble compounds with high and low permeability, compounds with special formulations to improve the absorption etc,) are most prone for absorption related interactions with this octreotide formulation. The applicant presented the argumentation and this issue is currently considered to be resolved.

2.10.8.8. Discontinuation due to adverse events

The pattern of AEs leading to study drug discontinuation in the Phase 3 studies was consistent with the overall safety profile of octreotide and the disease burden of acromegaly; the study drug was most frequently discontinued due to GI events.

Table 3.3.7.9 Adverse events leading to study drug discontinuation in the Phase 3 studies with octreotide capsules

	Patients with at least 1 AE leading to discontinuation, n (%)	Preferred terms
Study OOC-ACM-302		
Run-in phase (OC; N = 146)	14 (9.6)	In 5 patients (3.4%): nausea In 2 patients (1.4%) each: diarrhoea, vomiting, dizziness, headache, somnolence In 1 patient (0.7%) each: abdominal pain, abdominal pain upper, constipation, flatulence, pancreatitis acute, swollen tongue, myalgia, pain in extremity, malaise, post cholecystectomy syndrome, gastroenteritis, decreased appetite, depression, dermatitis allergic
RCT phase (N = 92)		

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Octreotide capsules (N = 55)	1 (1.8)	In 1 patient (1.8%): Toxicity to various agents
SRL injections (N = 37)	0	None reported
OLE phase (OC; N = 57)	1 (1.8)	In 1 patient (1.8%): cholecystitis acute
Study OOC-ACM-303		
Core treatment phase		
Octreotide capsules (N = 28)	2 (7.1)	In 1 patient (3.6%) each: nausea, dyspepsia, vomiting, abdominal discomfort, headache
Placebo (N = 28)	1 (3.6)	In 1 patient (3.6%): Headache
OLE phase (OC; N = 40)	1 (2.5)	In 1 patient (2.5%): Headache
Study CH-ACM-01		
Core treatment phase (OC)	22 (14.2)	In 7 patients (4.5%): Nausea In 4 patients (2.6%): diarrhoea In 2 patients (1.3%) each: abdominal pain, dyspepsia, vomiting, pyrexia In 1 patient (0.6% each): abdominal distension, abdominal pain upper, dry mouth, flatulence, frequent bowel movements, gastrointestinal motility disorder, rectal tenesmus, retching, adenocarcinoma of colon, meningioma, neoplasm malignant, pancreatic neoplasm, peripheral swelling, nodal arrhythmia, sinus bradycardia, bile duct obstruction, jaundice, rash, transaminases increased, headache, depression, oropharyngeal pain
OLE phase (OC)	1 (1.1)	In 1 patient (0.6%): gastritis erosive

study drug discontinuation. Nausea was the most frequent mentioned AE (5 patients, 3.4%). MedDRA SOC with the most frequent AEs was GIT disorders: 10 patients (6.8%) experienced 15 GIT disorders. Thus, GIT disorders were the most frequently AEs of octreotide capsules leading to study discontinuation.

In the RCT phase, 1 patient (1.8%) in the octreotide capsules group reported an AE leading to discontinuation. This patient died following accidental drug poisoning (coded as PT "toxicity to various agents"); the event was regarded as not related to study drug by the investigator. In the OLE phase, 1 patient reported an SAE leading to discontinuation (acute cholecystitis), which was assessed by the investigator as related to study drug.

In the core treatment phase of study OOC-ACM-303, 2 patients (7.1%) in the octreotide capsules group and 1 patient (3.6%) in the placebo group experienced at least 1 AE that led to study drug discontinuation. In the OLE phase, 1 patient discontinued study drug due to an AE. Except for headache, all AEs leading to discontinuation were GI events.

In study CH-ACM-01, 22 patients (14.2%) in the core treatment phase and 1 patient (1.1%) in the OLE phase reported at least 1 AE leading to study drug discontinuation. Except for pyrexia, all AEs that led to discontinuation in 2 or more patients were GI events.

2.10.8.9. Post marketing experience

Octreotide capsules were approved in the US in June 2020. Post-marketing information from 2 Periodic Adverse Drug Experience Reports (PADERs) is summarised below.

<u>PADER 1 (reporting period 26 June – 25 September 2020)</u>

- 42 patients were treated during the reporting period
- No serious events were reported.
- A total of 12 non-serious events were reported. Of those:

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- 4 events were unexpected (cardiac disorder, chest pain, product administration error, and product dose omission)
- 8 events were expected (abdominal discomfort, abdominal distension [2 events], flatulence, nausea, vomiting, headache, and hypertension)

PADER 2 (reporting period 26 September – 25 December 2020)

- 118 patients were treated during the reporting period.
- There were 2 serious, unexpected events (major depression and pneumothorax) and 1 serious, expected event (gastrointestinal disorder). The causality of the major depression event was not assessable by the sponsor, because no further details were provided. For the pneumothorax event, a possible relationship to octreotide capsules could not be excluded due to the temporal relationship; however, information such as medical history and clinical details was lacking.
- A total of 16 non-serious events were reported. Of those:
  - 6 events were unexpected (product dose omission issue, weight abnormal, limb deformity, memory impairment, alopecia, and hot flush)
  - 10 events were expected (diarrhoea, gastrointestinal disorder [2 events], nausea, drug ineffective for unapproved indication, pain [2 events], unevaluable event, and headache [2 events])

Post-marketing data of the reference medicinal product

The following ADRs of the reference medicinal product were derived from spontaneous reports:

- Blood and lymphatic system disorders: Thrombocytopenia
- Immune system disorders: Anaphylaxis, allergy/hypersensitivity reactions
- Skin and subcutaneous tissue disorders: Urticaria
- Hepatobiliary disorders: Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice
- Cardiac disorders: Arrhythmias (not specified)
- Investigations: Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels

Post-marketing data of parenteral somatostatin analogues

In the database of the WHO Collaborating Centre for International Drug Monitoring (VigiBase), a total of 21,788 records were found for the active ingredient octreotide, reported between 1988 and October 2020 (database access date: 03 November 2020).

Based on these records, the SOCs with the highest incidence were general disorders and administration site conditions (9384 ADRs), followed by gastrointestinal disorders (6730 ADRs), investigations (4709 ADRs), injury, poisoning and procedural complications (4613 ADRs); nervous system disorders (3565 ADRs); and neoplasms (2975 ADRs).

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2.10.9. Discussion on clinical safety

The primary clinical safety information on octreotide capsules is derived from the Phase 3 studies in patients with acromegaly. Supportive safety information is available from 11 clinical pharmacology studies, of which 9 were performed in healthy subjects, 1 in subjects with renal impairment, and 1 in subjects with hepatic impairment. In addition, safety information on the reference medicinal product sc Sandostatin IR is available.

During the clinical development programme, 571 human subjects received at least 1 dose of octreotide capsules. In the 3 Phase 3 studies, a total of 349 patients with acromegaly were exposed to octreotide capsules.

During the study OOC-ACM-302 run-in phase 72.6% of patients experienced at least 1 AE, 54.1% of patients had treatment related AEs. The most commonly (46.6%) reported TEAEs were belonged to the SOC gastrointestinal (GIT) disorders: nausea, diarrhoea, flatulence, abdominal pain and dyspepsia have been reported. During the RCT phase of this study GIT AEs nausea, dyspepsia and flatulence were the more commonly reported with octreotide capsules vs sc Sandostatin. Taking in to account that 9.6% patients with GIT AEs discontinued study due to AEs, it can be stated that abdominal distension, abdominal pain, abdominal upper pain were also more commonly reported in octreotide capsules group vs sc Sandostatin group. One of the GIT AEs (acute pancreatitis) was reported as an SAE; it was assessed by the investigator as related to study drug and led to study drug discontinuation. 1 patient reported an SAE related to study drug leading to discontinuation (acute cholecystitis). Except for headache, all AEs leading to discontinuation were GIT events. The detailed analysis of GI AEs presented by the applicant and toxicological study with cynomolgus monkeys show that oral octreotide does not produce an additional risk of GI ADRs compared to iSRL. The argumentation of the applicant was considered acceptable.

No differences in the degree of TPE-induced permeation were reported after 12 consecutive days repeated dosing of the octreotide-TPE formulation in rats. The safety in humans related to long-term exposure of TPE was discussed. It was concluded that long term exposure to TPE would not be expected to lead to an increase in adverse events, including infections or GI events.

The nervous system (NS) disorders were more frequently detected in octreotide capsules group. Even though headache is a symptom of acromegaly, this AE was more frequently detected in octreotide capsules group and was accepted as treatment related AE only in octreotide capsules group.

In the OLE phase, during long use of octreotide capsules, the proportions of patients with AEs and with treatment-related AEs were considerably lower than in the previous phases.

During the placebo controlled study OOC-ACM-303, the most frequent AEs that were reported in a greater proportion of patients in the octreotide capsules group vs placebo group were gastrointestinal events (diarrhoea, nausea, abdominal pain, vomiting, dyspepsia), cholelithiasis, headache, blood glucose increased. In the OLE phase of study OOC-ACM-303, the most frequent TEAEs were nausea, diarrhoea, vomiting, dizziness and blood glucose increased.

In the core treatment phase of study CH-ACM-01, the most frequent AEs were headache, nausea, arthralgia, asthenia, hyperhidrosis, diarrhoea, and peripheral swelling. In the OLE phase, headache, arthralgia, asthenia, and hyperhidrosis were reported in >10% of patients.

The serious adverse event (SAE) pattern in the Phase 3 studies was in line with the disease characteristics of acromegaly and with the known safety profile of octreotide. In the run-in and OLE phases of Phase 3 studies hepatobiliary SAEs (acute cholescystitis, post cholecystectomy syndrome, bile duct obstruction, cholelithiasis, transaminase increased) and acute pancreatitis were SAEs considered related to study drug. All these AEs have been included in SmPC. The applicant states that

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other SAEs were not considered related to study drug. However, cardiac SAEs have been reconsidered and bradycardia as AE was included in SmPC section 4.8.

A total of 4 deaths were reported in the clinical study programme of octreotide capsules. None of the deaths were considered related to study drug.

Because of its inhibitory action on growth hormone, glucagon, and insulin, octreotide may affect glucose regulation. The applicant states that the serious hypoglycaemia event in the core treatment phase of study CH-ACM-01 was considered not related to study drug. However, the applicant agrees that hypoglycaemia may be associated with SRLs, and it is listed as an ADR in the approved SmPC of MYCAPSSA.

The applicant stated that octreotide capsules were safe and well tolerated in subjects with renal impairment and that no dose adjustment is necessary in patients with mild, moderate, or severe renal impairment. There is a significant increase in octreotide exposure in patients with end stage renal disease (ESRD). Therefore applicant proposed different posology recommendations only for patients with ESRD. It was agreed that these patients should start taking MYCAPSSA 20 mg daily.

The applicant stated that octreotide capsules were safe and well tolerated in subjects with stable cirrhosis and portal hypertension. Patients with Child Pugh C have not been studied; careful monitoring of these patients initiating treatment with MYCAPSSA is recommended. However, study CH-PHT-01 was performed only with single dose octreotide capsules and limited number (18) of participants. On the other hand SmPC section 4.2 states that in patients with Child Pugh A or B; the MYCAPSSA dose should be up-titrated based on clinical response. This was considered acceptable.

The DDI safety information presented in the SmPC of octreotide capsules is in line with reference medicinal product Sandostatin. No other safety issues were noted in the presented DDI studies with octreotide capsules.

Additional expert consultation

None

Assessment of paediatric data on clinical safety

None

2.10.10. Conclusions on clinical safety

During the assessment it was concluded that clinical safety of Mycapssa required further confirmation and several other concerns addressing uncertainties for safety were raised (unknown comparative rates of ADRs and severities for both TEAE and ADRs, uncertain safety profiling in the SmPC, including profiling of risks of cardiotoxicity, hypoglycaemia, in elderlies, renal and liver impairments and risks stemming from post-marketing). The applicant has provided the requested information. The provided data show that the spectrum and frequency of GI and nervous system AEs for oral octreotide and injectable Sandostatin are mostly comparable. It was concluded that safety profile of Mycapssa is acceptable.

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2.11. Risk Management Plan

The Safety Specification (Part II, SI-SVIII) from RMP version 0.3, dated 13-07-2022 is assessed below.

2.11.1. Safety concerns

Summary of safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.11.1.1. Conclusions on the safety specification

Having considered the data in the safety specification the CHMP agreed that the absence of safety concerns as listed by the applicant is appropriate.

2.11.2. Pharmacovigilance plan

No additional pharmacovigilance activities are considered necessary for Mycapssa. Routine pharmacovigilance is sufficient to further characterise the safety concerns associated with the product.

2.11.3. Risk minimisation measures

No important identified or potential risks or missing information are included in the list of safety concerns in this RMP. According to the applicant routine risk minimisation activities as described in Section V.1 are considered sufficient to manage the safety concerns of the medicinal product.

2.11.3.1. Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that:

the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.11.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

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2.12. Pharmacovigilance

2.12.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.12.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the novel oral formulation of octreotide, the PRAC is of the opinion that a separate entry in the EURD list for Mycapssa is needed, as it cannot follow the already existing entry for octreotide. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 26.062020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.13. Product information

2.13.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for by the applicant is for the long-term maintenance treatment in patients with acromegaly (ACM) who have responded to and tolerated treatment with somatostatin analogues. This is a hybrid application for part of the indications authorised for Sandostatin s/c in patients with ACM and that is: "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."

ACM is a serious and life-threatening rare disease usually caused by a GH-secreting pituitary adenoma. It is a chronic condition with significant morbidity and mortality. The definition of ACM is based on a set of biochemical and clinical criteria. ACM mortality determinants include GH >2.5 ng/mL and elevated IGF-1, hypertension, cardiovascular and cerebrovascular disease, requirement for glucocorticoid replacement, and prior pituitary radiation.

The CHMP approved modified indication for Mycapssa in line with the SmPC Guideline: "for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues".

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3.1.2. Available therapies and unmet medical need

Treatment options for acromegaly include surgical resection of the pituitary adenoma, radiotherapy, and drug therapy to reduce GH and IGF-1 levels to normal values. 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.

Currently, there are 3 drug classes available for the treatment of acromegaly: SRLs or somatostatin analogues (SSAs; octreotide, lanreotide, and pasireotide), dopamine agonists (bromocriptine and cabergoline), and a GH receptor antagonist (pegvisomant). At present, SRLs are the most widely used drugs to control acromegaly. Current injectable therapies for acromegaly are suboptimal for multiple reasons. One of these is that the injections are poorly tolerated. Patients experience long-term sequelae associated with their injection, including persistent pain (lasting up to days), nodules, haemorrhage, inflammation, and scarring. Hence, there is a need of an efficacious oral octreotide treatment.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is from three clinical Phase 3 studies in patients with acromegaly evaluating the efficacy of octreotide capsules: OOC-ACM-302, a randomised, open-label, active-controlled (RCT phase: n=92; Octreotide capsules: n=55; SRL injections: n=37), preceded by a run-in phase, followed by an OLE phase study; OOC-ACM-303, a randomised, double-blind, placebo-controlled (DPC phase: n=56; Octreotide capsules: 28; placebo: 28), followed by an OLE phase, and CH-ACM-01 a single-arm, baseline-controlled (Core treatment phase: n=155), followed by an OLE phase. Thus, the applicant performed two concurrently controlled (one with active control and one with placebo control) and one baseline controlled pivotal studies.

3.2. Favourable effects

In one of the main phase 3 studies (Study 302), the proportion of patients with biochemical control (primary endpoint) and differences between Mycapssa and SRL inj were 50/55 [90,9%] vs 37/37 [100%], difference [95%CI] is -9.1 [-19.9, 0.5] which meets the statistical NI margin of 20%. The maintenance of biochemical control after switch from SoC in Study 302 was assessed in an enriched population as time weighted average (TWA) of IGF-1 <1.3xULN during the randomised clinical trial (RCT) phase (average of week 62 and week 58, starting RCT phase from Week 26).

In the second pivotal study (study 303), the proportion of patients with biochemical control (primary endpoint) and differences between Mycapssa and PBO were 16/28 [57,1%] vs 5/28 [17.9%], difference [95%CI] is 38.74 [10.68, 59.90] which meets statistical and clinical superiority. The maintenance of biochemical control after switch from SoC in Study 303 was assessed as average of IGF-1 <1xULN during the double-blind placebo control (DPC) phase (measuring the last 2 available assessments between weeks 34 and 36 in the DPC period).

In the third pivotal study ACM-01 the proportion of patients with biochemical control (primary endpoint) [95%CI] was 98/151 [64.9%; 58.4, 74.2] which meets statistical and clinical superiority. The maintenance of biochemical control after switch for SoC in Study ACM-01 was assessed as average of IGF-1 <1.3xULN at the end of core treatment period (at least 7 Months).

Additionally, in pivotal Study 302 the proportion of patients with maintenance of clinical and clinical + biochemical control after switch from SoC (secondary and co-secondary endpoint) and differences between Mycapssa and SRL inj were 40/55 [72.7%] vs 25/37 [67.6%] and 36/55 [65.5%] vs 27/37 [73%], differences [95%CI] are 5.4% [-13.2, 25.2] and -6.8% [-25.3, 13.2] for clinical and clinical +

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biochemical controls, respectively.

3.3. Uncertainties and limitations about favourable effects

The pivotal Study 302 was designed as an enrichment study with a run-in phase during which a substantial proportion of patients withdrew after the switch from SoC due to different reasons and this questions generalizability of study results for the targeted population.

The biochemical control in Study 302 was settled as time weighted average (TWA) of IGF-1 <1.3xULN during the RCT phase. Similarly, Study ACM-01 used the same IGF-1 <1.3xULN cut-off value. This definition of control represents partial biochemical control only, not full control which would be IGF-1 <1xULN (e.g., TWA).

The fitting into noninferiority (NI) margin is very close to lower boundary and this questions robustness of study results however the applicant argued the acceptability of the NI margin satisfactorily during the procedure.

3.4. Unfavourable effects

In general, TEAE/ADRs were observed in 70.9/34.5% and 70.3/40.5% of Mycapssa and SRL patients in Study 302, respectively and comparable or only numerically different between Mycapssa and Pbo in Study 303 (in 100/7.1% and 96/3.6%, respectively).

The most important unfavourable effects were gastrointestinal (GI) TEAE, that were leading to withdrawal during switch period from SRL in pivotal study 302 (leading to 9,6% withdrawal from the run-in phase), headache during RCT phase (in 4.8% and 1.8% of Mycapssa and SRL inj patients in Study 302, respectively) and pancreatitis in 0.7/1.8% and 0% of Mycapssa and SRL patients in Study 302.

3.5. Uncertainties and limitations about unfavourable effects

During the assessment the applicant was requested to provide details increasing granularity of TEAE or ADRs, observed, i.e.:

- ADR rates vs rates of patients with at least 1 ADR
- Comparative severity rates of both TEAE and ADRs per PT/SOC
- Comparative duration and reversibility of TEAE and ADRs
- Qualitative characteristics of GI, headache and pancreatitis at least for the MoA of GI ADR (the local effect of enhancer is not addressed) and ability to predict, monitor, treat and prevent al other main risks.

The required information has been provided during the procedure. TEAE were comparable between the octreotide capsules group and the SRL injection group and also between the octreotide capsules group and the placebo group.

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3.6. Effects Table

Effect	Short Description and Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects					
Proportion of Patients with Biochemical control	IGF-1 <1.3xULN TWA during the RCT phase and NI difference with 95%CI	50/55 [90,9%]	SRL inj:	SoE: Clinically relevant NI with margin of 20% U: Marginal NI; partial biochemical control (no full normalisation), enrichment design, high withdrawal rate after switch.	Study 302
		-9.1 [-19.9, 0.5]			
	Average IGF-1 1xULN during the DPC phase and difference with 95%CI	16/28 [57.1%]	Pbo: 5/28 [17.9%]	SoE: Clinical superiority in full biochemical control U: Questionable clinical meaningfulness of minimal RR of ~11%	Study 303
		38.74 [10.68, 59.90]			
	IGF-1 <1.3xULN and GH <2.5 ng/mL with 95%CI	98/151 [64.9%; (58.4, 74.2)]	BL	SoE: (-) U: partial biochemical control (normalisation); questionable clinical meaningfulness of maximal RR of ~74.2%	Study ACM-01
Proportion of Patients with Clinical control	AIS score maintained or improved during the RCT phase and difference with 95%CI	40/55 [72.7%]	SRL inj: 25/37 [67.6%]	SoE: Clinically relevant comparability U: enrichment design, high withdrawal rate after switch; SEP.	Study 302
		5.4% [-13.2, 25.2]			
Proportion of Patients with Clinical and biochemical control	IGF-1 <1.3xULN TWA and AIS score maintained or reduced during the RCT phase and difference with 95%CI	36/55 [65.5%]	SRL inj: 27/37 [73%]	SoE: Comparable clinical and biochemical control U: Questionable NI, partial biochemical control (normalisation), enrichment design, high withdrawal rate after switch, SEP.	Study 302
		-6.8% [-25.3, 13.2]			
Unfavourable Effects					

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Effect	Short Description and Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
TEAE / ADR	Patients experienced at least 1 TEAE or ADR (%)	Study 302: 70.9/34.5 Study 303: 100/7.1	Study 302: 70.3/40.5 Study 303: Pbo 96/3.6	SoE: Comparable TEAEs U: Unknown comparative severity rates, duration and reversibility of TEAE/ADRs	Studies 302, 303
TEAE leading to withdrawal		Study 302: 9.6 Study 303: 7.1	Study 302: N/A Study 303: Pbo 3.6	SoE: High withdrawal rate during switch period from SRL inj to Mycapssa U: ADR rates unknown	Studies 302, 303
GI		34	SRL inj: 24.3	U: ADR rates unknown	Study 302
Headache		4.8	SRL inj:1.8	U: ADR rates unknown	Study 302
Pancreatitis		0.7/1.8	SRL inj: not known	SAE leading to withdrawal during switch period/TEAE during OLE	Study 302

Abbreviations: AIS - Acromegaly Index of Severity; BL – baseline; DPC – double blind placebo control; NI – non-inferiority; OLE – open label extension; RR: responder rate; SEP – secondary endpoint; SAE – serious AE; SoE: Strength of Evidence; SRL inj: parenteral somatostatin receptor ligand; TWA - time weighted average; U: Uncertainty

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important effects observed are (in order of importance), a maintenance of biochemical control after switch from SoC in enriched population (primary endpoint) and differences between Mycapssa and SRL inj which were 50/55 [90,9%] vs 37/37 [100%] with a difference [95%CI] of -9.1 [-19.9, 0.5] which meets the statistical noninferiority (NI) margin of 20%.

This is supported by the (1) maintenance of Biochemical control after switch from SoC (primary endpoint) between Mycapssa and PBO and were 16/28 [57,1%] vs 5/28 [17.9%] with difference [95%CI] of 38.74 [10.68, 59.90] and (2) as compared to BL 98/151 [64.9%; 58.4, 74.2] which meets statistical and clinical superiority.

Moreover, maintenance of biochemical control after the switch is supported by the maintenance of clinical and clinical + biochemical control after switch from SoC (secondary and co-secondary endpoint) and differences between Mycapssa and SRL inj and were 40/55 [72.7%] vs 25/37 [67.6%] and 36/55 [65.5%] vs 27/37 [73%], differences [95%CI] are 5.4% [-13.2, 25.2] and -6.8% [-25.3, 13.2] for clinical and clinical + biochemical controls, respectively.

The maintenances of biochemical and clinical controls are considered clinically reasonable endpoints, the effect size of NI in enriched population is considered clinically meaningful and the supportive data

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are in concordance with primary effect in Study 302.

The TEAE/ADRs were observed either in comparable rates between Mycapssa and active control SRL inj (70.9/34.5% and 70.3/40.5% of Mycapssa and SRL patients in Study 302, respectively) or only numerically different rates between Mycapssa and Pbo in Study 303 (in 100/7,1% and 96/3,6%, respectively).

3.7.2. Balance of benefits and risks

The benefit/risk balance of Mycapssa for the proposed indication is positive.

3.8. Conclusions

The overall benefit /risk balance of Mycapssa is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Mycapssa is not similar to Signifor within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Mycapssa is favourable in the following indication:

"Mycapssa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

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- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

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