24 April 2025
EMA/164079/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Oczyesa

International non-proprietary name: Octreotide

Procedure No. EMEA/H/C/006322/0000

Note

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

Administrative information

Name of the medicinal product:	OCZYESA
Applicant:	Camurus AB Rydbergs torg 4 SE-224 84 Lund SWEDEN
Active substance:	Octreotide hydrochloride
International Nonproprietary Name/Common Name:	Octreotide
Pharmaco-therapeutic group (ATC Code):	Hypothalamic hormones, somatostatin and analogues H01CB02
Therapeutic indication(s):	Oczyesa is indicated for maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues
Pharmaceutical form(s):	Prolonged-release solution for injection
Strength(s):	20 mg
Route(s) of administration:	Subcutaneous use
Packaging:	pre-filled syringe (glass) in pre-filled pen

Package size(s):	1 pre-filled pen

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List of abbreviations

AcroQoL	Acromegaly Quality of Life Questionnaire
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIS	Acromegaly Index of Severity
AP	Applicant's Part (or Open Part) of an ASMF
API	Active Pharmaceutical Ingredient = Active substance
AS	Active substance = Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Autogel
AUC	Area under the plasma concentration-time curve
AUCinf	AUC extrapolated to infinity
BMI	Body mass index
BCRP	Breast cancer resistance protein
CAM2029	abbreviation of octreotide injection depot
Cav	Average concentration
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLCR	Creatinine clearance
Cmax	Maximum plasma concentration
CMA	Critical Material Attribute
CMS	Concerned Member State
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
CTR	Clinical trial report
Ctrough	Trough (plasma) concentration
CYP	Cytochrome P450
DMF	Drug Master File = Active Substance Master File
DoE	Design of Experiments
DP	(1) Decentralised (Application) Procedure, (2) Drug product
DS	(1) Design space, (2)Drug substance
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
ESI-MS	Electrospray ionization mass spectrometry
ETA	Ethanolamine
ETO	Ethylene oxide
FP	finished product
GC	Gas Chromatography
GC-FID	Gas Chromatography flame ionisation detector
GDO	Glycerol dioleate
GEP-NET	Gastroenteropancreatic neuroendocrine tumours
GH	Growth hormone
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hBSEP	Human bile salt export pump

HDPE	High Density Polyethylene
hMRP2	Human multidrug resistance-associated protein 2
HPLC	High Performance Liquid Chromatography
HPLC-UV/DAD	High performance liquid chromatography with UV diode array detector
HVLD	High Voltage Leak Detection
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IC50	Half maximum inhibition
IGF-1	Insulin-like growth factor-1
IM	Intramuscular(ly)
Imax	Maximum inhibition
IMP	Investigational medicinal product
IPC	In-process control
IR	(1) Infrared spectroscopy, (2) Immediate release
ISR	Injection site reaction
ITT	Intention-to-treat
IU	International Units
KF	Karl Fischer
LAR	Long-acting repeatable
LC	Liquid Crystals
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAA	Marketing authorisation application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MS	Mass Spectrometry
ND	Not detected
NET	Neuroendocrine tumours
NfG	Note for Guidance
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NT	Not tested
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OOS	Out of Specifications
PD	Pharmacodynamic(s)
PDE	Permitted Daily Exposure
PE	Polyethylene
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetic(s)
PLD	Polycystic liver disease
PopPK	Population PK
PopPKPD	Population PK and PD
PP	Polypropylene
PRO	Patient-reported outcome
PVC	Polyvinyl chloride
QC	Quality Control
QoL	Quality of life
QOS	Quality Overall Summary
QTcF	QT interval corrected for heart rate by Fridericia’s formula
QTPP	Quality Target Product Profile
RH	Relative Humidity

RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RTF	Ready-to-fill
SAE	Serious adverse event
SAP	Statistical analysis plan
SAXD	Small angle x-ray diffraction
SC	Subcutaneous(ly)
SIAQ	Self-Injection Assessment Questionnaire
SmPC	Summary of Product Characteristics
SoC	Standard of care
SPC	Soybean Phosphatidylcholine
SPPS	solid phase peptide synthesis
SRL	Somatostatin receptor ligand
SSTR	Somatostatin receptor type
SUKL	State Institute of Drug Control
TAMC	Total Aerobic Microbial Count
t½	Half-life
t.i.d.	Three times daily (ter in die)
TSE	Transmissible spongiform encephalopathy
TSQM	Treatment Satisfaction Questionnaire for Medication
TYMC	Total Yeast/Mould Count
UHMW	Ultra-high-molecular-weight
ULN	Upper limit of normal
UV	Ultraviolet
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
(P)XRD	(Powder) X-Ray Diffraction

* This is a general list of abbreviations - not all abbreviations might be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Camurus AB submitted on 26 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Oczyesa, 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 30 March 2023.

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) of Directive 2001/83/EC.

The applicant applied for the following indication: treatment of acromegaly in adult patients in whom surgery is inappropriate or ineffective.

Oczyesa was designated as an orphan medicinal product EU/3/09/645 on 12 Jun 2009, in the following condition: treatment of acromegaly

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, a bioequivalence study with the reference medicinal product Sandostatin and appropriate non-clinical and clinical data.

The chosen reference product is:

Reference medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Sandostatin 50 µg/ml, solution for injection; Sandostatin 100 µg/ml solution for injection; Sandostatin 500 µg/ml, solution for injection
- Marketing authorisation holder: Novartis Ireland Limited
- Date of authorisation: 18-11-1988
- Marketing authorisation granted by:
  - Member State (EEA): Ireland
    - National procedure
- Marketing authorisation number: PA0896/028/001-003

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.

1.4.2. Derogation(s) from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a claim addressing the following derogations laid down in Article 8.3 of the same Regulation: the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product and the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

1.5. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
3 December 2009	EMEA/H/SA/1406/1/2009/PA/SME/III	Dr Kristina Dunder, Prof. Minne Casteels and Prof. Brigitte Blöchl-Daum
21 February 2013	EMEA/H/SA/1406/2/2012/PA/III	Dr Bart van der Schueren and Dr Kerstin Wickström
4 September 2013	EMEA/H/SA/1406/2/FU/1/2013/PA/II	Dr Bart van der Schueren and Prof. Kerstin Westermark

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- *In vitro* dissolution testing; transition from in vial to PFS in commercial product
- bioequivalence between acetate and hydrochloride salts of octreotide to support non-clinical safety; need for additional reprotoxicity studies
- Phase 1 study in HV to support start of Phase 3, lack of exploratory PD information to plan Phase 3; Sandostatin LAR as comparator; single Phase 3 study to support MAA; design of Phase 1 study in HV: PK, dose exploration, PD plans; demonstration of Significant Benefit (OD); Phase 3 study plans: study population, single arm design not endorsed, randomised study comparing to Sandostatin LAR needed, efficacy endpoints, study duration, statistical analysis plan, non-inferiority margin, dosing regimen, data supporting self-injection, safety exposure; Revised Phase 3 design: 2-arm open label comparative trial. study endpoints, statistical analysis plan, safety database, dose and dose adjustments;
  Demonstration of Significant Benefit (OD)

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Jean-Michel Race

The Rapporteur appointed by the PRAC was: Eamon O Murchu

The application was received by the EMA on	26 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	04 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	25 March 2025
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	09 April 2025
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 Oczyesa on	25 April 2025
The CHMP adopted a report on similarity of Oczyesa with Mycapssa on (Appendix on similarity)	25 April 2025
The CHMP adopted a report on derogations applicable to similar orphan products for Oczyesa on (see Appendix on derogations)	25 April 2025

2. Scientific discussion

2.1. Introduction

The legal basis of MAA for Oczyesa is Article 10(3) of Directive 2001/83/EC, a so-called "hybrid" application to the reference medicinal product Sandostatin (MA number PA0896/028/001-003), which was first approved in the European Union on 18-11-1988. During the clinical programme, Oczyesa (name used during development: CAM2029) has been compared with Sandostatin and Sandostatin LAR.

CAM2029 utilises the FluidCrystal injection depot technology with prior use in the Buvidal, approved in the EU since 2018. Buvidal (buprenorphine) is a prolonged-release formulation for the treatment of opioid dependence. Upon injection in the tissue, the lipid-based solution immediately starts forming a liquid crystalline gel that encapsulates and slowly releases the active ingredient at a controlled rate as the depot is gradually biodegraded.

CAM2029 was developed as a prolonged-release formulation of octreotide for subcutaneous (SC) use for self-administration and home use, with a dosing of 20 mg every 4 weeks, administered with a pre-filled pen in the abdomen, thigh, and buttock. This hybrid application partially relies on the results of non-clinical and clinical data on Sandostatin, and reference is being made to the Irish SmPC and the published literature on Sandostatin.

CAM2029 is ready-to-use and should be stored at room temperature, i.e., does not require reconstitution or temperature conditioning before administration.

CAM2029 has been developed in two configurations: a pre-filled pen (autoinjector) with a nonvisible needle, and a pre-filled syringe with an automatic needle-stick safety device. The Applicant was seeking approval for the pre-filled pen only.

The efficacy and safety of Oczyesa (CAM2029) are comparable to the efficacy and safety of the reference product Sandostatin.

Table 1 Comparison between CAM2029 and the reference product

	CAM2029	Sandostatin
Active substance	octreotide hydrochloride	octreotide acetate
Therapeutic indication	Treatment of acromegaly in adult patients in whom surgery is inappropriate or ineffective	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.
Strength	20 mg/ 1mL	50 microgram/1mL 100 microgram/1mL 500 microgram/1mL
Pharmaceutical form	prolonged-release solution for injection	solution for injection
Route of administration	subcutaneous injection	subcutaneous injection

The Applicant was applying for the following indication: "treatment of acromegaly in adult patients in whom surgery is inappropriate or ineffective".

This indication is part of the indication for treatment of acromegaly, as approved for Sandostatin: "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."

The CHMP has approved the following indication:

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

Disease or condition

Acromegaly is a rare, chronic, progressive disorder characterised by excessive secretion of growth hormone (GH) resulting from a pituitary adenoma, which in more than 90% of the cases is benign. Chronic excessive secretion of GH stimulates production of increased levels of insulin-like growth factor-1 (IGF-1) from effector organs that leads to disordered somatic growth, metabolic abnormalities, decreased quality of life (QoL). Patients with uncontrolled acromegaly have a higher risk of mortality than the general population.
Based on its clinical presentation, acromegaly is regarded as a serious and chronically debilitating condition with high impact on patient QoL (Bolfi et al 2018, Bolfi et al 2019).

Epidemiology

The prevalence of acromegaly in Europe and the US is estimated to be around 8 cases per 100,000 people.

Worldwide, the prevalence is 1/7,500 to 1/35,800. The annual incidence is 1/91,000 to 1/526,000.

Patients with uncontrolled acromegaly have a higher risk of mortality than the general population due to e.g., metabolic complications and cardiovascular events such as hypertension and other symptoms such as fatigue, weakness, excessive perspiration, joint pain, edema, sleep apnea, and excessive snoring. (Bolfi et al 2018, Bolfi et al 2019, Holdaway et al 2008, Mizera et al 2018).

Clinical presentation, diagnosis

Acromegaly is diagnosed clinically by symptoms and confirmed biochemically via elevated GH and IGF-1 serum levels and lack of growth hormone suppression after glucose administration.
Once the diagnosis of acromegaly has been confirmed on the basis of the results of endocrine testing, a pituitary magnetic resonance imaging (MRI) examination should be obtained to detect a pituitary adenoma, which is the cause of acromegaly in most cases. A computed tomography examination of the brain (with special attention to the sella) can be obtained in patients with contraindications to MRI. In one study, 3.2% of patients (6 of 190) with acromegaly had no evident pituitary tumor on standard MRI.

Clinical symptoms include signs and symptoms attributed to tumour mass effects compressing the surrounding structures (e.g., headaches and vision loss), and by the chronic overproduction of both GH and IGF-1 leading to disordered growth (progressive skeletal and soft tissue overgrowth, mainly at the extremities and head) and metabolic complications including insulin resistance, increased blood glucose levels, hyperinsulinemia, diabetes, and dyslipidaemia (Colao et al 2019).
A recent study based on administrative claims data showed that patients with acromegaly had significantly more comorbidities and were prescribed more concomitant medications than matched patients without acromegaly but with other underlying conditions. Cardiovascular disorders were the most prevalent comorbidities and were reported in 67.6% of the patients in the acromegaly cohort versus 48.4% in the control cohort. Hypopituitarism and hypothalamic disorders, sleep apnoea, malignant neoplasms and cancer, as well as arthritis and musculoskeletal disorders were also common in the acromegaly cohort (Fleseriu et al 2022).

Management

Broadly, the goals of treatment in patients with acromegaly include normalization of GH secretion or (at least) GH action as indicated by a normal IGF-1 level as well as by resolution of tumor-induced mass effects, acromegaly-related symptoms, and associated comorbidities, all aiming at mitigating excess mortality while preserving normal pituitary function.

The existing therapeutic strategy includes surgery (first-line therapy) and/or medical treatment and/or radiotherapy (Melmed et al 2018, Giustina et al 2020).

According to clinical practice guidelines and expert consensus, medical therapy is recommended for the treatment of acromegaly in patients who have persistent or recurrent disease despite surgery, or who are waiting for radiotherapy, or who are not candidates for surgery or radiotherapy because of poor health (Melmed et al 2018, Gisutina et al 2024).

Current medical treatment options for the management of acromegaly include somatostatin receptor ligands (SRLs), GH-receptor antagonists and dopamine agonists SRLs are established as first–line medical treatment with potential for further improvements and lead to limited disease control with biochemical response rate of 30-55%, continued symptoms, and increased mortality (Melmed et al 2018, Ershadina et al 2022).

About the product

- Mechanism of action

Pharmacotherapeutic group: Somatostatin and analogues, ATC code: H01CB02.

Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action.

In the treatment of acromegaly, the primary action of octreotide is to decrease abnormal secretion of growth hormones by suppressing hormone release from the pituitary gland and from growth hormone-secreting adenomas. Somatostatin binds to five subtypes of G-protein coupled transmembrane receptors (SSTR1–5) and besides its GH-inhibiting activity, somatostatin also inhibits the secretion of other hormones such as thyroid-stimulating hormone (TSH) and almost all gastro-entero-pancreatic hormones (i.e. gastrin/cholecystokinin, insulin, glucagon, vasoactive intestinal polypeptide), as well as exocrine gastrointestinal and pancreatic secretions. It also inhibits intestinal motility, delays gastric emptying, and impedes the proliferation of normal and neoplastic cells. An inhibition of immunoglobulin synthesis and lymphocyte proliferation in lymphoid tissues has also been observed as well as antiproliferative potential by inhibiting epidermal and vascular growth factors, and IGF-1. Octreotide has been extensively studied in clinical trials and has been used world-wide for more than 30 years. In the treatment of acromegaly, octreotide administration decreases abnormal GH secretion by suppressing hormone release from the pituitary gland and from GH-secreting adenomas.

CAM2029 is a ready-to-use, prolonged-release octreotide hydrochloride formulation with a safety profile consistent with the one of injectable first-generation SRLs. Additionally, CAM2029 provides enhanced octreotide exposure and can be administered by patients themselves or their caregivers.

Upon injection in the tissue, the lipid-based solution immediately starts forming a liquid crystalline gel that encapsulates and slowly releases the active ingredient at a controlled rate as the depot is gradually biodegraded. The dose of CAM2029 for the treatment of acromegaly is 20 mg every 4 weeks, administered subcutaneously in the abdomen, thigh, and buttock.

- The development programme/compliance with CHMP guidance/scientific advice

The CHMP Guidelines were followed. Scientific advice has been considered during drug product development.

The non-clinical program for CAM2029 is based on a combination of sponsor-conducted studies and supplementary published data (i.e. the data from Sandostatin SmPC was supplemented by directed literature searches in the public domain on the toxicology of octreotide).

The sponsor-conducted studies included pharmacokinetic (PK) studies, single- and repeated dose toxicity studies (including local tolerance) and *in vitro* genotoxicity studies. The program and the individual studies were designed to establish bridging to existing non-clinical documentation on octreotide where relevant. In some studies, Sandostatin LAR was included as comparator.

The choice of species was made based on data on Sandostatin, Sandostatin LAR and scientific literature (4, 5, 6) supporting that rat and dog are appropriate species for evaluating non-clinical pharmacology, pharmacokinetics and toxicity of octreotide.

Since octreotide is well characterized, pharmacology assessments of octreotide per se were not considered relevant for the non-clinical development program of CAM2029.

The clinical development programme for CAM2029 in acromegaly includes 7 clinical trials. This MAA includes the final clinical trial reports (CTRs) for 6 of these trials and an interim CTR containing main part data for the ongoing Phase 3, long-term safety trial HS-19-647. All trials were performed in compliance with the principles of Good Clinical Practice.

Four of the clinical trials were Phase 1 trials in healthy volunteers, which featured single- and repeated-dose investigations of the pharmacokinetic (PK) and pharmacodynamics (PD) profiles, as well as safety and tolerability of CAM2029 ([HS-05-194], [HS-07-291], [HS-11-411] and [HS-19-664]).

CAM2029 formulations of representative, albeit slightly different compositions were investigated and compared in the early phase trials ([HS-05-194], [HS-07-291], [HS-11-411] and [HS-12-455]). CAM2029 as octreotide acetate was used in the first Phase 1 trial. In all other trials, octreotide hydrochloride was used for improved stability.

• The clinical development programme was initiated with the single-ascending dose trial, [HS-05-194], which assessed the PK, PD (IGF-1) and safety of CAM2029 in healthy volunteers. Three different doses of CAM2029 (octreotide acetate) were administered by SC injections, whereof 1 dose was also administered as an IM injection. To improve stability of the formulation and allow room temperature storage, the acetate salt was later exchanged with the hydrochloride one.

The 2 following trials in healthy volunteers compared the PK of octreotide after repeated doses of CAM2029 with the PK of octreotide LAR and/or octreotide IR. In these trials, PD and safety were assessed as secondary objectives.

• [HS-07-291] investigated a 30-mg/mL formulation of CAM2029 (-BG) with ethanol as the only solvent in the formulation. Three SC injections of CAM2029 (10, 20 and 30 mg) every 4 weeks were compared with 3 IM injections of octreotide LAR (20 mg) also given every 4 weeks. This trial also compared SC injections of CAM2029 in the buttock versus abdomen

• [HS-11-411] investigated three 20-mg/mL formulations of CAM2029 (-BP, -BR and -BV), with slightly different co-solvent and stabiliser compositions (-BP and -BR: ethanol and propylene glycol; -BV: ethanol and EDTA). The reduction in octreotide hydrochloride concentration and the variation in solvent composition were performed to assess and optimise the release profile, targeting consistent and sustained plasma octreotide concentrations during the treatment period of 4 weeks. Three SC injections of CAM2029 (10, 20 and 30 mg every 4 weeks) were given in the buttock and were compared with 3 IM injections with octreotide LAR (30 mg) every 4 weeks. A single dose of octreotide IR (0.20 mg) was given to all subjects as a run-in treatment

Based on similar PK profiles for CAM2029-BP, -BR and -BV in [HS-11-411] and considering the injectability properties of the 3 formulations, CAM2029-BR was selected as the target lead formulation for the first trial of CAM2029 in patients. [HS-12-455] was a Phase 2, open-label, multi-centre, randomised, trial to assess the PK, PD, efficacy and safety of CAM2029 in adult patients with acromegaly or functional, well-differentiated NET.

Clinical trials in patients include a Phase 2 trial [HS-12-455] in patients with acromegaly or functioning neuroendocrine tumours (NET), and two Phase 3 trials in patients with acromegaly [HS-18-633] and [HS-19-647].

The Phase 3 trial [HS-18-633] was a randomised, double-blind, parallel group, placebo-controlled trial in patients with acromegaly. Eligible patients were on stable dose with octreotide LAR or lanreotide ATG for at least 3 months and had IGF-1 ≤1× upper limit of normal (ULN) and mean GH <2.5 µg/L at screening. After randomisation, patients received SC injections of CAM2029 20 mg or the corresponding volume of placebo every 4 weeks (±1 week) for 24 weeks. The injections were given in the abdomen or thigh, using a pre-filled

syringe. The dose could be reduced to CAM2029 10 mg (or the corresponding volume of placebo) if required based on safety/tolerability.

Efficacy was evaluated by the proportion of patients with normal IGF-1 levels at the end of the double-blind treatment period (mean of measurements at Week 22 and Week 24). The combined response for IGF-1 ≤1xULN and mean GH <2.5 µg/L, time to loss of response of IGF-1, IGF-1 levels over time, patient-reported outcomes (PROs), tumour size, and safety and tolerability were also assessed.

Long-term safety and efficacy were evaluated in the ongoing, open-label Phase 3 trial, [HS-19-647], including patients who rolled over from [HS-18-633], and new patients who were on stable doses of octreotide or lanreotide for at least 3 months and with screening IGF-1 ≤2×ULN. Patients in this trial received SC injections of 20 mg CAM2029 every 4 weeks (±1 week) in the abdomen, thigh or buttock using either the pre-filled pen or pre-filled syringe. The CAM2029 dose could be reduced to 10 mg if required based on safety/tolerability.

No formal bioequivalence trials were conducted during the clinical programme since the final market formulation and device configuration of CAM2029 were assessed in the Phase 3 trials.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a prolonged-release solution for injection in pre-filled pen containing 20 mg of octreotide, as active substance, The product contains the hydrochloride salt of octreotide.

Other ingredients are glycerol dioleate, soybean phosphatidylcholine, ethanol anhydrous, propylene glycol (E 1520), edetic acid, ethanolamine.

The product is available in a 1 mL pre-filled pen supplied as a single-dose, sterile, ready-to-use syringe (glass, Type I) with plunger stopper (fluoropolymer-coated bromobutyl rubber), a non-visible needle (½ inch, 12.7 mm, 22 gauge) and a protective cap with needle shield (synthetic rubber), fitted in an autoinjector, as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of octreotide hydrochloride is D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninol cyclic (2 →7)-disulfide hydrochloride salt corresponding to the molecular formula $C_{49}H_{66}N_{10}O_{10}S_2$ (free base). It has a relative molecular mass of 1019.3 (free base) and the structure in Figure 1.

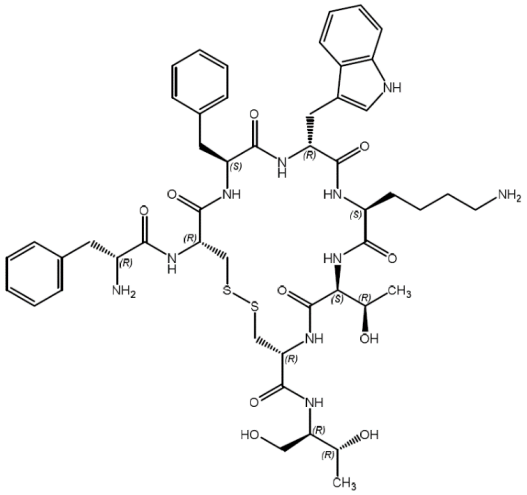


Figure 1: Active substance structure

The chemical structure of octreotide hydrochloride was elucidated by a combination of amino acid analysis and ESI-MS/MS on octreotide acetate and additional ESI-MS on octreotide hydrochloride. The secondary structure was assessed with far-UV circular dichroism. The solid-state properties of the active substance were measured by powder X-ray diffraction (PXRD), Raman spectroscopy, differential scanning calorimetry (DSC), and hot stage microscopy.

Octreotide hydrochloride is a white to off-white powder (lyophilisate), very hygroscopic, freely soluble in water, methanol, ethanol and acetic acid, and very slightly soluble in ammonium hydroxide, 2-propanol, acetonitrile and diethyl ether.

All optically active amino acid residues in octreotide hydrochloride are in L-configuration with the exception of D-Phe1 and D-Trp4.

Polymorphism has not been observed for octreotide hydrochloride.

Octreotide is described in Ph. Eur. monograph 04/2023:2414. However, this monograph refers to octreotide in form of acetate and the proposed substance is in form of hydrochloride. The solubility of both forms is comparable.

2.2.2.1. Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The manufacturing process is divided in six steps. Octreotide hydrochloride is synthesized by standard solid phase peptide synthesis (SPPS). The proposed starting materials are acceptable. A brief overview of their purity and control of stereoisomers was presented and considered satisfactory.

The manufacturing process description has been provided in sufficient detail in the Applicant´s part of the ASMF. The active substance is not sterile. The quality of water used in the last step of synthesis has been confirmed in line with EMA Guideline on the quality of water for pharmaceutical use. Information regarding the control of critical steps and intermediates has been provided. In conclusion, the information provided about manufacture and its control strategy is acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guidelines and the general monograph "Substances for pharmaceutical use (2034) which is applicable for peptides obtained by chemical synthesis.

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

No genotoxic or carcinogenic risk has been identified for related substances, reagents and solvents. Possible genotoxic/carcinogenic impurities are either satisfactorily controlled or it has been demonstrated that they are present at acceptably low levels. Potential nitrosamine impurities are discussed in the finished product section.

The active substance is packaged in amber glass bottles which comply with Ph. Eur. 3.2.1, closed with white caps made from PP, HDPE, and PVC that comply with EC 10/2011 or PE bags which comply with EC 10/2011 as amended.

2.2.2.2. Specification(s)

The active substance specification, includes tests for appearance (visual, Ph. Eur.), identification (ESI-MS, IR, HPLC, reaction of chloride), purity (HPLC), related impurities (HPLC), assay (HPLC), chloride content (titration), water content (KF), acetic acid content (IC), residual solvents (GC), bacterial endotoxins (Ph. Eur.) and microbial purity (Ph. Eur.).

The AS specification used by the finished product manufacturer is the same as presented in the Applicant´s part of ASMF.

The proposed specification contains almost all tests contained in the Ph. Eur. monograph of octreotide acetate. The limits for specified impurities and unspecified impurities have been set tighter than in the Ph. Eur. Monograph which is considered acceptable. Other limits, e.g. bacterial endotoxins, residual solvents, etc. are acceptable as they have been set in line with Ph. Eur. requirements or applicable EMA guidelines.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. The information regarding the reference standards used for assay and impurities testing has been provided and is acceptable.

Batch analysis data (6 batches) of the AS is provided. The results are within the specifications and consistent from batch to batch. The batch size corresponds to the proposed commercial scale.

2.2.2.3. Stability

Stability data from four production scale batches of active substance from the proposed manufacturer stored in both types of the container closure system representative of that intended for the market for up to 48 months under long term conditions (-20 °C / RH (not controlled) and 5 °C / RH (not controlled)) and for up to 6 months under accelerated conditions (25 °C / 60% RH and one batch at 40 °C / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, purity, related impurities and water content. The analytical methods used were the same as for release, they have been demonstrated to be stability indicating.

Data have shown that batches are stable for up to 48 months at -20 °C and 5 ±3 °C. No difference in results has been observed for the two proposed packaging systems. This satisfactorily supports the requested retest period of 36 months in both types of packaging.

Octreotide hydrochloride is stable at 25 °C with a slight increase in water content after 6 months of storage (not exceeding the acceptance criterion). A slight decrease in purity and increase in water content is observed at 40 °C/ 75% RH after 6 months of storage. However, during 14 days of storage up to 60 °C, no significant influence of temperature was observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. The substance shows an increase in impurities, a decrease in purity and change of appearance after exposure to the light. This supports the proposal for storage conditions restriction: "Store protected from light".

Stress testing was performed on one AS batch which was exposed to higher temperature and moisture in the solid state as well as to oxidising, basic, and acidic conditions in solution. The substance shows an increase in water content under humidity exposure. The AS shows only a slight increase in impurities in aqueous solution except under basic conditions, where a significant decrease in purity and an increase in impurities was observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months and storage conditions "Store between 2 °C and 8 °C, protected from light" in the proposed types of containers.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product (FP) is a sterile filtered yellowish to yellow clear liquid filled into pre-sterilized, ready-to-fill, 1 mL long clear glass syringes with grey plunger stoppers (hereinafter denoted CAM2029). It is a lipid-based parenteral prolonged-release solution for subcutaneous injection in pre-filled pen based on the proprietary FluidCrystal technology.

The proposed product has been developed as a hybrid of the reference medicinal product Sandostatin. The reference product pharmaceutical form is solution for injection/infusion and thus differs from the proposed product which is a prolonged-release solution for injection. Hence, the qualitative composition of the proposed product is different to the reference product and has been developed independently by the applicant and the formulation and delivery mechanism (from vial + needle, prototype devices, and the pre-filled pen) changed throughout the clinical programme. The CHMP considered that the applicant hadn't provided adequate bridging data to demonstrate that the quality of batches used throughout clinical development and the proposed commercial product in the pre-filled pen are equivalent. Furthermore, bridging quality data between the proposed commercial product and the reference product were also deficient, resulting in a Major Objection. The applicant provided additional data and justification concerning the reference product, and in addition, bridging *in vitro* data for the finished product batches used during the development and clinical phases. Furthermore, the changes made in the medical device part during the development have been justified. The provided data was considered satisfactory, and the MO is resolved.

The finished product is a non-aqueous liquid formulation CAM2029 with the AS dissolved in a mixture of lipids and co-solvents. The formulation comprises the AS with a long chain glycerol ester lipid, soy phospholipid and a co-solvents ethanol and propylene glycol; a stabiliser is also used. The two key excipients, glycerol dioleate

(GDO) and soy phosphatidylcholine (SPC) have been previously used in other prolonged-release marketed products. 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 list of excipients is included in section 6.1 of the SmPC.
The injectable liquid precursor formulation forms a highly viscous gel-like liquid crystalline phase *in situ* upon contact with aqueous body fluids, resulting in a monolithic depot that slowly releases the AS over time. The properties of the liquid crystalline phase (or gel) formed *in situ*, such as nanostructure, viscosity and release rate, are controlled by the lipid composition of the formulation (the ratio between glycerol dioleate and soy phosphatidylcholine). The choice of the lipids and co-solvents has been justified, the physicochemical properties critical for the excipient's selection were discussed. The QTTP of the product has been provided, quality attributes related to QTPP have been identified and their criticality assessed. A Major Objection was initially raised concerning the exact details of the release mechanism of the drug from the depot technology and its control, including the QC control method. In their response the applicant thoroughly discussed the release mechanism of the AS from the depot technology and its control. In addition, the effect of different level of water when administration is provided subcutaneously on the formation of the lipid depot and octreotide release from the depot was discussed adequately and it was confirmed that the hydration of the depot is governed by the lipid composition rather than the co-solvent composition including water. The interaction of the active substance with the excipients in the FluidCrystal technology has also been elaborated. The additional information resolved this part MO.
The other part of the same MO concerned the non-standard control release method developed especially for the Oczyesa. The method uses a 2-step approach: in step 1, the product is exposed to water resulting in formation of the fluid crystal matrix; in step 2, release from the matrix is monitored using the basket apparatus with a buffered solution to mimic *in vivo* conditions. However, the CHMP considered that the method had not been adequately justified, that there was no demonstrated correlation to *in vivo* behaviour, and that discriminatory power had not been demonstrated. In their response the applicant further justified the choice of the dissolution parameters and provided sufficient method validation data. The dissolution medium was justified in that it mimics the *in vivo* environment including the pH; the surfactant helps degrade the liquid crystal by analogy with the lipases which are responsible for this *in vivo*. Furthermore, it was shown that the method is discriminatory when the composition of the main lipid excipients varied.
Comparative data was also provided showing an equivalent release profile of batches used in the clinic.
Overall, the response was deemed satisfactory, and the MO was resolved in its totality.

The FP is manufactured by sterile filtration and aseptic filling. Compatibility between the formulation and the sterile filter has been confirmed. The pre-sterilization bioburden of the formulation is in line with EU guidelines. Pre- and post-filter integrity test methods and acceptance criteria have been defined. The sterilisation method chosen has been justified according to the decision tree in EMA guidance.

The product is classified as an integral drug device combination. A Major Objection was raised because the Notified Body Opinion (NBOp) was not provided with the initial submission. This was resolved as the applicant submitted the missing documentation which was found acceptable.

The relevant information as per the Guideline on quality documentation for medicinal products when used with a medical device has been presented. The primary and secondary packaging shows adequate protection against moisture ingress, solvent loss, and exposure to oxygen and light. The functional aspects of the medical device have been qualified in line with its complexity and include the rationale for the choice and optimisation of the relevant aspects of design and performance (such as dose-delivery performance and mechanical functionality of the device).

The manufacturers and sites responsible for the sterilisation of the immediate packaging components have been clearly listed and compliance with relevant ISO standards has been confirmed.

The primary packaging, a 1 mL pre-filled pen, is supplied as a single-dose, sterile, ready-to-use syringe (glass, Type I) with plunger stopper (fluoropolymer-coated bromobutyl rubber), a non-visible needle (½ inch, 12.7 mm, 22 gauge) and a protective cap with needle shield (synthetic rubber), fitted in an autoinjector. The material complies with Ph. Eur. and ISO standards. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.1. Manufacture of the product and process controls

The responsibility of each manufacturer has been stated. The GMP status of the sites has been confirmed.

The FP manufacturing process includes 8 conventional pharmaceutical processing steps, i.e. weighing and compounding, sterile filtration, filling and stoppering, visual inspection, assembly in the autoinjector, labelling, and packaging in protective secondary packaging followed by other secondary packaging.

The process itself is relatively simple and conventional. However, as it includes non-terminal sterilisation and considering the finished dosage form, the process is considered to be a non-standard manufacturing process.

The manufacturing process has been described adequately and the requested information about sterilisation of equipment has been provided. Equipment and critical process parameters (CPP), including settings have been set for the commercial manufacturing process and the commercial batch scale. The batch formula for the proposed batch size has been provided. The same batch size was subject of process validation.

The critical process parameters and in-process controls have been identified and their set-points and/or ranges set based on the development studies. The description of the manufacturing process includes the operations relating to the integration of device and drug product including assembly and packaging. No intermediates are defined within the proposed process.

The storage of the sterile bulk product has been described and justified. The proposed process and holding times are supported either by data presented within the pharmaceutical development or confirmed by the process validation, hence they are acceptable. The maximum filtration time has been adapted in line with validation data. Three consecutive full-scale batches were manufactured for finished product validation, which fulfils the guideline requirements. A filter validation study was successfully completed including bacterial challenge tests, filter compatibility, and establishment of product specific integrity test values. Processing times as well as important process parameters were verified, and the applied settings will be used for routine production. Media fill studies were also successfully completed. The device assembly, primary packaging sterilisation and secondary protective packaging steps were also validated.

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 and pharmaceutical form.

2.2.3.2. Product specifications

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form including appearance (visual), identification of octreotide (HPLC-UV/DAD), assay (HPLC-UV), degradation products (HPLC-UV), water content (Ph. Eur.), ethanol content (GC-FID), viscosity (Ph. Eur.), *in vitro* release (in house - Ph. Eur.), uniformity of dosage units (Ph. Eur.), extractable volume (Ph. Eur.), EDTA content

(HPLC-UV), peroxide value (Ph. Eur.), activation force (ISO 11608-5), injection time (ISO 11608-5), sub-visible particles/particulate matter (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and container closure integrity (HVLD).

Release and shelf-life specifications have been presented in tabular form, with brief reference to the methods used. As per the Guideline on quality documentation for medicinal products when used with a medical device, the FP specification includes tests relating to the integral medicinal product performance and functionality (activation force and injection time). The limits are based on the outcome of pharmaceutical development. The proposed specifications are considered appropriate and meet the requirements of ICH Q6A.

The potential presence of elemental impurities in the FP has been assessed according to a risk-based approach as per ICH Q3D. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product was presented in the initial submission. CHMP did not consider the risk evaluation to be sufficiently thorough as it didn't take into account all potential sources of nitrosamines impurities resulting in a major objection. In response, the risk evaluation was updated and presented as requested, 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 "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided, it is accepted that no risk of presence of nitrosamine impurities in the active substance or the related finished product was identified. Therefore, no additional control measures are deemed necessary and the Major objection was resolved.

The analytical methods have been sufficiently described and non-compendial methods validated in accordance with the ICH guidelines. The stability indicating nature of the HPLC method has been proven. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for five production scale batches used in Phase 1 and 3 clinical studies. All results comply with the specification limits, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.3. Stability of the product

Stability data from three commercial scale batches of the finished product stored for up to 18 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The stability batches were packed in the primary packaging proposed for marketing but there were some minor differences in the manufacturing process compared to the commercial process. These changes were evaluated as non-significant for the product performance. Thus, the stability batches are considered representative of those proposed for marketing.

Stability samples were tested for appearance, assay, degradation products, ethanol content, viscosity, EDTA content, water content, *in vitro* release, extractable volume, peroxide value, sub-visible particles and container closure integrity. The analytical methods used were the same as for release. No significant changes were observed during long-term and accelerated stability studies. The results of functionality tests did not change significantly over time either.

A photostability study according to ICH Q1B was performed for the product in different packaging formats: naked syringe, pre-filled pen and the pen in protective Al pouch. The results showed that CAM2029 product packed only in a naked syringe is sensitive to light. The autoinjector offers some protection from light and full protection is achieved by the commercial secondary packaging.

A stressed stability study (forced degradation) according to ICH Q2(R1) was also performed. The following stress factors were studied: acidic stress, alkaline stress, thermal stress, light stress, oxidative stress, and iron stress. The study results showed varying degrees of degradation which was most prominent under acidic conditions. The stability indicating power of the assay and degradation products methods was also demonstrated.

Stability under frozen storage conditions was investigated for 15 weeks at less than -15 °C concluding that the product remains stable. No stability concerns have been found at frozen storage. On the other hand, under refrigerated conditions, silicone used in the internal walls of the glass barrel may form oil droplets, depending on temperature. Thus, the additional labelling statement "do not refrigerate" has been included in the SmPC is considered justified and appropriate. A temperature cycling study for the FP in the protective Al pouch was carried out for 12 days with acceptable results. The FP is stable to potential temperature excursions during shipping.

The CAM2029 pre-filled pen has been shown to be stable under both long-term conditions (25 °C/60% RH) and the accelerated condition (40 °C/75% RH). A shelf-life of 30 months is proposed for the CAM2029 pre-filled pen, based on statistical evaluation and extrapolation in line with the ICH guidance.

Based on available stability data, the proposed shelf-life of 30 months and storage conditions "do not refrigerate" and "store in the original package in order to protect from oxygen and light", as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.2.3.4. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information about the active substance was submitted in an ASMF and is considered acceptable. No major objection has been raised in relation to the AS. The AS is a chemically synthesised cyclic 8-amino acid peptide, an analogue of somatostatin. The information about the control strategy for active substance applied by the finished product manufacturer is satisfactory.

The finished product is a prolonged-release solution for injection in a pre-filled pen containing 20 mg of octreotide in form of octreotide hydrochloride, It is packed in a pre-filled syringe fitted in an autoinjector and intended for subcutaneous administration. It is a single-dose, sterile, ready-to-use pharmaceutical form.

Satisfactory information on the FP development has been provided. A Major Objection was raised in relation to the release mechanism of the drug from the depot technology and the analytical method used for its

control. Another Major Objection was raised because of insufficient *in-vitro* comparison of the test and reference product, as well as between different batches used in clinical studies and the proposed commercial product. A third Major Objection related to the inadequate risk assessment for the potential presence of nitrosamine impurities. The last major objection has been raised on medical device used and its compliance with MDR and the missing Notified Body Opinion in the original submission. All MOs have been satisfactorily resolved by provision of additional data and justifications as requested by the CHMP.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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 the clinic.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Octreotide is a well-known active substance used in several pharmaceutical products authorized in the EU. The applicant relied on references to Sandostatin (immediate release) SmPC and literature data and performed bridging non-clinical studies. Oczyesa (CAM2029) relies on the FluidCrystal (FC)technology already approved in the Buvidal product in 2018 in the EU. The Applicant has provided PK/PD studies, single- and repeated-dose toxicity studies (including local tolerance) with different formulations of CAM2029 and *in vitro* genotoxicity studies with the hydrochloride salt of octreotide. Safety and local tolerance studies performed with the FC Vehicle with small compositional variations compared to the to-be-marketed formulation of CAM2029, were also provided. CAM2029 does not contain novel excipients and their safety in Oczyesa formulation was discussed.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

No *in vitro* pharmacology assessment of octreotide was performed as part of the non-clinical development program of CAM2029.

During the development of CAM2029, several formulations were tested, differing by their content in excipients and their concentration in octreotide (both hydrochloride and acetate salts tested). The applicant has presented pharmacokinetic and toxicology studies comparing *in vivo* pharmacological response to subcutaneously or intramuscularly administered octreotide with different CAM2029 formulations in rats and dogs, by assessing the reduction of insulin-like growth factor 1 (IGF-1) levels. CAM2029 showed no major differences among formulations tested, with a rapid and clear effect on the endogenous IGF-1 levels, with maximum suppression 1-2 days after the administrations in rats and up to 8 days in dogs, followed by

gradual recovery. The IGF-1 levels remained below baseline (pre-dose) levels throughout the respective study/sampling periods, which is consistent with a sustained release from the depot product. Those results suggest that the choice of excipients and octreotide salt had no significant effect on the pharmacological effects of CAM2029. The IGF-1 response to CAM2029 administration as well as the plasma IGF-1 profile comparison with Sandostatin LAR have also been evaluated in clinical trials HS-07-291, HS-11-411. Moreover, when investigating potential effect of accidental IM injection, CAM2029 showed to be sufficiently efficient to suppress IGF-1 in a small number of dogs (<80% of baseline) for up to 56 days.

2.3.2.2. Secondary pharmacodynamic studies

No studies on secondary pharmacodynamics have been performed with Oczyesa.

2.3.2.3. Safety pharmacology programme

No standalone safety pharmacology study was performed with Oczyesa, since there is a long clinical experience with octreotide and the safety pharmacology effects are well known from currently approved products on the EU market. The cardiovascular effects of octreotide acetate and octreotide hydrochloride were monitored in a 13-week repeated-dose toxicology study in Beagle dogs and did not reveal article-related effect up to the highest dose tested of 60 mg q4w.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been done with Oczyesa.

2.3.3. Pharmacokinetics

The analytical methods included ELISA and LC/MS/MS to quantitate the amount of octreotide and IGF-1.

Absorption

The absorption and the exposure profile of octreotide following administration of the CAM2029 formulations was assessed in plasma in non-GLP-compliant single-dose SC pharmacokinetic studies in rats and dogs. In addition, the pharmacokinetics following IM administration was assessed in dogs. Absorption after repeated-dose administration of CAM2029 was evaluated in dogs as part of GLP-compliant repeated-dose toxicity studies.

In general, from the different PK studies reported, it can be concluded that different compositions tested during CAM2029 development did not produce major differences in PK profiles. For all CAM2029 formulations, a rapid and clear absorption of octreotide followed by a sustained release was typically observed over a period of approximately 4 weeks in rats and dogs. The exposure was approximately proportional to the dose.

The effect on the release of octreotide from the final CAM2029 formulation *in vivo* upon mechanical challenge was evaluated in a PK study in rats by rubbing/massaging the site of injection or squeezing the depot at different timepoints. This did not affect the PK profile of octreotide. Moreover, similar plasma concentration profiles of octreotide were observed following IM and SC administration of CAM2029 in dogs providing evidence that accidental IM injection of CAM2029 is not expected to cause any adverse effects with respect to octreotide exposure.

Distribution

According to literature available, the highest concentrations of octreotide after an IV administration to rats were detected by using radiolabelled material in the kidney, skin and liver. By following the time-course of

organ distribution of total radioactivity and of unchanged octreotide it was apparent that elimination from presumed target organs such as pituitary and pancreas was much slower when compared with nontarget tissues such as muscle, lung and heart. This indicates high-affinity binding to target receptors. The volume of distribution for octreotide in rats was small (0.4 L/kg). Studies with radiolabelled octreotide showed *in vitro* plasma protein binding of ca 60%. The degree of *in vivo* protein binding of total radioactivity was slightly higher, i.e., 71-75%. *In vitro* distribution of octreotide in rat blood revealed that 96% of the drug was present in plasma. This result was confirmed in *in vivo* studies where no octreotide was detected in rat blood cells.

No distribution studies have been performed with CAM2029. This is acceptable to the CHMP.

Metabolism

According to literature available, as expected for a peptide, extensive degradation into small fragments and amino acids was evident in all tissues within the first minutes after intravenous injection of radiolabelled somatostatin in rats, indicating that rapid breakdown of the natural peptide not only takes place in the blood but also in tissues. In contrast, investigations with octreotide in another study revealed good stability both in blood and tissues.

No metabolism studies have been performed with CAM2029. This is acceptable to the CHMP.

Excretion

In literature, elimination mechanisms of radiolabelled octreotide in rats were investigated. Most of the radioactivity was initially found in kidney and liver. About 50% and 20% of the applied dose are excreted as unchanged octreotide in bile and urine, respectively, indicating the importance of biliary excretion in the hepatic clearance of octreotide. In humans, the hepatic extraction ratio of octreotide has been estimated to be between 30% and 40% in healthy subjects, pointing to an extensive hepatic metabolism of octreotide. The clearance of octreotide in rats has been measured to 4.2 mL/min.

No excretion studies have been performed with CAM2029. This is acceptable to the CHMP.

Pharmacokinetic drug interaction

Four *in vitro* drug interaction studies have been provided by the Applicant in the clinical part of the dossier.

2.3.4. Toxicology

The choice of species was made based on data on Sandostatin, Sandostatin LAR and scientific literature, supporting that rat and dog are appropriate species for evaluating non-clinical pharmacology, pharmacokinetics and toxicity of octreotide.

2.3.4.1. Single dose toxicity

In rat, a single administration of CAM2029 (formulation with octreotide acetate) up to 13.5 mg of octreotide, resulted in limited systemic toxicity, which consisted in minor drug substance related effects on body weight and food consumption, perturbations in haematology (notably white cell parameters and prolonged prothrombin time in females), clinical chemistry (mainly electrolyte disturbances), changes in organ weights (notably adrenals, liver and brain) and adrenal histopathology (micro-vesicular vacuolation). All findings were reversible. Regarding local tolerance at injection site, slight dose-dependent oedema, haemorrhage and granulomatous inflammation were noted. Clear evidence of reversibility of those effects were observed.

In dogs, single-dose toxicity studies did not provide any indication of systemic effects up to 20 mg of octreotide. Only local inflammatory reactions at injection sites with signs of recovery were noted.

2.3.4.2. Repeat dose toxicity

Two repeated-dose toxicity studies have been conducted in dogs up to 60 mg q4w for 13 weeks. In addition, a 13-week repeated-dose toxicity study has been conducted in rats at 20 mg q2w, as part of the qualification of Monoamide B (C18:1) impurity.

Findings were consistent among species with those observed in the single-dose toxicity studies. Limited toxicity was observed in rats with effects observed on body weight gain (decrease), coagulation, adrenal glands, acinar secretion of zymogen in the pancreas, and decrease liver weight. In dogs, toxicity was limited to soft faeces and vomiting, body weight loss, decrease in food consumption, quiet behaviour and difficulty in standing. In both species, local effects consisted in swelling, consistent with the physical presence of the depot, as well as inflammatory reactions associated with varying degrees of fibrosis. All findings were considered reversible.

2.3.4.3. Genotoxicity

Reference is made to Sandostatin where octreotide was shown to be devoid of mutagenic potential. To bridge to the Sandostatin data, where the active ingredient is octreotide acetate, two *in vitro* mutagenicity tests were performed with octreotide hydrochloride. The designs of *in vitro* tests were based on appropriate OECD test guidelines.

In *in vitro* bacterial reverse mutation assay, octreotide hydrochloride was negative in all Salmonella test strains. The results obtained with the negative and positive controls demonstrated the sensitivity of the tests and the efficacy of the S-9 mix metabolic activation system. It was concluded that octreotide hydrochloride was not mutagenic in this Ames test.

In the *in vitro* mouse lymphoma mutation assay, octreotide hydrochloride was negative in cultures treated. A significant increase of small mutant colonies was observed at high dose without S9-mix, however, it was not deemed biologically relevant as it was associated with high cytotoxicity.

Overall, the absence of mutagenicity has been demonstrated for octreotide acetate salt in the reference product Sandostatin. The negative *in vitro* tests performed by the Applicant (bacterial reverse mutation assay and mouse lymphoma mutation assay) confirmed the absence of mutagenic potential of octreotide as hydrochloride salt.

2.3.4.4. Carcinogenicity

No carcinogenicity studies have been conducted with CAM2029, which is acceptable to the CHMP for this product. Reference is made to the SmPC for Sandostatin.In rats receiving octreotide acetate at daily doses up to 1.25 mg/kg body weight, fibrosarcomas were observed, predominantly in a number of male animals, at the s.c. injection site after 52, 104 and 113/116 weeks. Local tumours also occurred in the control rats, however development of these tumours was attributed to disordered fibroplasia produced by sustained irritant effects at the injection sites, enhanced by the acidic lactic acid/mannitol vehicle.This non-specific tissue reaction appeared to be particular to rats. Neoplastic lesions were not observed either in mice receiving daily SC injections of octreotide at doses up to 2 mg/kg for 98 weeks (14 times the clinical dose of CAM2029 20 mg every 4 weeks (based on body surface area)), or in dogs treated with daily SC doses of the drug for 52 weeks.

Octreotide hydrochloride was not genotoxic and is not expected to have a carcinogenic potential different from octreotide acetate as the systemic concentration of octreotide itself is the relevant parameter.

2.3.4.5. Reproduction toxicity and developmental toxicity

There are no reproductive toxicity studies conducted for CAM2029. Octreotide hydrochloride is expected to behave the same as octreotide acetate regarding reproductive toxicity as the systemic concentration of octreotide itself is the relevant parameter. Therefore, the available reproductive toxicity data relating to octreotide acetate (Sandostatin SmPC) are considered fully appropriate for octreotide hydrochloride.

2.3.4.6. Toxicokinetic data

Toxicokinetic data were included in the single-dose and repeated-dose toxicity studies. The results were consistent with what has been observed in the pharmacokinetics studies i.e. a PK profile showing a rapid octreotide absorption after administration in both species, followed by a slow decline of octreotide plasma levels over a period of approximately 4 weeks, consistent with a sustained release from the depot. The results show that the total exposure (AUC) could be adjusted by dose volume and by drug load (octreotide concentration). Calculated safety margins from repeat dose toxicity studies were of 9.8 and 3.1 respectively for Cmax and AUC in dogs and of 90 and 128 in rats for Cmax and AUC respectively.

2.3.4.7. Local tolerance

No stand-alone local tolerance study has been performed. Instead, the local reactions in response to the SC administration of CAM2029 have been included as endpoints in both the single-dose and the repeated-dose toxicity studies in rats and dogs. Across species, the findings have been similar, consisting of observations of swellings, considered to be due to the physical presence of the depot matrix in the tissue, gross findings at necropsy, and microscopic changes. The test items were generally well tolerated. The SC injection site reactions consist in a localised inflammatory response consistent with a foreign body reaction to the depot and in fibrosis in the subcutaneous tissue. Clear signs of reduction of the local reactions over time were observed. Complete resolution was recorded in some of the animals and was generally depending on the duration of the studies. The principal histopathological change noted at the injection site ranged from acute inflammation to a chronic, granulomatous inflammation depending on the duration between dose administration and microscopic evaluation. In the repeated-dose toxicity study in dogs at doses of up to 60 mg octreotide in CAM2029, injection sites harvested 35 days post injection were dominated by foamy macrophages with neutrophilic granulocytes present, while at the older sites (60 and 90 days post injection), granulomatous inflammation was observed where the foamy macrophages were replaced by pigmented macrophages, reflecting a more advanced stage of inflammation and clearing of the test item. There was no indication of spread of the inflammatory response to adjacent tissues. The inflammatory response was often associated with cavitation and fibrosis. The cavitation was considered to represent the site of test article deposition, and the fibrosis frequently encapsulated the cavitation site. The characterization of toxicity associated with IM injection of the drug product in dogs revealed equivalent to milder local toxicity compared to the SC injections.

Additionally, the local tolerance of the FluidCrystal vehicle alone has been evaluated in two GLP compliant chronic toxicity studies of 26 weeks and 39 weeks conducted in rats and dogs, respectively. Moreover, a non-GLP compliant 8-week toxicity study was also conducted in dogs. Taken together, in both rats and dogs the treatment-related observations for the FluidCrystal vehicle were limited to reactions at the injection sites. Swellings were observed at the SC sites, considered to represent the physical presence of the depot matrix in the SC tissue, all of which reduced in size with time. There was clear evidence of on-going recovery. The local

inflammatory response at injection sites was in agreement with what has been shown with CAM2029 formulations in repeat-dose studies. No sign of systemic toxicity due to the FC vehicle alone was observed during those studies.

2.3.4.8. Other toxicity studies

- Impurity

During stability studies of the CAM2029 drug product, it was shown that the impurity (degradation product) monoamide B(C18:1) increases during storage and may exceed the limit of 1% set forth in the guideline ICHQ3B. Then, the genotoxic potential of monoamide B (C18:1) was evaluated in two *in vitro* assays (bacterial reverse mutation assay and mammalian chromosomal aberration test).

In the bacterial reverse mutation assay, conducted according to according to ICH S2(R1) and OECD n°471 (2020) guidelines, the test material did not induce a dose-related increase in the number of revertant (His+) colonies in any of the four tester strains (TA1535, TA1537, TA98 and TA100) or in the number of revertant (Trp+) colonies in tester strain WP2uvrA neither in the absence nor presence of S9-metabolic activation. The negative and strain-specific positive control values were within the laboratory historical control data ranges indicating that the test conditions were adequate, and that the metabolic activation system functioned properly. Hence, it was concluded by the Applicant that monoamide B(C18:1) was not mutagenic in the Ames test and thus considered a Class 5 according to ICH M7. This is endorsed.

In the mammalian chromosomal aberration test, conducted according to ICH S2(R1) and OECD n° 473 (2016) guidelines, negative and positive controls proved that the test conditions were adequate, and that the metabolic activation system (S9-mix) functioned properly. The test material did not induce any statistically significant or biologically relevant increase in the number of cells with chromosome aberrations in the absence and presence of S9-mix, in either of the two independently performed experiments. In conclusion, Monoamide B (C18:1) is deemed not clastogenic in human lymphocytes under the experimental conditions of this assay.

In addition a 13-week impurity toxicity study was performed in rats by subcutaneous route. In this study, all CAM2029 formulations (with and without Monoamide B (C18:1)) were well-tolerated both locally and systematically in rats, including the formulation with up to 4.74% of Monoamide B (C18:1), at a dose of 10 mg q2w.

- Excipients

There are no novel excipients used in CAM2029.

In CAM2029, phosphatidylcholine originating from soy is used (SPC). PC is a naturally occurring phospholipid comprising diglycerides, linked to the choline ester of phosphoric acid. A review of the literature indicates that PC has low toxicity following oral, IV and/or SC administration. Glycerol dioleate (GDO) is a diglyceride, the diester of glycerin and oleic acid. The GDO used in the CAM2029 drug product may be regarded as a purified version of the excipients described in the monograph for mono- and diglycerides (USP/NF) that allows a diglyceride content of up to 60% and the monograph for glyceryl monooleate (European Pharmacopeia) that specifies up to 50% of diacylglycerols or diglycerides. Both SPC and GDO were evaluated as components in the once-weekly and once-monthly SC injection depot product Buvidal, a drug product based on the FluidCrystal technology comprising of the active substance buprenorphine. Buvidal obtained approval by the European Commission in 2018. At the highest octreotide dose for the proposed indication (20 mg, q4w) a maximum daily dose of GDO and SPC of 14.6 mg/day is administered. For the Buvidal drug product, the highest weekly dose

of Buvidal contains 260 mg GDO and 260 mg SPC, equating to a maximum daily dose of 37.1 mg. This dose is approximately 2.5-fold higher compared with the GDO and SPC doses of the CAM2029 20 mg drug product.

Ethanol (EtOH) is a well-known solvent for which the toxicity profile is generally well understood. EtOH is extensively used in parenteral pharmaceutical products. The ICH Guidance Q3C classifies EtOH as a Class 3 solvent, which is a solvent with no known human health hazards at levels normally used in pharmaceuticals. Ethanol is administered as part of the CAM2029 formulation at a dose level of 62.6 mg q4w, which is lower than the PDE of 50 mg or more per day allowed by ICH Q3C.

Propylene glycol (PG) is used as a solvent in the CAM2029 formulation. PG is a well-known solvent, extensively used in parenteral pharmaceutical products. A PDE of 50 mg/kg has been established (EMA, 2017). This is well above the 62.6 mg q4W exposure for the proposed indication.

Small amounts of ethylenediaminetetraacetic acid (EDTA, 0.096 mg per dose) and ethanolamine (ETA, 0.081 mg per dose) are included in CAM2029 as stabilizing and solubilizing components, respectively. Both components are included in approved products in EU and according to data available in the public domain, there is no indication of toxicological concern at the low exposure expected from the CAM2029 administration.

2.3.5. Ecotoxicity/environmental risk assessment

Table 6 Summary of main study results

Substance (INN/Invented Name): Octreotide/Oczyesa			
CAS-number (if available):			
PBT screening		Result	Conclusion
Bioaccumulation potential- log Kow	OECD107 shake flask method	-0.49(neutral pH)	Potential PBT: N
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log Kow		not B
PBT-statement:	Octreotide is not considered as PBT, nor vPvB		
Phase I			
Calculation	Value	Unit	Conclusion
PECsw, default	0.00357	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

Screening for PBT

In Buchwald and Bodor, the determination of the distribution coefficient of several peptides including octreotide was evaluated using the shake flask approach, which is one of the recommended methods in the guideline. The log D (partitioning coefficient determined at neutral pH) was reported to be -0.49, which is well below the partition coefficient limit of 4.5 set forth in the ERA guideline (EMEA/CHMP/SWP/4447/00, June 2006). Therefore, octreotide is not considered to be bioaccumulative, and no further PBT (Persistent, Bioaccumulative and Toxic) assessment is required.

- PEC calculation

The PECSW is calculated using default values from the ERA guideline and the following assumptions:

• 1% of a population receive the active substance daily.

• The sewage system is the main route of entry of the active substance into the surface water.

• There is no biodegradation or retention of the active substance in the sewage treatment plant (STP).

• There is no metabolism in the patient.

PECSW is calculated using the following formula:

$$PECSW = \frac{DOSEai * Fpen}{WASTEWinhab * DILUTION}$$

Where the parameters are determined as follows:

Parameters	Description	Unit	Default value
PECSW	Predicted environmental concentration for surface water calculated in Phase I	mg/L	-
DOSEai	Maximum daily dose of the active substance consumed per inhabitant	mg/inhab/day	-
Fpen	Fraction of a population receiving the substance	-	0.01
WASTEWinhab	Amount of wastewater per inhabitant per day	L/inhab/day	200
DILUTION	Dilution factor	-	10

For Oczyesa, the maximum daily dose of the active ingredient octreotide is obtained by dividing the maximum recommended dose, 20 mg every 4th week by 28 days = 0.714 mg/inhab/day.

Thus, the PECSW for octreotide in Oczyesas can be calculated as:

$$PECSW = \frac{0.714\ mg * 0.01}{200\ L * 10} = 3.57 * 10^{-6}\frac{mg}{L} = 3.57 * 10^{-3}\frac{\mu g}{L} = 0.00357\frac{\mu g}{L}$$

As this calculation leads to a PECSW below the action limit of 0.01 µg/L set forth in the ERA guideline, further Phase II environmental fate and effects assessment is not required.

Precautionary and safety measures to be taken for administration, disposal and labelling.

The environmental risk as a result of the prescribed usage of the medicinal product Oczyesa containing octreotide is negligible, and specific precautionary and safety measures are not necessary.

In order to enhance environmental protection, the package leaflet and the SmPC include a statement regarding disposal of unused product.

Octreotide is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Octreotide is a well-known active substance used in several pharmaceutical products authorized in the EU. The applicant relied on references to Sandostatin (Immediate Release) SmPC and literature data, as well as performed bringing studies. The Applicant provided PK/PD studies, single- and repeated-dose toxicity studies (including local tolerance) with different formulations of CAM2029 and *in vitro* genotoxicity studies with the hydrochloride salt of octreotide. Provided that CAM2029 is intended to have similar clinical pharmacokinetic exposure range and bioavailability as Sandostatin IR, the risk from octreotide exposure in CAM2029 is covered by current clinical exposure with Sandostatin. Safety and local tolerance studies performed with the FC Vehicle with small compositional variations compared to the to-be-marketed formulation of CAM2029, were also provided. Those were already evaluated and approved in the Buvidal dossier. The lipid excipients used in the final market formulation, glycerol dioleate (GDO) and soybean phosphatidylcholine (SPC), as well as ethanol, are present in the approved sustained release product Buvidal. For the solvent propylene glycol (PG), the stabilizing agent ethylenediaminetetraacetic acid (EDTA) and the solubilizing agent ethanolamine (ETA), reference is made to previous documented use in various approved parenteral drug products in EU.

The part of the section 5.1 of the SmPC relative to the mechanism of action is identical to the one displayed in the SmPc of the reference product Sandostatin. This is endorsed from a non-clinical perspective.

The IGF-1 response to CAM2029 administration as well as the plasma IGF-1 profile comparison with Sandostatin LAR have also been evaluated in clinical trials. Moreover, when investigating potential effect of accidental IM injection, CAM2029 showed to be sufficiently efficient to suppress IGF-1(<80% of baseline) up to 56 days, although this was tested only a small number of dogs were tested and results should be taken with caution.

The secondary pharmacodynamics of octreotide for the treatment of acromegaly is well known from other currently EU-approved medicinal products with the same active substance. Therefore, the lack of appropriate data regarding secondary pharmacodynamics provided by the Applicant is not considered a limiting factor for the non-clinical assessment of Oczyesa and the lack of new independent secondary pharmacodynamics study is considered as acceptable.

No standalone safety pharmacology study was performed with CAM2029. This is acceptable, since the safety pharmacology effects are well known from currently approved products on the EU market containing octreotide. Cardiovascular effects of octreotide acetate and A 13-week repeated-dose toxicology study in dogs did not reveale any cardiovascular effects up to the highest dose tested of 60 mg q4w.

Drug-drug interaction studies with octreotide were provided in the clinical part of the dossier.

Overall, the approach of the Applicant regarding the non-clinical pharmacology programme is acceptable.

Absorption, distribution, metabolism and excretion of the active substance octreotide have been summarized using published data from the literature. This is acceptable.

In general, from the different PK studies reported, it can be concluded that the different compositions tested during CAM2029 development did not produce major differences in PK profiles. The effect on the release of

octreotide from the final CAM2029 formulation in vivo upon mechanical challenge was evaluated in a PK study in rats. Similar plasma concentration profiles of octreotide were observed following IM and SC administration of CAM2029 in dogs, providing evidence that accidental IM injection of CAM2029 is not expected to cause any adverse effects with respect to octreotide exposure. This is endorsed.

In relation to the environmental risk assessment, the PECsurfacewater for Oczyesa is below the action limit of 0.01 µg/L and Oczyesa is not a PBT substance as log Kow does not exceed 4.5. Therefore, octreotide is not expected to pose a risk to the environment.

Therefore, the main points of attention of this non-clinical assessment are related to:

1. The toxicity of the product and local tolerance of the excipients composing the final FluidCrystal Vehicle formulation for CAM2029.

2. The qualification of the impurity Monoamide B (C18:1).

1. Toxicity and local tolerance

All findings of single-dose toxicity studies were reversible. Only local inflammatory reactions at injection sites with signs of recovery were noted.

Overall, the findings of repeat-dose toxicity studies were consistent among species with those observed in the single-dose toxicity studies. All findings were considered reversible and are in line with known undesirable effects due to octreotide as reported in section 4.8 of the SmPC. This is endorsed. No specific concern was revealed, as appropriately reported in the section 5.3 of the SmPC.

Overall, all studies on local tolerance have concurred by showing swelling at injection sites due to physical presence of the depot and local inflammatory response associated with various degree of fibrosis, considered as consistent with a physiological reaction in response to the injection of a biodegradable material. The findings were considered as reversible as there were signs of recovery during recovery periods. This is endorsed.

The absence of mutagenicity has been demonstrated for octreotide acetate salt in the reference product. No difference of mutagenic potential was expected for the hydrochloride salt of octreotide. This was confirmed by two *in vitro* tests performed by the Applicant (bacterial reverse mutation assay and mouse lymphoma mutation assay). Uncertainties remains regarding actual level of test items tested as in those two *in vitro* tests performed, the certificate of analysis of the test item is missing and no analysis was performed to determine the test item concentration, homogeneity or stability achieved in the formulations or test plates. However, no difference of mutagenic potential was expected between the two salts of octreotide. The CHMP has concluded that no additional genotoxicity assay was necessary.

The applicant did not conduct any additional carcinogenicity or DART study with CAM2029. This approach is acceptable.

There are no novel excipients, and their known toxicological profiles do not raise any concern for their use in CAM2029.

2. The qualification of the impurity Monoamide B (C18:1).

The impurity monoamide B (C18:1) has been tested in negative Ames and chromosomal aberration assays, as well as in a 3-month repeated-dose toxicity study consisting in a well–tolerated administration of 10 mg q2w of the final CAM2029 formulation in rats with or without monoamide B (C18:1) up to 4.74%. Overall, the results obtained support the qualification of the impurity at the specification level proposed by the Applicant.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical programme was based in part on data generated during development of Sandostatin, as well on literature data. The applicant performed additional primary PD, PK, single and repeat-dose toxicity studies (including local tolerance) and in vitro genotoxicity studies with CAM2029, which demonstrated that the novel formulation of octreotide is suitable and safe for subcutaneous administration. The SmPC of Oczyesa was aligned with the reference product whenever needed. All issues revealed as non-clinical concerns were resolved.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a prolonged-release solution for injection containing octreotide.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of octreotide based on published literature. The SmPC is in line with 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.

Table 7 Tabular overview of clinical studies

To support the application, the applicant has submitted 7 clinical trials.

Trial/ EudraCT number	Trial Objectives/ Population	Trial design	Trial status
[HS-05-194] 2005-005845-20	PK, PD, safety Healthy male volunteers	Phase 1, randomised, double-blind, parallel group, placebo-controlled, single-dose trial assessing the PK and relative bioavailability of CAM2029. Subjects first received an injection (right buttock) of either placebo (7 subjects in each group) or saline (1 subject in each group) and then an injection (left buttock) of CAM2029 (6 subjects in each group), placebo (1 subject in each group), or saline (1 subject in each group).	Completed
[HS-07-291] 2009-	PK, PD, safety Healthy volunteers	Phase 1, randomised, open-label, parallel group, repeated-dose trial assessing the PK, PD, safety, and tolerability of CAM2029.	Completed

Trial/ EudraCT number	Trial Objectives/ Population	Trial design	Trial status
012217-21			
[HS-11-411] 2011-001548-31	PK, PD, safety Healthy volunteers	Phase 1, randomised, open-label, parallel group, repeated-dose, active controlled trial assessing the PK, PD, safety, and tolerability of 3 formulations of CAM2029 compared to octreotide LAR in healthy volunteers. Subjects first received octreotide IR as run-in treatment.	Completed
[HS-12-455] 2013-000533-12	PK, PD, efficacy, safety Patients with acromegaly or NET	Phase 2, randomised, open-label, multi-centre trial assessing the PK, PD, efficacy, and safety of CAM2029 in patients previously treated with octreotide LAR.	Completed
[HS-19-664] 2020-002643-35	PK, PD, safety Healthy volunteers	Phase 1, randomised, open-label, single- and repeated-dose trial, assessing the PK, PD, safety, and tolerability of different doses, dosing configurations and manufacturers of CAM2029. Subjects first received octreotide IR as run-in treatment.	Completed
[HS-18-633] 2019-001191-11	Efficacy, safety Patients with acromegaly	Phase 3, randomised, double-blind, placebo controlled, multi-centre trial assessing the efficacy and safety of CAM2029 in patients with acromegaly treated with octreotide LAR or lanreotide ATG at enrolment.	Completed
[HS-19-647] 2019-002190-66	Long-term safety, efficacy Patients with acromegaly	Phase 3, open-label, single-arm, multi-centre trial assessing the long-term safety and efficacy of CAM2029 in patients with acromegaly treated with octreotide LAR or lanreotide ATG at enrolment. No control.	On-going/ Interim CTR (data cut-off date: 23 May 2023) Main part CTR (data cut-off date: 30 April 2024)

ATG: autogel; CTR: clinical trial report; IR: immediate release; LAR: long-acting repeatable; NET: neuroendocrine tumours; PD: pharmacodynamic(s); PK: pharmacokinetic(s)

For HS-19-647 an interim report was provided in the initial MAA. Upon request from CHMP a final report of the Main Part (data cut-off 30 April 2024) of the study was provided during the procedure. Therefore, information in this EPAR includes information from both study reports.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Studies with formulation to be commercialised were phase I study HS-19-644, and the two phase III studies HS-18-633 and HS-19-647.

A population pharmacokinetics (PopPK) analysis was performed based on the plasma octreotide concentration results from the Phase 1 trial of the final market formulation, HS-19-664, together with the plasma octreotide concentration results from the Phase 3 trials HS-18-633 and HS-19-647. The exposure of octreotide based on the PopPK model data together with IGF-1 and GH concentrations in HS-18-633, HS-19-647 and HS-19-664 were included in a population pharmacokinetics and pharmacodynamics (PopPKPD) evaluation.

- PK, PD and immunology bioanalytical methods

Method validations are well summarised. The most important validation reports, concerning all data included in the population PK modelling thereafter, could be found.

IGF-1 analysis was well presented, results can be considered reliable for PKPD modelling.

Immunogenicity evaluation methods are presented and validated.

- Formulation development

The marketed product, formulation CY, was used in the phase 1 HS-19-664 study, as well as phase III studies HS-18-633 and HS-19-647. Of note, only these studies were also used for population PK modelling. The bridging between formulations was thus kept to the minimum by the applicant. However, the PK of the final, marketed formulation is appropriately documented.

- PK studies

HS-19-664

HS-19-664 was a phase 1, randomized, open-label trial in healthy volunteers, using formulation CY that will be commercialised, with two manufacturers, prefilled pens or syringes, and using 10 or 20 mg of octreotide, with a comparison with octreotide IR. The study design and population handling were well detailed and acceptable. The bioanalysis was well documented and acceptable. The relative bioavailability results, dose proportionality and pre-filled pen vs. pre-filled syringe conclusions are agreed upon.

Dose proportionality was observed between 10 and 20 mg doses, and the relative bioavailability of octreotide for CAM2029 versus Sandostatin IR was 92% to 98%. The pre-filled syringes and pens appeared to give similar PK profiles. There was a slight difference in Cmax between manufacturers, but AUCs were similar.

HS-11-411

HS-11-411 was another phase I study comparing other formulations under development. The bioavailability of the different formulations tested (CAM2029-BP, BR and BV) compared to octreotide LAR and IR was in similar

ranges between the formulations. The relative bioavailability (AUCtau) of octreotide for CAM2029 formulation variants versus octreotide IR was between 0.684 to 0.907, comparable with the to-be-commercialised formulation CY, while it was 0.172 for octreotide LAR versus octreotide IR. The relative bioavailability of octreotide for CAM2029 formulation variants versus octreotide LAR was between 4.0 and 5.3 (i.e., 400% – 530%).

Other studies

HS-05-194 used formulation CAM2029-P

HS-07-291 used formulation CAM2029-BG and showed about 7-fold higher bioavailability compared to octreotide LAR.

HS-12-455 was a phase II study which was performed in acromegaly patients using formulation BR, but did not hold more additional relevant information for this application.

- Population PK modelling and simulation

The disposition of octreotide PK was best described by a two-compartment model with a first-order elimination from the central compartment. CAM2029 absorption was described by two parallel fast and slow first-order processes (MATfast = 89.2 h and MATslow = 459 h, respectively) while Sandostatin absorption was described by a first-order process (MAT = 1.28 h).

In acromegaly patients, a parameter was estimated to describe the concentrations due to pre-treatment with octreotide. Injection site of CAM2029 administration had an impact on MATfast resulting in a reduction of MATfast by 35% and 53% when CAM2029 was administered in thigh and buttock, respectively, as compared with administration in abdomen.

Clearance and volume parameters were allometrically scaled with WT with fixed exponents of 0.75 and 1, respectively and the WT effects on Cmax,ss and AUCt,ss were within the reference area (80-125% margins relative to the reference subject) for both parameters.

The analysis did not identify effects of any of the following covariates: age, sex, creatinine clearance, AST, total bilirubin (TBIL) and BMI. In particular following administration of CAM2029, there was no evidence of an impact of the drug product manufacturer on the PK of octreotide. No marked difference in PK between healthy subjects and acromegaly patients was identified and the model described both populations well.

Further, the model did not identify a significant difference in MATfast and MATslow between doses 10 and 20 mg. Octreotide PK was not found to be time-dependent.

The simulation-based comparison indicated that the average concentration during a dosing interval at steady state (Cav,ss) was similar for CAM2029 20 mg administered every 4 weeks and Sandostatin 0.25 mg every 8 hours. The geometric mean of Cmax,ss to minimum concentration during a dosing interval at steady state (Cmin,ss) ratio was 12.7 for CAM2029 and 13.6 for Sandostatin. Following administration of CAM2029 20 mg q4w in abdomen in a 75-kg subject, steady-state exposure was reached at the second dose.

- Pharmacokinetic interaction studies

Although PK interactions with the tested CYPs isoforms by inhibition is not expected based on *in vitro* results, pharmacodynamic interactions with CYP3A4 are likely to occur due to pharmacological cascade reaction. Indeed, GH suppression is followed by down-regulation of IGF-1, which holds a determinant role in the insulin-mediated down-regulation of various CYPs including CYP3A4, CYP2C, CYP1A and CYP2D (Konstandi et Johnson,

2023) Therefore, clinically significant interaction could not be excluded with CYP3A4 substrates, especially those with narrow therapeutic window.

The Oczyesa SmPC has included information from the Sandostatin SmPC, on the interaction with cyclosporine, cimetidine, and bromocriptine, due to its reduced absorption leading to the delayed absorption of cimetidine, the increase in bromocriptine bioavailability. This is endorsed by the CHMP.

- Pharmacokinetics using human biomaterials

Interactions with other medicinal products are reported for Sandostatin as drug reference product for the present hybrid application but *in vitro* studies were also provided to assess octreotide inhibition potential for CYPs isoforms (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4), and transporters (OAT-1 and -3, MRP2, BSEP, and BCRP, P-gp). The inhibition of uptake transporters such as OATP1A1, OATP1B1, OCT1, and OCT3 was not studied. This is acceptable given octreotide has not been reported to interact with these transporters.

The potential of octreotide to inhibit human CYP enzyme activity was assessed in pooled human liver microsomes, whereas the transporters inhibition was tested using inside-out vesicle containing efflux transporters and using HEK cells over-expressing human renal uptake transporters OAT1 and OAT3. Octreotide concentrations were tested up to 20 µM for CYPs inhibitors assessment and up 10 µM for transporter inhibition. Probe substrate concentrations used were approximately equal to Km values and probe substrate metabolism was assessed by LC-MS/MS analysis of specific metabolite formation. The determined IC50 were above the highest tested concentration of octreotide, (>20µM for tested CYPs, and >10µM for transporters) except for P-gp where IC50 was estimated to 0.749µM.

Based on these results, no clinically relevant interactions with the tested CYPs (i.e. 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4), and transporters (i.e. OAT-1 and -3, MRP2, BSEP, and BCRP, P-gp) are expected.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. However, PD clinical data with CAM2029 were provided from the phase 1 studies, phase 2 study and phase 3 studies.

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

Overall, the PK of CAM2029 was adequately characterised, and the population PK model fitted and used for simulation can be considered adequate with some clarifications needed. CAM2029 has a different PK than octreotide LAR with a significantly faster onset of octreotide release compared to octerotide LAR, which reached peak concentrations around 1-4 hours after administration, compared to 2 to 3 weeks for octreotide LAR. This relevant advantage of CAM2029 compared to octreotide LAR allows to avoid the injections of octreotide IR during the first 3 weeks of treatment (initial lag phase).). Of note, the bioavailability of octreotide for CAM2029 versus octreotide IR was determined to 92% to 98% and established a bridge between CAM2029 and the reference medicinal product Sandostatin. There are also no major concerns on drug-drug interactions with the product.

Pharmacodynamics

The primary pharmacodynamic effect of CAM2029 in acromegalic patients is the inhibition of the GH/IGF-1 axis (IGF-1 mediates most of the growth-promoting actions of GH).

Overall, the results from the non-clinical pharmacodynamic evaluations demonstrate a clear suppression of IGF-1 by subcutaneous injection of CAM2029 formulations. The onset of suppression is relatively fast, with the maximum inhibition observed after about 2 days (rat) or up to about 8 days (dogs) followed by a gradual recovery. The IGF-1 levels remained below baseline (pre-dose) levels throughout the respective study/sampling periods.

In a comparative repeated-dose toxicity study in dogs, the IGF-1 levels decreased more rapidly after the first dose of the CAM2029 formulations as compared to Sandostatin LAR, consistent with the difference in the respective pharmacokinetic profiles.

No stand-alone safety pharmacology studies were performed. There were no effects on electrocardiology parameters in a repeated-dose toxicology study in dogs with CAM2029.

Pharmacodynamic data in human

Similar results were also observed in the phase 1 studies in healthy volunteers [HS-05-194], [HS-07-291], [HS-11-411], [HS-19-664], in acromegalic patients in the phase 2 study [HS-12-455] and in the phase 3 studies [HS-18-633] and [HS-19-647].

The CAM2029 formulations exhibited significantly faster onset of octreotide release compared to octerotide LAR, and reached peak concentrations around 1-4 hours after administration, compared to 2 to 3 weeks for octreotide LAR.

In the different studies, after administration of different doses and formulations of CAM2029, there was a rapid and prolonged octreotide release over time with a significantly higher octreotide AUC and bioavailability (four to five-fold), and higher or similar trough concentration, compared to octreotide LAR 10 mg or 30 mg/month. This leads to an immediate decrease of the IGF-1 levels to a nadir 4-7 days after dose and then a gradual rise continuing to 21-28 days after dose. This relevant advantage of CAM2029 compared to octreotide LAR allows to avoid the injections of octreotide IR during the first 3 weeks of treatment (initial lag phase).

Of note, the bioavailability of octreotide for CAM2029 versus octreotide IR was determined to 92% to 98% and established a PK bridge between CAM2029 and the reference medicinal product Sandostatin IR.

Although there was some variability in IGF-1 concentrations among the treatment groups, a dose-response relationship for CAM2029 was apparent with greater mean IGF-1 reductions in the 30 mg dose group than in the 20 mg and 10 mg dose groups.

Based on the PD data of study [HS-11-411], after the 3rd injection of CAM2029 (10, 20, 30 mg) and octreotide 30 mg LAR (steady state), trough values of IGF-1 were comparable between the treatments. Indeed, the mean (SD) steady-state Ctrough 28 days after the third monthly injection of 30 mg CAM2029-BR was 1.03 (1.02) ng/mL (n=14), which was similar to the mean (SD) steady-state Ctrough after the third monthly injection of 30 mg octreotide LAR (1.02 [0.33] ng/mL) (n=13).

Of notethe dose of 30 mg octreotide LAR is the dose usually recommended for the maintenance of treatment.

In study [HS-07-291], Ctrough of 20 mg octreotide LAR is 0.32 ng/mL. The recommended starting dose of octreotide LAR is 20 mg.

However, $C_{trough,ss}$ of octreotide is considered to be the most critical PK surrogate marker to represent the minimum effective concentration of octreotide required to maintain normal IGF-1 levels in patients with acromegaly and is an indicator of sustained efficacy of treatment.

As the cthrough for 20 mg CAM2029 every 4 weeks was higher than ctrough for octreotide LAR 20 mg but similar to ctrough for octreotide LAR 30 mg. Therefore, the dose of 20 mg CAM2029 every 4 weeks rather corresponds to a maintenance dose than a starting dose.

Moreover, it was also observed in study [HS-11-411] that a maximum inhibition after the third period was above 40% for CAM2029-BR, 30 mg, and CAM2029–BV, 20 mg and 30 mg; in both cases, this was compared to octreotide LAR 30 mg. Of note, for CAM2029-BP 10 mg, Imax was 35.82% and for CAM2029-BV 10 mg Imax was 31.51%.

Likewise, in the PK bridge study [HS-19-664], the IGF-1 mean reduction with single dose of 20 mg CAM2029 was slightly greater (range maximum inhibition [Imax] 33% to 41%; AUCIlast 20.8 to 25.8×10^3%*h) than following the single dose of 10 mg CAM2029 4qw (Imax 32%; AUCIlast 15.5×10^3%*h) compared to 0.25 mg x4 octreotide IR.

The applicant was asked to discuss these results from the [HS-11-411] and [HS-19-664] studies, in relation to the effect of different doses of CAM2029 on the inhibition. It was clarified that there was a clear trend towards greater inhibition in IGF-1 with increasing dose in both trials, particularly when comparing 20 mg vs 10 mg CAM2029. A concentration-response relationship was established and given the dose-linear PK; this demonstrates that there is a dose-response relationship. Thus, the recommended CAM2029 dosing, 20 mg every 4 weeks, has been confirmed in the Phase 3 trials with a positive benefit/risk profile.

The choice of dose 20 mg CAM2029 every 4 weeks for the phase 3 studies mainly relied on clinical data from phase 1 [HS-11-411] and phase 2 [H S-12-455] and was confirmed in the phase 3 studies, PK bridge study [HS-19-664] as well as in the popPK and popPKPD models. However, the clinical data from the phase 2 study were limited.

Therefore, the choice of dose for the phase 3 studies was mainly based on the results of the phase 1 study [HS-11-411], where the healthy subjects did not present with the elevated IGF-1 level at screening typical for untreated patients with acromegaly. Dose-response relationship in healthy adults is relatively flat due to the low IGF-1 levels in this population. Differences in IGF-1 response between the three CAM2029 doses might not be detectable, especially if the inter-individual variability in PD response is large.

The applicant has argued that comparative PK and PD did not appear to be sensitive to potential population effects relating to SC tissues differences or baseline IGF-1 levels based on data from a pop PK model and popPKPD model. However, these models used doses of octreotide IR which are recommended for maintenance of the treatment and not to start the treatment especially in treatment-naïve patients. Thus, the approved indication was restricted to the maintenance of treatment in well-controlled patients with somatostatin analogues.

Regarding the different formulations used in the phase 1 and phase 2 studies only differed from the final formulation of the marketed product by very small changes in co-solvents and stabilizers which were added to improve the storage stability profile. This minor change in the composition had no impact on the PK.

Regarding the dose variations related to the change of injection sites of administration of the product in the

studies, based on the PopPK analysis, a reduction of the mean absorption time by 35% for thigh and 53% for buttock as compared with abdominal administration was demonstrated. This effect translated into an increase of Cmax,ss by 50% (90% CI: 40%, 70%) for thigh administration and 90% (90% CI = 50-160%) for buttock administration, but importantly, no effect was seen on AUCτ,ss. When simulating IGF-1 concentrations in a typical subject following CAM2029 administration in either abdomen, buttock or thigh, no difference was observed between the IGF-1 profiles over time. The safety profile for buttock injection of CAM2029 was found to be similar to the abdominal injection.

The higher bioavailability (4 to 5-fold) exposure and Cmax of CAM2029 compared to octreotide LAR could have an impact on the short and long-term safety. However, the safety data are reassuring for the well-controlled patients in the phase 3 studies but not in the healthy volunteers (in the phase 1 study) and pharmacologically washed-out patients (in study HS-19-647) as higher frequencies of gastro-intestinal events and cholelithiasis were highlighted in these patients. This can be managed with a dose titration of the product as recommended and usually clinically necessary for the other SRLs.

Given there were no treatment-naïve patients in the 2 phase 3 studies, the safety of CAM2029 is not characterized in these patients and cannot be extrapolated from clinical data in healthy volunteers (phase 1 studies) and in the pharmacologically washed-out patients (study HS-19-647).

In the phase 1 [HS-11-411], phase 2 [HS-12-455], in the PK Bridge phase 1 study [HS-19-664] and in popPK and popPKPD models, the doses of comparators are the doses recommended for the maintenance of treatment and not as starting doses for treatment- naïve patients. Indeed, the results showed that the effects on the reduction of IGF-1 levels are comparable between 20 mg q4w CAM2029 and these comparators.

In the simulations popPK and popPKPD models, the dose of 20 mg 4qw CAM2029 was compared to octerotide IR 0.25 mg or 0.50 mg TID which are higher than the optimal dose recommended in the SmPC of octreotide IR: 0,3 mg/day. Of note the maximal dose of octreotide IR recommended is 1,5 mg /day. These models have shown comparable effects between the two treatments while the dose of the comparator is higher than the optimal dose of treatment.

The applicant has also provided the simulation between 20 mg and10 mg 4qw CAM2029 compared to the optimal dose of octreotide IR (0.3 mg/ day), but no conclusion can be drawn from this simulation.

The dose of 20 mg every 4 weeks is considered more adapted to the target population who does not need a dose titration and the restricted indication which was approved reflected this finding.

Regarding the secondary pharmacology, due to the multiple inhibitory effects of somatostatin and SRLs on many exocrine and endocrine secretion parameters, there are potential secondary effects of CAM2029 on other biological parameters which are considered as "class effects" such as inhibition of release of TSH, post-prandial release of insulin, glucagon, gastrin, other peptides of the GEP endocrine system, and arginine-stimulated release of insulin and glucagon, pancreatic polypeptide, vasoactive intestinal peptide, serotonin, and motilin. Therefore, there are specific monitoring recommended in the SmPC (section 4.4). The applicant has also accepted to include liver haemangioma as ADR in the SmPC (section 4.8) with the frequency uncommon and to monitor neoplasms in the future PSURs.

2.4.4. Conclusions on clinical pharmacology

CAM2029 is a new, ready-to-use, long-acting octreotide product. The delivery system provides favourable pharmacokinetics by combining a rapid onset and long-acting release of octreotide.

CAM2029 has a different PK than octreotide LAR with significantly faster onset of octreotide release compared to octerotide LAR, which reached peak concentrations around 1-4 hours after administration, compared to 2 to 3 weeks for octreotide LAR. This relevant advantage of CAM2029 compared to octreotide LAR allows to avoid the injections of octreotide IR during the first 3 weeks of treatment (initial lag phase). Of note, the bioavailability of octreotide for CAM2029 versus octreotide IR was determined to 92% to 98% and established a PK bridge between CAM2029 and the reference medicinal product Sandostatin.

The dose of 20 mg 4qw CAM2029 mainly based on the results of a phase 1 study [HS-11-411] is not adapted for the treatment-naïve patients.

The dose of 20 mg/week is considered more adapted for the target population of the 2 phase 3 studies "patients well controlled with other SRLs" as this population does not need a dose titration. As a consequence, the applicant accepted to restrict the indication in line with the target population of the 2 phase 3 studies in "*maintenance treatment of acromegaly patients who have responded to and tolerated treatment with somatostatin analogues*".

There are no major concerns on drug-drug interactions.

2.4.5. Clinical efficacy

Table 8 Description of clinical efficacy trials in the CAM2029 clinical development program

Trial Identifier **EudraCT Number** **NCT Number** **Location of Clinical Trial Report [Module]**	**Number of Trial Centres with Enrolled/ Randomised Patients**	**Trial Start** **Enrolment Status and Date** **Total Enrolment/ Enrolment Goal**	**Trial Design** **Trial Objectives** **Type of Control**	**Diagnosis**	**IMP(s)** **Dosage Regimen** **Route of Administration**	**Duration of Treatment with CAM2029**	**Number of Patients Enrolled/ Completed Trial**	**Main Efficacy Endpoints**
[HS-12-455] 2013-000533-12 NCT02299089 Module 5.3.4.2 (6)	7 (whereof 4 enrolled patients with acromegaly)	FPFV: 09-Jan-2015 Early terminated: 01-Oct-2015 LPLV: 16-Feb-2016 12 enrolled/ 24 planned	Phase 2, randomised, open-label, multi-centre trial assessing the PK, efficacy, and safety of CAM2029 in patients previously treated with octreotide LAR Control: Octreotide LAR	Patients with acromegaly treated with a stable dose of octreotide LAR (10, 20 or 30 mg) for at least 2 months before screening	**Octreotide LAR** Single IM injection of 10, 20 or 30 mg (last pre-trial injection of the ongoing therapy) **CAM2029** 6 SC injections of 10 mg (0.5 mL) every 2 weeks or 3 SC injections of 20 mg (1.0 mL) every 4 weeks in the upper thigh	3 months	**Patients with acromegaly** 7 patients enrolled/ 7 patients completed **Patients with NET** 5 patients enrolled/ 5 patients completed	• Change in IGF-1 over time • Change in GH over time
[HS-18-633] 2019-001191-11 NCT04076462 Module 5.3.5.1	33	FPFV: 19-Aug-2019 LPLV: 02-May-2023 72 enrolled/ 78 planned	Phase 3, randomised, double-blind, placebo-controlled, multi-centre trial assessing the efficacy and safety of CAM2029 in patients treated with octreotide LAR or lanreotide ATG at time of enrolment Control: Placebo	Patients with acromegaly treated with a stable dose of octreotide LAR (10, 20, 30 or 40 mg) or lanreotide ATG (60, 90 or 120 mg) for at least 3 months before screening, and having IGF-1 ≤1×ULN (average of the assessments at screening and Week -2)	**CAM2029 treatment arm** 6 SC injections of 20 mg (1.0 mL) CAM2029 in the abdomen or thigh every 4 weeks **Placebo treatment arm** 6 SC injections of 1.0 mL placebo in the abdomen or thigh every 4 weeks	24 weeks	**CAM2029** 48 patients enrolled/ 46 patients completed **Placebo** 24 patients enrolled/ 24 patients completed	**Primary efficacy endpoint** • Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 (average of the two measurements) **Key secondary efficacy endpoints** • Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24, including patients who had their dose decreased to 10 mg CAM2029 (or 0.5 mL placebo) • Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 and mean GH <2.5 µg/L at Week 24

Trial Identifier EudraCT Number NCT Number Location of Clinical Trial Report [Module]	Number of Trial Centres with Enrolled/ Randomised Patients	Trial Start Enrolment Status and Date Total Enrolment/ Enrolment Goal	Trial Design Trial Objectives Type of Control	Diagnosis	IMP(s) Dosage Regimen Route of Administration	Duration of Treatment with CAM2029	Number of Patients Enrolled/ Completed Trial	Main Efficacy Endpoints
								Other Secondary Efficacy Endpoints • Time to IGF-1 >1×ULN • IGF-1 and GH at Week 24 and over time • Change in tumour size from screening to Week 24 • Severity scores of clinical signs and symptoms of acromegaly over time • TSQM scores over time using all 4 domains of TSQM (effectiveness, side effects, convenience, and satisfaction) • Patient satisfaction scale scores at Week 24 • Change from baseline in AcroQoL scores • Change from the PRE module to the POST module in SIAQ scores
[HS-19-647] 2019-002190-66 NCT04125836 Module 5.3.5.2	45	FPFV: 10-Oct-2019 Enrolment completed; trial ongoing Data cut-off: 23-May-2023 135 enrolled/ 140 planned	Phase 3, open-label, single-arm, multi-centre trial assessing the long-term safety and efficacy of CAM2029 in patients treated with octreotide LAR or lanreotide ATG at time of enrolment	**New patients** New patients with acromegaly treated with a stable dose of octreotide LAR (10, 20, 30 or 40 mg) or lanreotide ATG (60, 90 or 120 mg) for at least 3 months before screening. Having either IGF-1 >1×ULN and ≤2.0×ULN (average of	**New patients** 13 SC injections of 20 mg (1.0 mL) CAM2029 (or 10 mg [0.5 mL] in case of down-titration) in the abdomen, thigh or buttock every 4 weeks in the main part of the trial, and SC injections of the same treatment in	**New patients** 52 weeks (main part) + 52 weeks (extension part) **Roll-over patients** 28 weeks (main part) + 52 weeks	**New patients** Main part: 81 patients enrolled/ 60 patients completed (15 patients ongoing at interim analysis) Extension part: 2 patients	**Secondary efficacy endpoints** • Proportion of patients with mean IGF-1 ≤1×ULN at Week 50 and Week 52 (average of the two measurements) • Proportions of patients with mean GH <1.0 and <2.5 µg/L at Week 52 • Proportion of patients

Trial Identifier EudraCT Number NCT Number Location of Clinical Trial Report [Module]	Number of Trial Centres with Enrolled/ Randomised Patients	Trial Start Enrolment Status and Date Total Enrolment/ Enrolment Goal	Trial Design Trial Objectives Type of Control	Diagnosis	IMP(s) Dosage Regimen Route of Administration	Duration of Treatment with CAM2029	Number of Patients Enrolled/ Completed Trial	Main Efficacy Endpoints
			No control	the assessments at screening and Week -2) with or without prior radiotherapy, or IGF-1 ≤1×ULN at screening with (or without) prior pituitary radiotherapy at least 3 years before screening and confirmed disease activity (IGF-1 >1×ULN) during the period from 3 to 9 months before screening **Roll-over patients** Roll-over patients from the CAM2029 and placebo treatment arms in HS-18-633	the extension part of the trial **Roll-over patients** 7 SC injections of 20 mg (1.0 mL) CAM2029 (or 10 mg [0.5 mL] in case of down-titration) in the abdomen, thigh or buttock every 4 weeks in the main part of the trial (starting at Week 24), and SC injections of the same treatment in the extension part of the trial	(extension part)	enrolled and ongoing **Roll-over patients** 54 patients enrolled/ 43 patients completed (10 patients ongoing at interim analysis) Extension part: 4 patients enrolled and ongoing	with mean IGF-1 ≤1×ULN at Week 50 and Week 52 (average of the two measurements) and mean GH <2.5 µg/L at Week 52 • Change from baseline in IGF-1 and GH • Proportion of patients retained in treatment at Week 52 • Change from baseline in tumour size • Severity scores of clinical signs and symptoms of acromegaly over time • TSQM scores over time using all 4 domains of TSQM (effectiveness, side effects, convenience, and satisfaction) • Patient satisfaction scale scores at Week 24 and Week 52 • Change from baseline in AcroQoL scores • Change from PRE module to the POST module in SIAQ scores

2.4.5.1. Dose response studies

The dose of 20 mg 4qw CAM2029 was mainly chosen based on the clinical data from the phase 1 study [HS-11-411] as the clinical data in phase 2 study [HS-12-455] are very limited (only 5 acromegalic patients completed the study).

1) Phase 1 Study [HS-11-411]

Design

[HS-11-411] was a phase 1, open-label, randomised, parallel-group trial assessing 3 formulation variants of CAM2029 after 3 doses in 122 healthy volunteers given every 4 weeks.

The trial featured: a single SC dose (buttock) of octreotide IR 0.2 mg as run-in treatment, 3 formulation variants of CAM2029 (-BP, -BR, and -BV) 20 mg/mL, and the comparator, IM octreotide LAR, 30 mg. CAM2029-BP and –BV were administered SC at 10 mg (0.5 mL), 20 mg (1.0 mL) and 30 mg (1.5 mL) dose levels and CAM2029-BR was administered SC at a dose of 30 mg (1.5 mL).

After a single dose of octreotide immediate release (IR) 200 µg on day 0 in order to provide a normalizing reference for octreotide bioavailability and IGF-1 response. After a 7-day washout period, subjects were randomized to one of eight groups to receive three monthly injections of octreotide s.c. depot A (BP) 10, 20 or 30 mg, B (BR) 30 mg, C (BV) 10, 20 or 30 mg or long-acting octreotide (octreotide LAR) 30 mg.

Three doses of the CAM2029 treatments and 30 mg octreotide LAR were given SC in the buttock with 4 weeks between the doses. The CAM2029 formulations were provided in vials and administered with disposable syringes.

Objectives and endpoints

The primary objective of the trial was to characterise the multiple-dose PK-profile (following three repeat once monthly injections) of octreotide for CAM2029-BP, CAM2029-BR and CAM2029-BV and blood samples for analysis of plasma octreotide concentrations and assessment of PK parameters were collected for that purpose over the 105-day duration of the trial. Also, the dose-adjusted Cmax and Ctrough values for the third dose of CAM2029 and octreotide LAR were compared. Analyses of dose proportionality and dose linearity were performed for CAM2029-BP and CAM2029-BV.

Secondary objectives included comparison of the PK and characterization and comparison of the PD profiles following three repeat once monthly injections of CAM2029-BP, CAM2029-BR and CAM2029-BV vs. octreotide LAR, assessment of the safety and tolerability of repeated injections of CAM2029-BP, CAM2029-BR and CAM2029-BV and octreotide LAR and assessment of the bioavailability of octreotide when administered as CAM2029-BP, CAM2029-BR and CAM2029-BV compared with octreotide LAR and IR.

Blood samples for analysis of IGF-1 were collected over the 105-day duration of the trial with the purpose of characterising the reduction of IGF-1 of CAM2029-BP, -BR and -BV and to compare the PD profile of CAM2029-treatments with that of octreotide LAR.

Changes in IGF-1 from baseline were calculated, the maximum inhibition of IGF-1 levels compared to baseline, and the integrated IGF-1 inhibition (AUC) during the 3 injections were calculated. Maximum and integrated IGF-1 inhibitions after CAM2029 treatments were compared with those of octreotide LAR. Dose-response and exposure-response relationships were explored as were correlations of PK and PD.

Secondary endpoints included assessments of safety and tolerability (systemic and at injection site).

Subject Disposition and Demographics

60 of 123 subjects were female (48.8%) and 122 of 123 were 'White or Caucasian' (99.2%). The age of the subjects ranged from 21 to 50 years with a median age of 41 years. Mean (SD) BMI was 24.4 kg/m2 (2.63). Demographic characteristics were similar among treatment groups.

Of the 18 subjects who discontinued, 10 (8.1%) withdrew consent, six (4.9%) discontinued because of an AE, one (0.8%) was withdrawn because of non-compliance with the protocol (subject tested positive for tetrahydrocannabinol) and one non-randomized subject (0.8%) withdrew because of pregnancy.

Results

Dose linearity and approximately dose-proportional PK were observed for octreotide CAM2029-BP and CAM2029-BV for the third injection for both Cmax and AUC(0,τ). Cmax and AUC(0,τ) values for CAM2029-BR 30 mg were similar to those of CAM2029-BP and CAM2029-BV 30 mg.

Steady-state was achieved following the second injection for all treatments except for CAM2029-BV 20 mg and octreotide LAR. All treatments achieved steady-state following the third injection.

The establishment of steady-state conditions provided the basis for comparing the bioavailability of randomized treatments. For the third injection, statistically significant differences were found for all dose-adjusted comparisons of AUC(0,τ) and Cmax for the octreotide s.c. depot formulations vs. octreotide LAR.

The relative octreotide bioavailability (AUC(0,τ) ratios (for the EVAL population)) of depot variants vs. octreotide IR and, vs. octreotide LAR 30 mg, was approximately four- to five-fold greater than octreotide LAR 30 mg : 3.97 (90% CI 3.35, 4.71) to 5.27 ng ml−1 h (90% CI 4.43, 6.27).

Octreotide s.c. depot formulation variants showed dose proportionality and linearity over the range 10–30mg (as observed from CAM2029-BP and -BV). Of note, Ctrough of CAM2029-BR 30 mg was similar to Ctrough of octreotide LAR 30 mg (0.60 ng/mL)

The study showed that mean Cmax for the CAM2029 sustained-release formulations (-BP (A), -BR (B) and –BV (C)) at steady-state was about 9 ng/mL (10 mg dose) close to the mean Cmax value for a single dose of octreotide IR (0.2 mg) of 7.0 ng/mL and about 20 ng/ml for the 20 mg , while the mean cmax of the CAM2029 sustained-release formulations (-BP, -BR and -BV) at steady-state was 35 ng/mL (30 mg dose) and the mean Cmax for octreotide LAR (30 mg) was 1.8 ng/mL at steady-state.

Mean AUCτ values for the CAM2029 sustained-release formulations ranged from about 1000 h*ng/mL (10 mg dose) to 3700 h*ng/mL (30 mg dose) at steady state across all CAM2029 formulations and strengths in comparison to 733 h*ng/mL for octreotide LAR (30 mg dose).

Cmax for octreotide IR (200 µg) was 7.0 ng ml−1, which was comparable with the mean Cmax values for the 10 mg doses of the octreotide s.c. depot formulations (approximately 9 ng ml−1). Of note, the mean Cmax for the formulations of 20 mg SC depot (16,9-21.1 ng. ml−1) and for octreotide LAR 30 mg was 1.8 ng ml−1. Although Cmax for the 30 mg doses of octreotide s.c. depot was higher compared with octreotide LAR 30 mg (27–35 vs. 1.8 ng ml−1) and the relative bioavailability of the octreotide s.c. depot formulations was four- to five-fold higher, the tolerability profile appeared comparable.

Maximum suppression of IGF-1 after the third injection (steady-state) was highest for CAM2029-BR (30 mg) and for CAM2029-BV (20 and 30 mg), with a mean inhibition of (43-45% maximum suppression) in all cases

compared to octretide LAR 30 mg (35.7%-41.4%). Of note, for CAM2029-BP 10 mg the suppression is around (36-41,9%).

Table 9 Concentration of IGF-1: maximum inhibition (percentage) for the first, second, and third randomized injections (EVAL population)

Characteristic	Oct s.c. depot A 10 mg *n* = 17	Oct s.c. depot A 20 mg *n* = 16	Oct s.c. depot A 30 mg *n* = 17	Oct s.c. depot B 30 mg *n* = 14	Oct s.c. depot C 10 mg *n* = 15	Oct s.c. depot C 20 mg *n* = 14	Oct s.c. depot C 30 mg *n* = 15	Oct LAR 30 mg *n* = 14
First injection Mean (SD), %	41.9 (6.0)	39.4 (12.0)	42.8 (10.0)	43.8 (16.4)	39.5 (13.0)	44.2 (7.0)	43.3 (12.3)	35.7 (11.2)
Second injection Mean (SD), %	37.2 (8.5)	37.5 (18.3)	39.1 (9.9)	46.2 (14.5)	36.3 (10.6)	40.0 (12.5)	45.7 (10.3)	41.2 (12.9)
Third injection Mean (SD), %	36.3 (6.4)	33.5 (16.0)	39.3 (12.2)	44.8 (15.7)	35.6 (15.1)	45.4 (10.6)	43.4 (7.4)	41.4 (12.0)

Oct s.c. depot A=CAM2029-BP; Oct s.c. depot B=CAM2029-BR; Oct s.c. depot C=CAM2029-BV

However, it is difficult to extrapolate the safety clinical data from healthy volunteers to acromegalic patients as they have not high levels of IGF-1 at baseline and have a different subcutis.

The CHMP recommended to the applicant to perform a PK study in acromegalic patients to ensure that the data obtained in healthy volunteers can be reproduced in patients and to provide information regarding octreotide exposure. Indeed, acromegalic patients have changes in their subcutaneous tissue that may affect PK.

The applicant concluded that the lowest IGF-1 values were observed for CAM2029-BR, 30 mg; however, no statistical difference could be seen in the area under inhibition versus time curve (AUCI) of IGF-1 inhibition or maximum inhibition between CAM2029 treatment groups and octreotide LAR 30 mg at steady-state, after the third injection. Indeed, trough values of IGF-1 were comparable between the treatments.

2) Phase 2 study [HS-12-455]

Design

This was a phase 2, open-label, multicentre, randomised, trial assessing the PK, PD, efficacy, and safety of two dosing regimens of CAM2029-BR in adult patients with acromegaly or functional, well-differentiated NET with carcinoid symptoms.

Patients were treated with octreotide LAR (10, 20 or 30 mg) for at least 2 months before they received their first dose of CAM2029. Only 12 patients with acromegaly and NET were included in this trial. 2 patients with acromegaly were excluded from the PAS due to protocol violations and incorrect dose of treatment.

The trial consisted of 3 periods:

• Period 0: A 4-week period in which patients received their last pre-trial single injection of their ongoing therapy with IM octreotide LAR (10, 20, or 30 mg, treatment A, B and C respectively),

• Period 1: A 3-month CAM2029-BR treatment period into which patients were randomised to receive either 20 mg (1.0 mL) of CAM2029-BR 20 mg/mL, every 4 weeks (3 injections in total), or 10 mg (0.5 mL) of CAM2029-BR 20 mg/mL, every 2 weeks (6 injections in total)

• Period 2: A 28-day post-treatment (follow-up) period.

Objectives and endpoints

The primary objective of the trial was to characterise the PK profile of octreotide after each dose of CAM2029 as compared with the baseline PK for octreotide LAR in patients with acromegaly or NET. Blood samples for analysis of plasma octreotide concentrations and assessment of PK parameters were collected for this purpose over the duration of the trial.

Secondary endpoints in patients with acromegaly included measurements of IGF-1 and GH to compare the effect of octreotide SC depot on response rate of IGF-1 normalization and mean growth hormone (GH) levels < 2.5 µg/L in period 1 and period 0, to characterize IGF-1 and GH profiles in period 1 and period 0, and to compare the proportion of patients with GH < 2.5 µg/L and normalized IGF-1 levels in period 1 and period 0. Safety and tolerability were assessed in all patients.

Demographic and Baseline Disease Characteristics

Seven patients with acromegaly (and 5 patients with NET) were enrolled and completed the trial. Four (57.1%) of the 7 patients with acromegaly were men and 3 (42.9%) women. The median age among patients with acromegaly was 65.0 years (range 42 to 70 years) and the mean (standard deviation; SD) body mass index (BMI) was 26.9 (4.41) kg/m2.

Pharmacokinetic and Efficacy Results

CAM2029 provided rapid and extended octreotide release with well-maintained control of disease biomarkers and symptoms after switching from octreotide LAR. Octreotide maximum observed plasma concentration (Cmax), trough plasma concentration (Ctrough) and area under the plasma concentration-time curve (AUC) after the first injection of CAM2029 were similar for the first and third injection.

The octreotide exposure (AUC0 28d and Cmax) was several-fold higher during treatment with CAM2029 10 mg every 2 weeks and CAM2029 20 mg every 4 weeks than during treatment with octreotide LAR 10 or 30 mg every 4 weeks.

Ctrough, considered as an established PK indicator of sustained octreotide efficacy in patients with acromegaly based on publications, was similar for the two CAM2029 regimen compared to octreotide LAR IM 30 mg doses (in 4 patients). The PK parameters were lowest in one patient who was treated with octreotide IM LAR 10 mg.

Three of the 5 evaluable patients with acromegaly had IGF-1 levels within the normal range when switching to CAM2029 and kept their IGF-1 levels within the normal range also at the end of treatment (Day 84). Two of the patients with acromegaly had IGF-1 above the upper limit of normal (ULN) when switching to CAM2029 and experienced some improvement in IGF-1 levels during treatment with CAM2029 (though remaining >ULN). Four patients had GH <2.5 µg/L at all time points, while 1 patient had GH>2.5 µg/L.

Overall Pharmacokinetic and Efficacy Conclusions

A key limitation to the interpretation of the results of study [HS-12-455] is the small sample size; due to difficulties in patient recruitment (screening failures, refusal of patients to participate, available patients switching to other treatment options), only 12 patients could be recruited out of the planned 24.

The trial demonstrated that CAM2029 administered as subcutaneous doses of 10 mg every 2 weeks or 20 mg every 4 weeks provided rapid and extended octreotide release over time with a significantly higher octreotide AUC and bioavailability, and higher or similar trough concentration, compared to octreotide LAR 10 mg or 30 mg. Of note, the only patient with acromegaly on 20 mg Octreotide LAR was withdrawn from the PK analysis.

Furthermore, administration of CAM2029 resulted in sustained or decreased levels of the established efficacy biomarker IGF-1, as well as GH, when compared to prior treatment with octreotide LAR leading to the maintenance of the biochemical control in patients with acromegaly.

Efficacy and safety parameters were similar between the two dosing schedules (q2w and q4w) of CAM2029. In patients with acromegaly, switching from octreotide 30 mg LAR IM to CAM2029 resulted in maintenance or improvement of biochemical control in terms of IGF-1 and GH levels.

Ctrough, an established PK indicator of sustained octreotide efficacy in patients with acromegaly, was similar for the two octreotide SC depot regimen and octreotide LAR IM 30 mg doses (treatment C in 4 patients). The PK parameters were lowest in one patient who was treated with octreotide IM 10 mg.

In period 1, Cmax, AUC 0–28d, and Ctrough were similar after first injection (day 0) and after multiple injections (day 56).

The development of the product was made using the FDA Guidance on acromegaly for Industry (January 2023) as reference. This states that all IGF-1 and GH levels should be obtained at Ctrough, before the administration of the next dose. Indeed, IGF-1 and GH levels are biomarkers of efficacy.

3) Results of phase 3 studies and PopPKPD modelling and simulations

The recommended dosing regimen of 20 mg CAM2029 administered every 4±1 weeks was confirmed by the results from the phase 3 studies [HS-18-633] and [HS 19-647] and by PopPKPD modelling and simulation.

- In the phase 3 pivotal study [HS-18-633], the dose of 20 mg 4qwCAM2029 was used as a fixed dose in patients previously treated with other SLRs (octreotide LAR or lanreotide Autogel) and well controlled and the dose can be reduced to 10 mg only in case of adverse events or worsening of symptoms of acromegaly. No naïve patients were enrolled in this study. No patients have reduced the dose to 10 mg in this study. In [HS-18-633] study, after 24 weeks of treatment in the double-blind period, the mean (SD) IGF-1/ULN (mean of the values at Week 22 and Week 24) was 0.798 (0.261) in the CAM2029 treatment arm, whereas it had increased to 1.235 (0.700) in the placebo treatment arm.

- In the long-term open-label, phase 3 study [HS-19-647], "new patients" previously treated with other SRL treatments (octreotide LAR or lanreotide Autogel), well controlled or not well-controlled patients, roll-over patients from the phase 3 study [HS-18-633] with CAM2029 roll over patients and "pharmacologically washed-out patients" from the placebo group were enrolled in the study. They have been treated with CAM2029 20mg dose 4qw. In this study, only one "pharmacologically washed-out patient" reduced the dose to 10 mg due to a mild diarrhoea. As per the interim data, in the groups of patients who rolled over to [HS-19-647], the mean (SD) IGF-1/ULN at Week 24 was 0.756 (0.188) in CAM2029 roll-over patients and 1.341 (0.712) in placebo roll-over patients (placebo baseline, mean of Week 22 and Week 24). After 28 weeks of treatment in the [HS-19-647] trial, IGF-1/ULN (mean of the values at Week 50 and Week 52) remained below 1×ULN in the

"CAM2029 roll-over patients" (mean [SD]: 0.729 [0.181]), and decreased to <1×ULN (0.700 [0.168]) in the "placebo roll-over patients" as they were switched to CAM2029 and regained biochemical response.

In contrast to the patients in [HS-18-633], the "new patients" on stable treatment with SoC who started treatment with CAM2029 in [HS 19 647] on Day 1 were not required to be biochemically controlled. These patients could have elevated IGF 1 at screening, up to and including 2×ULN. The mean IGF 1/ULN in the new patients remained stable around 1.2 to 1.3×ULN throughout the trial.

Of note, in both phase 3 studies, the dose cannot be increased and can be reduced to 10 mg only in case of adverse events.

(For more details, see the results in the part related to the main studies).

Table 10 Overall efficacy results based on IGF-1 and GH over time in [HS-18-633] and [HS-19-647] (ITT analysis sets, interim data)

		N		SoC Baseline[a] (Day 1)	Week 22/24 or Week 24[b]	Week 50/52[c] (HS-19-647)
IGF-1/ULN						
HS-18-633	CAM2029	48	Mean (SD)	0.760 (0.150)	0.798 (0.261)	N/A
	Placebo	24	Mean (SD)	0.775 (0.179)	1.235 (0.700)	N/A
HS-19-647	CAM2029 RO	36	Mean (SD)	0.759 (0.144)	0.756 (0.188)	0.729 (0.181)
	Placebo RO	18	Mean (SD)	0.748 (0.183)	1.341 (0.712)[d]	0.700 (0.168)
	New Patients	81	Mean (SD)	1.263 (0.289)	1.285 (0.476)	1.233 (0.367)
IGF-1 ≤1×ULN						
HS-18-633	CAM2029	48	n (%)	44 (91.7)	34 (70.8)	N/A
	Placebo	24	n (%)	22 (91.7)	9 (37.5)	N/A
HS-19-647	CAM2029 RO	36	n/N_{all} (%)	33/36 (91.7)	31/36 (86.1)	25/28 (89.3)
	Placebo RO	18	n/N_{all} (%)	17/18 (94.4)	5/18 (27.8)[d]	15/15 (100)
	New Patients	81	n/N_{all} (%)	12/81 (14.8)	23/69 (33.3)	20/60 (33.3)
GH (µg/L)						
HS-18-633	CAM2029	48	Mean (SD)	0.6188 (0.5262)	0.8011 (0.6535)	N/A
	Placebo	24	Mean (SD)	0.6534 (0.6700)	1.2853 (0.9956)	N/A
HS-19-647	CAM2029 RO	36	Mean (SD)	0.6222 (0.5517)	0.6930 (0.6288)	0.7623 (1.2779)
	Placebo RO	18	Mean (SD)	0.5696 (0.4420)	1.4372 (1.0333)[d]	0.6226 (0.5349)
	New Patients	81	Mean (SD)	1.4766 (1.5928)	1.3587 (0.9620)	1.4485 (1.2643)
GH <1.0 µg/L						
HS-18-633	CAM2029	48	n (%)	40 (83.3)	28 (58.3)	N/A
	Placebo	24	n (%)	19 (79.2)	9 (37.5)	N/A
HS-19-647	CAM2029 RO	36	n/N_{all} (%)	30/35 (85.7)	27/36 (75.0)	21/26 (80.8)
	Placebo RO	18	n/N_{all} (%)	14/18 (77.8)	6/18 (33.3)[d]	11/14 (78.6)
	New Patients	81	n/N_{all} (%)	40/81 (49.4)	30/69 (43.5)	27/60 (45.0)
GH <2.5 µg/L						
HS-18-633	CAM2029	48	n (%)	46 (95.8)	41 (85.4)	N/A
	Placebo	24	n (%)	23 (95.8)	20 (83.3)	N/A
HS-19-647	CAM2029 RO	36	n/N_{all} (%)	35/35 (100)	35/36 (97.2)	25/26 (96.2)
	Placebo RO	18	n/N_{all} (%)	18/18 (100)	16/18 (88.9)[d]	14/14 (100)
	New Patients	81	n/N_{all} (%)	67/81 (82.7)	63/69 (91.3)	51/60 (85.0)

GH: growth hormone: IGF-1: insulin-like growth factor-1; ITT: intention-to-treat; N: number of patients in the analysis set; n: number of responders; N_{all}: number of patients with available value at certain visit; N/A: not applicable; RO: roll-over patients

a Mean of Week -2 and pre-dose Day 1 for IGF-1 and mean values on Day 1 (pre-dose) for GH (or mean values at screening in HS-19-647 if the Day 1 value was missing)

b Mean of Week 22 and Week 24 for IGF-1 in HS-18-633 and placebo roll-over patients in HS-19-647, values at Week 24 for IGF-1 in new patients and CAM2029 roll-over patients in HS-19-647, and mean values at Week 24 for GH for patients in both trials.

c Mean of Week 50 and Week 52 for IGF-1 and mean values at Week 52 for GH.

d Placebo baseline for placebo roll-over patients in HS-19-647.

HS-18-633: Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing also for other reasons.

HS-19-647: The table includes data from all patients with data at the specific visit. Data from retrieved dropouts were included.

- The popPK model provided simulations of comparisons between the dose of CAM2020 20 mg 4qw to octreotide IR 0.25 mg TID or octreotide 0.50 mg TID and octreotide LAR 20 mg/month and octreotide LAR 30 mg/month.

According to these simulations, Ctrough of CAM2029 20 mg 4qw is comparable to the Ctrough of octreotide 0.25 mg TID and octreotide LAR 30 mg/month which are doses recommended for the maintenance of treatment.

Table 11 Octreotide PK parameters at steady state after administration of 20 mg CAM2029 every 4 weeks (PopPK model), 0.25 mg and 0.50 mg octreotide IR t.i.d. (PopPK model), 20 and 30 mg octreotide LAR every 4 weeks (observed)

Product	Dose Regimen	Cumulative dose per 4 weeks	$C_{trough,ss}$[a] (ng/mL)	$C_{av,ss}$[b] (ng/mL)	$C_{max,ss}$[b] (ng/mL)
CAM2029[c]	20 mg q4w	20 mg	0.952 (0.48)	3.13 (22)	10.4 (27)
Octreotide IR[c]	0.25 mg t.i.d.	21 mg	0.723 (0.31)	3.22 (23)	8.99 (14)
Octreotide IR[c]	0.50 mg t.i.d.	42 mg	1.53 (0.74)	6.57 (25)	18.2 (15)
Octreotide LAR[d]	20 mg q4w	20 mg	0.32 (0.13)	0.51 (36)	0.75 (36)
Octreotide LAR[e]	30 mg q4w	30 mg	1.02 (0.33)	1.04 (32)	1.75 (30)

$C_{av,ss}$: average plasma concentration at steady state; $C_{max,ss}$: maximum plasma concentration at steady state; $C_{trough,ss}$: C_{trough} at steady state; CV: coefficient of variation; IR: immediate release; LAR: long-acting repeatable; PK: pharmacokinetic; PopPK: population PK; q4w: every 4 weeks; SD: standard deviation; t.i.d.: three times daily

a. Arithmetic mean (SD).
b. Geometric mean (geometric CV%).
c. Predicted PK parameters based on PopPK model after abdominal SC dosing in a typical subject weighing 75 kg.
d. Observed PK parameters in trial HS-07-291.
e. Observed PK parameters in trial HS-11-411.

The PopPKPD model described the link between octreotide concentration and inhibition of IGF-1, which was initiated rapidly but reached its maximum 3 to 7 days after dose.

The final PopPKPD model was used to simulate treatment with CAM2029 20 mg q4w either following pre-treatment with octreotide IR 0.25 mg t.i.d. of different durations (1 day or 1 week of dosing t.i.d.) or without pre-treatment. The simulations consistently showed that switching from octreotide IR to CAM2029 results in a robust IGF-1 mean response below ULN. Based on the PopPKPD model, no significant impact on plasma octreotide concentrations is expected if CAM2029 20 mg is administered 1 week before or 1 week after the recommended dosing schedule. Individual IGF-1 levels after the administration of CAM2029 q3w, q4w and q5w in a virtual population from [HS-18-633] and from [HS-19-647] indicate that similar IGF-1 concentrations over time can be expected at dosing intervals ranging from 3 to 5 weeks. This is reflected in section 4.2 of the SmPC: "Oczyesa may be administered up to 1 week before or 1 week after the scheduled 4-week dose."

For more details, please refer also tothe pharmacology part.

2.4.5.2. Main studies

[HS-18-633]

A Phase 3, randomized, double-blind, placebo-controlled, multi-centre trial to assess efficacy and safety of octreotide subcutaneous depot (CAM2029) in patients with acromegaly.

- **Methods**

This was a phase 3, randomized, double-blind, placebo-controlled, multi-centre trial that assessed the efficacy and safety of CAM2029 versus placebo in patients with acromegaly.

Eligible patients, who were biochemically controlled on treatment with long-acting SRLs (octreotide or lanreotide) and who had prior evidence of active acromegaly disease, were randomized to treatment with either CAM2029 or placebo in a 24-week double-blind treatment phase.

The trial was conducted at multiple trial sites in Europe and the US.

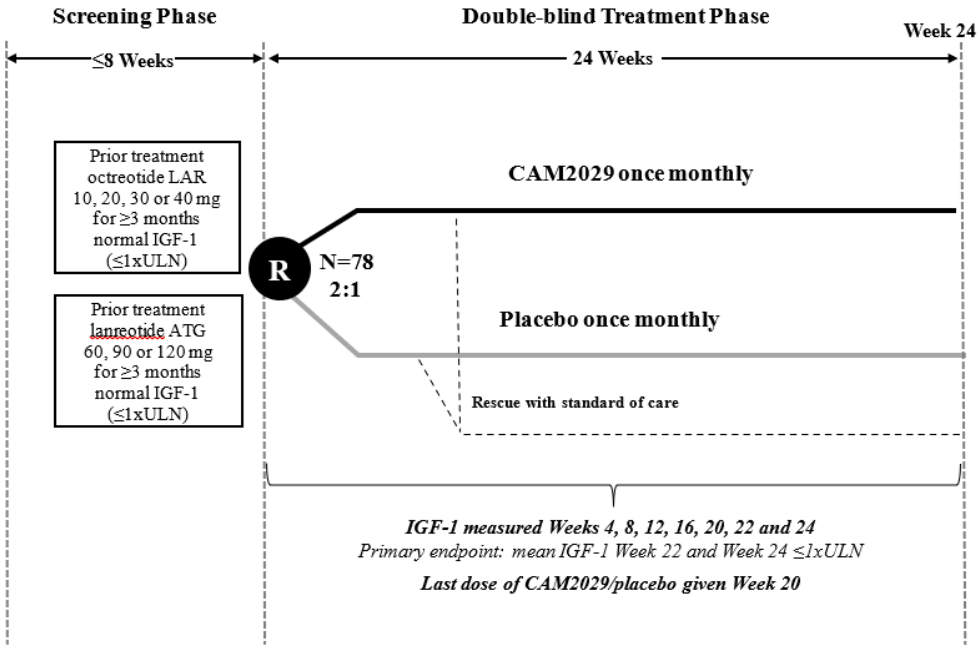
The trial consisted of 2 phases:

• Screening Phase – up to 8 weeks

• Double-blind Treatment Phase – 24 weeks

The total duration of participation for each patient was therefore up to 32 weeks.

Figure 2 Study schema



The double-blind design minimized the risk of potential bias. The double-blind period of 24 weeks in the current trial allowed comparison of efficacy and safety of CAM2029 versus placebo.

The double-blind period of 24 weeks also ensured that the effect size captured at the Week 24 was attributable to CAM2029 and not to a confounder such as inactive disease due to the cumulative effect of past therapies (e.g., pituitary surgery, drugs, or a combination of these).

Justification for use of placebo

In a slowly progressive disease like acromegaly, which is usually diagnosed 5 to 10 years after the first symptom onset (Reid TJ et al 2010), a 24-week treatment with placebo was considered a relatively short time frame with minimal or no negative impact on the overall disease history or patient disease outcome.

- **Study Participants**

The population consisted of patients with active acromegaly already well-controlled by stable doses of octreotide LAR (10, 20, 30 or 40 mg) or lanreotide ATG (60, 90 or 120 mg) for at least 3 months before screening, and having IGF-1 ≤1×ULN (average of the assessments at screening and Week -2).

Both patients with and without prior transsphenoidal surgery could be included in the trial, provided that at least 6 months had elapsed since surgery, in line with recent recommendations (Melmed S 2018). Patients who had received prior pituitary irradiation were, however, excluded.

Main inclusion criteria

1. Diagnosis of acromegaly by historical evidence of (persistent or recurrent) acromegaly as documented by:

    a. Pituitary adenoma on magnetic resonance imaging (MRI) or pathology report Computerized tomography was accepted if MRI could not be performed

    b. A lack of suppression of GH nadir to <1 µg/L after an oral glucose tolerance test with 75 g of glucose (not applicable for patients with diabetes) or a mean GH concentration of a 5-point profile within a 2-hour time period of >2.5 µg/L or IGF-1 levels >1×ULN (for patients who had undergone pituitary surgery, the measurement had to be performed at least 3 months after the surgery).

2. Treatment with a stable dose of octreotide LAR (10, 20, 30, or 40 mg) or lanreotide ATG (60, 90, or 120 mg) for at least 3 months as monotherapy prior to screening

3. IGF-1 levels ≤1×ULN (adjusted for age and sex; mean value of the first measurement at screening and the second measurement at 2 weeks before Day 1)

4. Adequate liver, pancreatic, renal, and bone marrow functions

5. Normal ECG

Main exclusion criteria:

1. GH ≥2.5 µg/L at screening (cycle)

2. Had received medical treatment for acromegaly with pasireotide (within 6 months prior to screening), pegvisomant (within 3 months prior to screening), dopamine agonists (within 3 months prior to screening) or other investigational agents (within 30 days or 5 half-lives prior to screening [whichever was longer])

3. Patients who usually took octreotide LAR or lanreotide ATG less frequently than every 4 weeks (e.g., every 6 weeks or 8 weeks)

4. Patients with compression of the optic chiasm causing any visual field defect for whom surgical intervention was indicated.

5. Patients who had undergone major surgery/surgical therapy for any cause within 1 month prior to screening.

6. Patients who had undergone pituitary surgery within 6 months prior to screening

7. Patients who had received prior pituitary irradiation

8. Patients with poorly controlled diabetes mellitus (hemoglobin A1c >8.0%)

- **Treatments**

The IMP (CAM2029 or placebo) was administered as an SC injection in the abdomen and/or thigh, regardless of who gave the injection (trial personnel, patient or partner).

The IMP was administered once monthly (every 28 days±7 days).

Duration of CAM2029/ placebo treatment: 24 weeks.

All administrations of the IMP were performed at the trial site. Self- or partner-administration of the IMP in the abdomen or thigh was allowed after appropriate training and under the supervision of trial personnel who had been adequately trained.

The patients randomized to CAM2029 received 20 mg CAM2029 on Day 1 regardless of their previous dose of octreotide LAR (10, 20, 30 or 40 mg) or lanreotide ATG (60, 90 or 120 mg).

Similarly, the patients randomized to placebo received 1.0 mL placebo (corresponding to 20 mg CAM2029) on Day 1, regardless of their previous dose of octreotide LAR or lanreotide ATG.

The first dose of 20 mg CAM2029/1 mL placebo was administered 4 weeks (±3 days) after the last dose of octreotide LAR or lanreotide ATG.

If needed, doses of IMP could be down-titrated from 20 mg to 10 mg once monthly for CAM2029 (or from 1.0 mL to 0.5 mL once monthly for placebo) for safety/tolerability reasons.

After down-titration, the patient could return to the previous dose or volume if the safety issue was resolved, and the benefit-risk evaluation allowed it. If the patient was on the lowest permitted dose (10 mg/0.5 mL) and a further dose reduction for safety reasons was required, the patient was discontinued from treatment but continued to be followed in the trial. All dose adjustments were discussed with the Medical Monitor prior to implementation.

Rescue therapies

Patients were discontinued from treatment with the blinded IMP and switched to rescue medication with SoC if they experienced worsening of signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3×ULN at 2 consecutive visits (including unscheduled visits).

If a patient experienced worsening of symptoms of acromegaly as judged by the Investigator, the Investigator contacted the Medical Monitor and obtained information regarding fulfillment of the IGF-1 criterion for switch to SoC.

Patients who were switched to rescue medication with SoC continued participation in the trial and followed the planned visits and assessments (except for the post-dose assessments at Week 20).

- **Objectives and endpoints**

1) Primary objectives

To assess the superiority of CAM2029 compared to placebo in biochemical response for IGF-1.

Primary endpoint

Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24 (average of the 2 measurements)

The primary analysis of the primary endpoint was performed by a common risk difference test using Mantel-Haenszel stratum weights stratified by prior treatment (octreotide LAR or lanreotide ATG). The ULN derived from the patient's sex and age at screening was used for the assessment of the individual patient's response.

The analysis was based on the ITT analysis set.

Definition of the primary estimand

Based on the expected intercurrent events, a composite variable strategy was chosen. The items that defined the primary estimand were:

1. Population of interest: Patients with acromegaly as defined by the inclusion/exclusion criteria in the trial.
2. Variable (or endpoint) of interest: Biochemical response defined as the mean of the IGF-1 values measured at Week 22 and Week 24 being ≤1×ULN (adjusted for age and sex). A patient was considered as non-responder if the mean of the IGF-1 values measured at Week 22 and Week 24 was >1×ULN (adjusted for age and sex).
3. Specification of how intercurrent events were reflected in the scientific question of interest:
    a. Discontinuation: Patients who discontinued treatment with CAM2029/placebo prior to Week 22 (regardless of IGF-1 values) were regarded as non-responders
    b. Rescue medication: Patients who received rescue medication were regarded as non-responders (as it resulted in treatment discontinuation)
    c. Dose decrease: Patients who had their dose decreased (due to safety or tolerability reasons) were regarded as non-responders.
4. Population level summary for the variable: Difference in the proportion of patients with biochemical response between CAM2029 and placebo arms, stratified by prior treatment.

The primary estimand was the difference in the proportion of patients who maintained the initial CAM2029/placebo dose and had biochemical response (average of the Week 22 and Week 24 values ≤1×ULN) between CAM2029 and placebo for patients with acromegaly. This estimand assumed that occurrence of intercurrent events other than those affecting dose received were considered irrelevant in defining the treatment effect of interest.

- The following statistical hypothesis with a one-sided alternative was tested at level 0.025 to address the primary efficacy objective:

H0: $\theta \leq 0$ versus H1: $\theta > 0$

where θ is the difference in the proportion of patients with biochemical response at Week 22 and Week 24 (average of the 2 measurements) between CAM2029 and placebo. The weighted common difference in proportions across strata (two-sided 95% CI) was estimated using the commonriskdiff (CL=MH) option of proc freq.

The main analysis of the primary endpoint was performed by the common proportion difference test using Mantel-Haenszel stratum weights, stratified by prior treatment (octreotide LAR or lanreotide ATG). The trial null hypothesis, H0, was rejected if the associated one-sided p-value was <0.025.

The odds ratio and its 95% CI (Mantel-Haenszel) were also given.

2) Secondary objectives and secondary endpoints

Table 12 Key secondary endpoints

Key Secondary Objectives	*Key Secondary Endpoints*[a]
• To assess the superiority of CAM2029 compared to placebo in biochemical response for IGF-1 irrespective of dose of investigational medicinal product	• Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24, including patients who have their dose decreased to 10 mg CAM2029 (or 0.5 mL placebo)
• To assess the superiority of CAM2029 compared to placebo in biochemical response for IGF-1 and GH	• Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24 and mean GH cycle levels <2.5 µg/L at Week 24

Table 13 Secondary endpoints

Secondary Objectives	*Secondary Endpoints*
• To assess time to loss of response of CAM2029 compared to placebo	• Time to IGF-1 levels >1×ULN • Time to IGF-1 levels ≥1.3×ULN
• To assess the efficacy of CAM2029 versus placebo for IGF-1 levels over time	• Change from baseline to Week 24 in IGF-1 levels
• To assess the efficacy of CAM2029 versus placebo for GH levels over time	• Change from baseline to Week 24 in GH levels • Proportion of patients with mean GH cycle levels <2.5 µg/L at Week 24 • Proportion of patients with mean GH cycle levels <1.0 µg/L at Week 24
• To assess use of rescue medication	• Proportion of patients who receive rescue medication with SoC
• To evaluate the effects of CAM2029 and placebo on tumor size	• Change in tumor size from screening to Week 24
• To assess the effects of CAM2029 and placebo on clinical signs and symptoms of acromegaly	• Severity scores of clinical signs and symptoms of acromegaly over time • Ring size over time
• To measure patients' satisfaction with CAM2029 and placebo	• TSQM scores over time using all 4 domains of TSQM (effectiveness, side effects, convenience, and satisfaction)

Objectives	Endpoints
	• Patient satisfaction scale scores at Week 24
• To measure the effects of CAM2029 and placebo on quality of life	• Change from baseline in AcroQoL and EQ-5D-5L scores
• To measure patients' satisfaction with self-administration of CAM2029 and placebo	• Change from PRE module to the POST module in SIAQ scores
• To assess supervised self- or partner-administration of CAM2029 and placebo	• Proportion of patients/partners declared competent by a healthcare professional to administer CAM2029 or placebo out of those trying
• To assess the safety and tolerability of CAM2029 and placebo	• Incidence of AEs and laboratory and ECG abnormalities • Changes in laboratory values, vital signs, ECG readings, and gallbladder imaging
• To assess the local tolerability of CAM2029 and placebo	• Incidence of injection site reactions (erythema and swelling) and level of injection site pain
• To assess the plasma concentrations of octreotide after administration of CAM2029 in patients with acromegaly	• Octreotide plasma concentrations over time

AcroQoL: Acromegaly Quality of Life Questionnaire; AE: adverse event; ECG: electrocardiogram; EQ-5D-5L: EuroQoL 5-dimension 5-level; GH: growth hormone; IGF-1: insulin-like growth factor-1; SIAQ: Self-Injection Assessment Questionnaire; SoC: standard of care; TSQM: Treatment Satisfaction Questionnaire for Medication; ULN: upper limit of normal

In protocol amendment 2, the GH cycle at Week 22 was replaced with a single GH (random) sample and the secondary endpoints based on GH cycle levels at Week 22 and Week 24 were subsequently revised to only include the Week 24 cycle. In protocol amendment 3 the patient satisfaction and quality of life endpoints were moved from the exploratory endpoints to the secondary endpoints. Furthermore, the endpoint of proportion of patients with mean GH cycle levels <2.5 µg/L at Week 24 was removed from the test order, and the endpoint of proportion of patients with mean GH cycle levels <1.0 µg/L was added. Please refer to Section 9.8.1 for details.

Estimands for the key secondary endpoints

1) Proportion of Patients with Biochemical Response Based on IGF-1 Levels, Irrespective of IMP Dose (Key Secondary Efficacy Endpoint I)

Definition of the Secondary Estimand

The secondary estimand for this endpoint was defined in a similar way as for the primary endpoint, including handling of intercurrent events.

The only difference was that patients who had their dose decreased (due to safety or tolerability reasons) were evaluated based on the mean of the IGF-1 values measured at Week 22 and Week 24 being ≤1×ULN (adjusted for age and sex). The secondary estimand was, thus, the difference in the proportion of patients who irrespective of IMP dose had biochemical response (average of the IGF-1 values at Week 22 and Week 24 being ≤1×ULN) between CAM2029 and placebo for patients with acromegaly. This estimand assumed that occurrence of intercurrent events other than those affecting dose received were considered irrelevant in defining the treatment effect of interest.

2) Proportion of Patients with Biochemical Response Based on IGF-1 Levels ≤1×ULN and GH Levels <2.5 µg/L (Key Secondary Efficacy Endpoint II)

The proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24 (average of the 2 measurements) and mean GH cycle levels <2.5 µg/L at Week 24 (i.e., mean of the 5 GH samples taken during the 2-hour period), was analyzed in a similar way as the primary efficacy endpoint (including sensitivity analyses). For the multiple imputation-based analyses of this endpoint, imputations were performed for IGF-1/ULN and GH values independently but using the relevant baseline information of both IGF-1/ULN and GH, as the two variables were assumed to be correlated.

The analysis was based on the ITT analysis set.

Definition of the Secondary Estimand

The secondary estimand for this endpoint was defined in a similar way as for the primary endpoint, including handling of intercurrent events.

The secondary estimand was the difference in the proportion of patients who maintained the initial CAM2029/placebo dose and had biochemical response (average of the IGF-1 values at Week 22 and Week 24 being ≤1×ULN and mean GH cycle levels <2.5 µg/L at Week 24) between CAM2029 and placebo for patients with acromegaly. This estimand assumed that occurrence of intercurrent events other than those affecting dose received were considered irrelevant in defining the treatment effect of interest.

- **Sample size**

For the sample size calculation, assumptions on absolute levels of biochemical response, defined as proportion of patients with mean IGF-1 levels at Week 22 and Week 24 ≤1×ULN by treatment arm were made. It should be noted that the treatment difference in biochemical response was based on the assumption of a very low response in the placebo treatment arm. It should also be noted that the actual endpoint calculated as the average of 2 measurements (Week 22 and Week 24) is not common in the literature. It was, thus, assumed that the proportion of patients with biochemical response for this endpoint would be very similar to a response based on a single measurement.

The proportion of responders at Week 22 and Week 24 (average of the 2 measurements) in the CAM2029 treatment arm was assumed to be 0.80.

For the group of patients receiving placebo, it was assumed that the proportion of responders would be 0.40 at Week 22 and Week 24 (average of the 2 measurements). It was also assumed that the missing data frequency would be low and have a limited impact on the sample size assumptions.

With 78 patients randomized in a 2:1 ratio, i.e., 52 patients in the CAM2029 treatment arm and 26 patients in the placebo treatment arm, the power was 90% to show a difference between CAM2029 and placebo, if the percentages of responders, as defined by the primary endpoint, were 80% for CAM2029 and 40% for placebo. The power calculation was based on the Chi-squared test (with a continuity correction).

The primary analysis of the primary endpoint was performed by a common risk difference test using Mantel-Haenszel stratum weights stratified by prior treatment (octreotide LAR or lanreotide ATG). Due to the stratification, the efficiency of the analysis could have increased (Kernan WN et al 1999), and the power of the applied model was assumed to be higher than 90%.

- **Randomisation and Blinding (masking)**

The eligibility criteria were randomized 2:1 to one of the treatment arms (CAM2029 or placebo), using an interactive randomization system (interactive web or voice response system). Before the trial was initiated, the log-in information and directions for the interactive randomization system were provided to each trial site.

Randomization was stratified based on previous treatment (octreotide LAR versus lanreotide ATG).

Blinding and Unblinding

The randomized treatment assignment to CAM2029 or placebo and all individual IGF-1 and GH results remained concealed to patients, Investigators, and the trial team until the trial was completed and a decision was made to unblind. IGF-1 results were monitored by an independent reader during the trial. PK and immunogenicity results were also concealed.

The blinding was supported by the placebo product being identical to the CAM2029 product regarding appearance, volume, and viscosity of the solutions.

The treatment allocation (CAM2029/placebo) of patients who were switched to SoC remained blinded until the trial was completed, and a decision was made to unblind.

No blinds were broken during the trial. There was one case of accidental unblinding of a patient.

- **Statistical methods**

Analysis Populations

The following analysis populations were defined:

- The intention to treat (ITT) analysis set, which included all patients randomised to a treatment arm (CAM2029: N=48; placebo: N=24)
- The modified intention to treat (mITT) analysis set, which included all patients from the ITT analysis set who did not have COVID-19 related missing IGF-1 measurements at Week 22 and Week 24 (CAM2029: N=48; placebo: N=24)
- The full analysis set (FAS), which included all randomised patients in the ITT analysis set who received at least one dose of the randomised IMP (CAM2029: N=47; placebo: N=24)
- The per protocol (PP) analysis set, which included all patients in the ITT analysis set who did not have any major protocol deviation that impacted the efficacy assessment (or who did not have an intercurrent event) (CAM2029: N=42; placebo: N=21)
- The safety analysis set, which included all patients who received at least one dose of the IMP (CAM2029: N=47; placebo: N=24)

All efficacy analyses were based on the ITT analysis set. The efficacy analysis of the primary endpoint was repeated for the FAS and the PP analysis set as supportive analyses. The supportive analysis based on the mITT analysis set was not performed since the mITT and ITT analysis sets were identical (no patients had missing samples due to COVID-19 at both Week 22 and Week 24). Safety analyses were based on the safety analysis set.

Primary Efficacy Analysis

The primary efficacy endpoint was the proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 (average of the two measurements). The ULN derived from the patient's sex and age at screening was used for the assessment of the individual patient's response.

The main analysis of the primary endpoint was performed by a common proportion difference test using Mantel-Haenszel stratum weights, stratified by prior treatment (octreotide LAR or lanreotide ATG). The trial null hypothesis of no effect of CAM2029 versus placebo was rejected if the associated one-sided p-value was <0.025.

• If one of the IGF-1 values at Week 22 or Week 24 was missing, the other value was used to define a responder/non-responder for the analysis. The variable (or endpoint) of interest was considered missing only if no IGF-1 value could be obtained from either of the Week 22 and Week 24 samples. If this was the case, 100 multiple imputations were made.

• If a patient had missing IGF-1 values at both Week 22 and Week 24 either due to being randomized and not treated or due to intercurrent events other than those affecting the dose received, then these were imputed under missing at random. Missing relative IGF-1 values (IGF-1/ULN adjusted for age and sex at screening) were imputed by multiple imputation using a monotone regression model from the treatment arm the patient was randomized to. The variables of treatment, stratum, and IGF-1 values from all available scheduled visits were included in the imputation model.

• All other patients with missing IGF-1 values at both Week 22 and Week 24, where it was either known or assumed that treatment was affected were regarded as non-responders.

Key Secondary Efficacy Analyses

The first key secondary efficacy endpoint was the proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 including patients who had their dose decreased to 10 mg CAM2029 (or 0.5 mL placebo). The second key secondary efficacy endpoint was the proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 and mean GH <2.5 µg/L at Week 24.

These endpoints were analysed in a similar way as the primary efficacy endpoint (including the sensitivity analyses), and a similar estimand definition was applied.

For the second key secondary efficacy endpoint, imputations were performed for IGF 1/ULN and GH values independently but using the relevant baseline information of both IGF-1/ULN and GH, as the two variables were assumed to be correlated.

All secondary efficacy analyses were performed on the ITT analysis set. For continuous endpoints, data from retrieved dropouts (i.e., following intercurrent events) collected up to and including the first pre-dose assessment after IMP discontinuation were used in the analyses, whereas all data collected after the first pre-dose assessment following IMP discontinuation, i.e., after the switch to SoC, were set to missing. In the statistical analyses of these endpoints, control-based multiple imputations were performed within a pattern-mixture model framework, assuming a 'missing not at random' mechanism.

Multiplicity Comparison

Three evaluations of biochemical control were performed. To control the overall significance level of 5%, a stepwise closed testing procedure with the following test order, from 1 to 3, was used:

1. Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 (average of the two measurements; primary efficacy endpoint)

2. Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24, including patients who had their dose reduced to 10 mg CAM2029 (or 0.5 mL placebo)

3. Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 and mean GH <2.5 µg/L at Week 24

This testing procedure allowed comparison to be eligible for superiority testing only if all previous comparisons, if any, had established superiority at the one-sided significance level of $p<0.025$. As this was a hierarchical closed testing procedure, no adjustment of the type I error rates of hypothesis tests was needed.

Other Secondary Efficacy Analyses

For continuous endpoints, data from retrieved dropouts (i.e., following intercurrent events) collected up to and including the first pre-dose assessment after discontinuation of the IMP were used in the analyses, whereas all data collected after the first pre-dose assessment following IMP discontinuation, i.e., after the switch to SoC, were set to missing. In the statistical analyses of these endpoints, control-based multiple imputations were performed within a pattern-mixture model framework, assuming a missing not at random mechanism.

Time to loss of response (i.e., time to IGF-1 >1×ULN) was analysed using a stratified log rank test. In addition, a Cox proportional hazards model was used. For the distribution of times to loss of response, a Kaplan Meier graph was prepared and the median time to loss of response and its 95% confidence interval (CI) was estimated.

Changes from baseline to Week 24 in IGF-1/ULN and GH were evaluated by a control-based imputation and estimated using an analysis of covariance (ANCOVA) model, including adjustment for baseline and strata. The proportions of patients with mean GH <2.5 µg/L and <1.0 µg/L at Week 24 were analysed in a similar way as the primary efficacy endpoint. Acromegaly Index of Severity (AIS) scores were calculated based on the acromegaly signs and symptoms. Changes from baseline in tumour size and domain scores for TSQM and AcroQoL were evaluated by a control-based imputation and estimated using an ANCOVA model, including adjustment for baseline and strata. Results from the SIAQ were summarised and changes in domain scores were presented.

Sensitivity Analyses

Six sensitivity and 6 supportive analyses were pre-defined. The sensitivity analyses were performed on the primary and key secondary efficacy endpoints, whereas the supportive analyses only were performed on the primary efficacy endpoint.

Several imputation methods were used to assess the impact of missing data on the primary endpoint by imputing values for missing IGF-1 data.

Analyses were then performed on each of the 100 datasets and results from the common risk difference test using Mantel-Haenszel stratum weights, stratified by previous treatment. The results from the 100 intermediate analyses were combined using Rubin's rule (Rubin DB 1987).

Supportive Analyses

As supportive analyses, the responder rates by treatment arm at Week 22 and Week 24 and the difference in responder rates between the two treatment arms were also estimated together with their respective 2-sided 95% CI.

Safety analyses

All safety analyses were performed on the safety analysis set.

Pharmacokinetic Endpoint Methodology

The plasma concentrations of octreotide were summarized using descriptive statistics (n, n [below the LLOQ], arithmetic mean, SD, coefficient of variation, geometric mean, percentage of geometric coefficient of variation, minimum, median, and maximum) over time. All concentrations below the LLOQ and any missing data were reported as such in the concentration data listings. Concentrations below the LLOQ were treated as zero in summary statistics of arithmetic mean and as LLOQ/2 in the calculations of geometric mean.

Individual and summarized octreotide concentration-time profiles were displayed graphically on linear and logarithmic scale. The FAS was used for these presentations.

Other Endpoint Methodology

Exposure-response Analysis: the relationship between octreotide exposure and QTcF change from baseline was explored using correlation plots presenting QTcF intervals versus octreotide concentrations and QTcF change from baseline versus octreotide concentrations.

Individual and summarized IGF-1 values (absolute values and IGF-1/ULN on the same plot) and GH concentrations versus octreotide concentration profiles were displayed graphically.Subgroup analyses were performed, but they were only exploratory and no statistical conclusion were drawn based on them regarding any of the primary or secondary variables.

The statistical approaches were endorsed.

Results

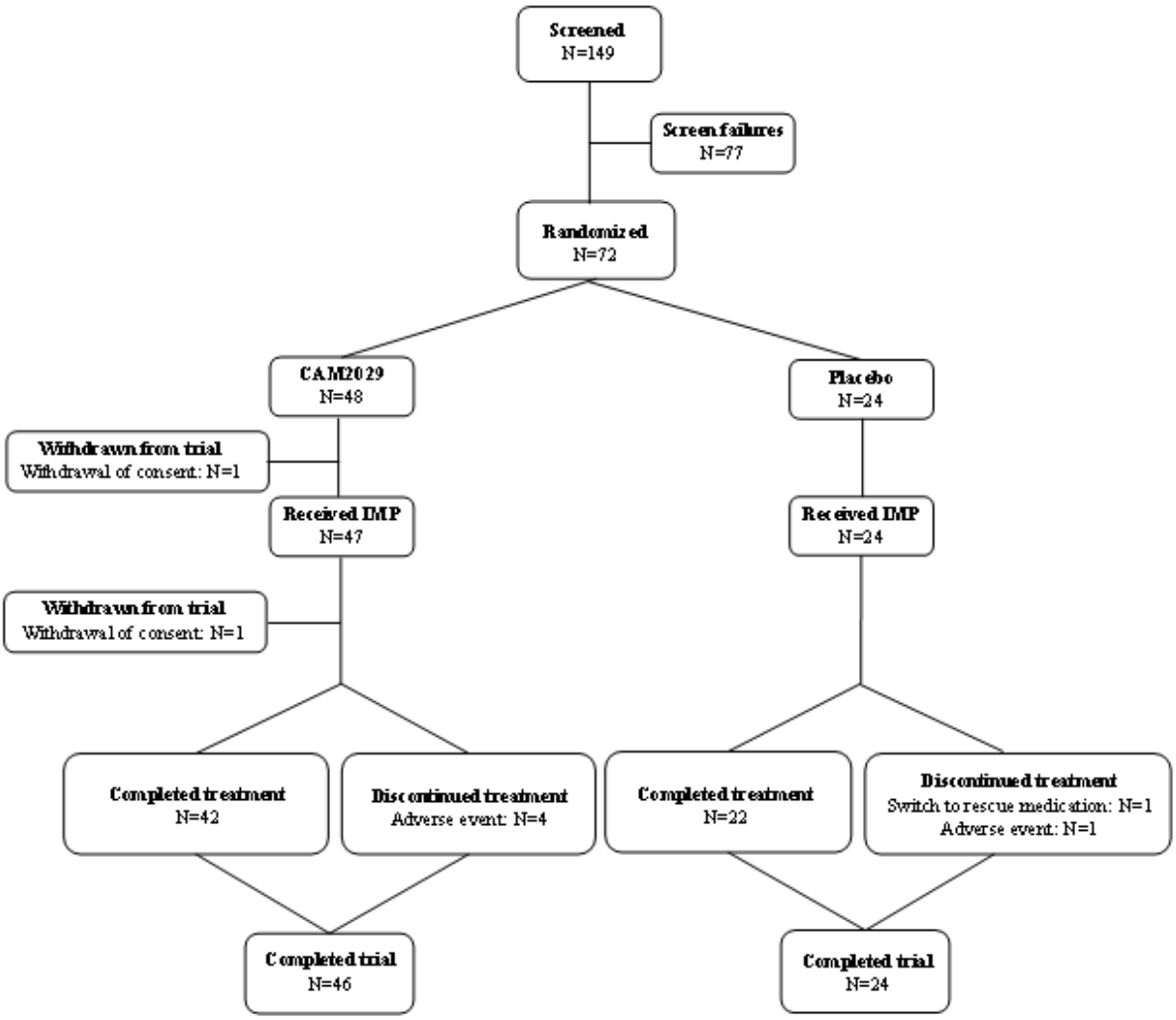
- **Participant flow**

72 patients were enrolled and randomised to treatment with CAM2029 (48 patients) or placebo (24 patients).

46 of the 48 patients in the CAM2029 treatment arm (95.8%) completed the trial [HS-18-633].
One patient in the CAM2029 treatment arm withdrew consent to participate in the trial before receiving the first dose.
Another patient withdrew consent after receiving the first dose of CAM2029.
All 24 patients in the placebo treatment arm completed the trial.
47 patients were exposed to at least one dose of CAM2029, and 24 patients were exposed to at least one dose of placebo.
42 patients (42/47= 89.4%) in the CAM2029 treatment arm and 22 patients (91.7%) in the placebo treatment arm completed treatment with IMP and were exposed to CAM2029 or placebo for ≥24 weeks [HS-18-633].
Four patients receiving CAM2029 and 1 patient receiving placebo discontinued treatment with IMP due to adverse events (AEs). An additional patient in the placebo treatment arm discontinued treatment with placebo due to worsening of clinical signs and symptoms of acromegaly in combination with increased IGF-1 levels and was switched to rescue medication with SoC [HS-18-633]. All 6 patients who discontinued treatment with IMP remained in the trial on SoC and performed all planned visits.
The overall mean (SD) duration of exposure was 26.43 (4.09) weeks, ranging from 7.6 to 31.4 weeks [HS-18-633]. The mean duration of exposure was similar in the two treatment arms.
No patient had their dose reduced during the trial.

Figure 3 Patient disposition in HS-18-633

IMP: investigational medicinal product



- **Recruitment**

The overall mean (SD) duration of exposure was 26.43 (4.09) weeks, ranging from 7.6 to 31.4 weeks [HS-18-633]. The mean duration of exposure was similar in the two treatment arms.

Trial Initiation Date (first patient first visit): 19-Aug-2019

Trial Completion Date (last patient last visit): 02-May-2023

Screening Phase

The Screening Phase had a duration of ≤8 weeks. During this period, the patients visited the site at least 2 times to perform the screening procedures. The visit at Week -2 (i.e., 2 weeks±3 days before the first dose of CAM2029/placebo on Day 1) was mandatory for establishing the baseline value of IGF-1 (average of the measurement at Week -2 and pre-dose on Day 1).

Double-blind Treatment Phase

Patients who met all the inclusion criteria and none of the exclusion criteria were enrolled in the trial.

Eligible patients were randomized in a 2:1 ratio to receive one of the following treatments:

• CAM2029 once monthly for 24 weeks or

• Placebo once monthly for 24 weeks

At Week 24, or 4 weeks after the last dose in case of premature withdrawal from the trial, the patients came to the trial site for an End of Trial (EOT) visit. Patients who completed the trial were offered to continue treatment with CAM2029 as roll-over patients in the long-term safety and efficacy trial [HS-19-647]. Alternatively, patients were switched back to their previous treatment for acromegaly.

- **Conduct of the study**

The initial trial protocol version 1.0 was issued on 08-Apr-2019 and was the version that was submitted to the US FDA. The protocol was subsequently updated to version 2 (dated 20-May-2019) following comments from the FDA. This was the protocol version that was submitted to and approved by subsequent authorities. Protocol version 2 was in effect when the first patient's first visit in the trial took place.

After the first patient had been recruited, there were 3 global amendments, and 3 country-specific amendments issued to the protocol.

- **Baseline data**

Baseline Demography

The patients in the trial were aged 20 to 82 years [HS-18-633]. The treatment arms were overall well balanced regarding the demographic characteristics; however, the mean age was slightly higher in the CAM2029 treatment arm (57.0 years) than in the placebo treatment arm (52.0 years). 19 patients (26.4%) were 65 years or older (CAM2029: 29.2%; placebo: 20.8%) [HS-18-633].
Overall, 44.4% of the patients were men (CAM2029: 41.7%; placebo: 50.0%) and 95.8% of the patients were categorised as 'White' (CAM2029: 93.8%; placebo: 100%) [HS-18-633].

64 patients (88.9%) were enrolled in countries in Europe, and 8 patients (11.1%) were enrolled in the US.

Table 14 Demographics (continuous data) by treatment arm and previous treatment (ITT analysis set)

		CAM2029			Placebo			Overall
Parameter [unit]	Statistics	Octreotide LAR (N=25)	Lanreotide ATG (N=23)	Overall (N=48)	Octreotide LAR (N=14)	Lanreotide ATG (N=10)	Overall (N=24)	(N=72)
Age [years]	n	25	23	48	14	10	24	72
	Mean (SD)	55.6 (10.5)	58.6 (12.0)	57.0 (11.2)	51.8 (14.5)	52.2 (16.7)	52.0 (15.1)	55.3 (12.8)
	Min - Max	29 - 70	39 - 79	29 - 79	20 - 82	31 - 74	20 - 82	20 - 82
Weight [kg]	n	25	22	47	14	10	24	71
	Mean (SD)	84.5 (17.2)	85.9 (18.4)	85.1 (17.6)	86.6 (14.8)	87.9 (21.1)	87.1 (17.3)	85.8 (17.4)
	Min - Max	59 - 128	60 - 140	59 - 140	63 - 111	55 - 127	55 - 127	55 - 140
Height [cm]	n	25	22	47	14	10	24	71
	Mean (SD)	168.2 (11.1)	168.4 (11.1)	168.3 (11.0)	172.1 (7.4)	170.6 (9.6)	171.5 (8.2)	169.4 (10.2)
	Min - Max	146 - 197	145 - 186	145 - 197	162 - 182	158 - 190	158 - 190	145 - 197
BMI [kg/m^2]	n	25	22	47	14	10	24	71
	Mean (SD)	29.9 (5.4)	30.3 (5.8)	30.1 (5.6)	29.4 (5.6)	30.1 (6.4)	29.7 (5.8)	29.9 (5.6)
	Min - Max	22 - 43	22 - 51	22 - 51	23 - 39	22 - 40	22 - 40	22 - 51

BMI: body mass index; ITT: intention-to-treat; n: number of patients within category; N: number of patients in the analysis set; Max: maximum; Min: minimum; SD: standard deviation
Source: Table 14.1.5.2

Table 15 Demographics (categorical data) by treatment arm and previous treatment (ITT analysis set)

		CAM2029			Placebo			Overall
Parameter [unit]	Statistics	Octreotide LAR (N=25) n (%)	Lanreotide ATG (N=23) n (%)	Overall (N=48) n (%)	Octreotide LAR (N=14) n (%)	Lanreotide ATG (N=10) n (%)	Overall (N=24) n (%)	(N=72) n (%)
Age [years]	18-64	19 (76.0)	15 (65.2)	34 (70.8)	13 (92.9)	6 (60.0)	19 (79.2)	53 (73.6)
	>= 65	6 (24.0)	8 (34.8)	14 (29.2)	1 (7.1)	4 (40.0)	5 (20.8)	19 (26.4)
Sex	Female	17 (68.0)	11 (47.8)	28 (58.3)	8 (57.1)	4 (40.0)	12 (50.0)	40 (55.6)
	Male	8 (32.0)	12 (52.2)	20 (41.7)	6 (42.9)	6 (60.0)	12 (50.0)	32 (44.4)
Ethnicity	Not Hispanic or Latino	25 (100)	22 (95.7)	47 (97.9)	14 (100)	9 (90.0)	23 (95.8)	70 (97.2)
	Hispanic or Latino	0	1 (4.3)	1 (2.1)	0	0	0	1 (1.4)
	Unknown	0	0	0	0	1 (10.0)	1 (4.2)	1 (1.4)
Race	White	24 (96.0)	21 (91.3)	45 (93.8)	14 (100)	10 (100)	24 (100)	69 (95.8)
	Asian	1 (4.0)	1 (4.3)	2 (4.2)	0	0	0	2 (2.8)
	Black or African American	0	1 (4.3)	1 (2.1)	0	0	0	1 (1.4)
Country	Russia	11 (44.0)	3 (13.0)	14 (29.2)	6 (42.9)	1 (10.0)	7 (29.2)	21 (29.2)
	Turkey	5 (20.0)	6 (26.1)	11 (22.9)	1 (7.1)	3 (30.0)	4 (16.7)	15 (20.8)
	Italy	1 (4.0)	4 (17.4)	5 (10.4)	3 (21.4)	1 (10.0)	4 (16.7)	9 (12.5)
	United States	3 (12.0)	1 (4.3)	4 (8.3)	2 (14.3)	2 (20.0)	4 (16.7)	8 (11.1)
	Spain	1 (4.0)	3 (13.0)	4 (8.3)	2 (14.3)	1 (10.0)	3 (12.5)	7 (9.7)
	Germany	1 (4.0)	3 (13.0)	4 (8.3)	0	2 (20.0)	2 (8.3)	6 (8.3)
	United Kingdom	1 (4.0)	3 (13.0)	4 (8.3)	0	0	0	4 (5.6)
	Hungary	1 (4.0)	0	1 (2.1)	0	0	0	1 (1.4)
	Poland	1 (4.0)	0	1 (2.1)	0	0	0	1 (1.4)

ITT: intention-to-treat; n: number of patients within category; N: number of patients in the analysis set; %: percentage of patients
Country is country of participation
Source: Table 14.1.5.5

Baseline Disease Characteristics

The treatment arms were overall well balanced regarding the disease history; however, the mean time since diagnosis of acromegaly was 11.5 (8.3) years and was longer in patients receiving placebo (13.0 years) than in patients receiving CAM2029 (10.8 years). Overall, 47.2% of the patients (CAM2029: 47.9%; placebo: 45.2%) were diagnosed with acromegaly less than 10 years before screening,

63 of the 72 patients (87.5% in each treatment arm) had undergone previous pituitary surgery.

Overall, diagnosis was documented by elevated IGF-1 levels in 67 patients (93.1%), by lack of suppression of GH nadir to <1 µg/L after an oral glucose tolerance test in 22 patients (30.6%), and by mean GH concentration of >2.5 µg/L in 10 patients (13.9%).

The mean (SD) IGF-1/ULN value at diagnosis was 2.948 (1.245) and the mean (SD) tumour size was 16.5 (8.2) mm.

All 72 randomized patients had a pituitary tumour at diagnosis. The presence of a pituitary tumour was confirmed by MRI/CT in 69 patients (95.8%) and the histopathologic confirmation of a GH-staining adenoma was recorded in 14 patients (19.4%) who had prior pituitary surgery.

Table 16 History of acromegaly by treatment arm and previous treatment (ITT analysis set)

		CAM2029			Placebo			Overall
Parameter [unit]	**Statistics**	**Octreotide LAR (N=25)**	**Lanreotide ATG (N=23)**	**Overall (N=48)**	**Octreotide LAR (N=14)**	**Lanreotide ATG (N=10)**	**Overall (N=24)**	**(N=72)**
Diagnosis Documented by	Confirmed pituitary tumor, n (%)	25 (100)	23 (100)	48 (100)	14 (100)	10 (100)	24 (100)	72 (100)
	Elevated IGF-1, n (%)	22 (88.0)	22 (95.7)	44 (91.7)	13 (92.9)	10 (100)	23 (95.8)	67 (93.1)
	GH nadir after GTT, n (%)	6 (24.0)	9 (39.1)	15 (31.3)	5 (35.7)	2 (20.0)	7 (29.2)	22 (30.6)
	Mean GH concentration, n (%)	6 (24.0)	2 (8.7)	8 (16.7)	1 (7.1)	1 (10.0)	2 (8.3)	10 (13.9)
Time Since Diagnosis [years]	n	25	22	47	14	10	24	71
	Mean (SD)	10.1 (6.0)	11.6 (7.7)	10.8 (6.8)	14.3 (11.5)	11.1 (9.6)	13.0 (10.7)	11.5 (8.3)
	Min - Max	2 - 26	2 - 32	2 - 32	2 - 37	3 - 36	2 - 37	2 - 37
Time Since Diagnosis	<10 years, n (%)	12 (48.0)	11 (47.8)	23 (47.9)	6 (42.9)	5 (50.0)	11 (45.8)	34 (47.2)
	≥10 to <20 years, n (%)	11 (44.0)	8 (34.8)	19 (39.6)	5 (35.7)	4 (40.0)	9 (37.5)	28 (38.9)
	≥20 years, n (%)	2 (8.0)	3 (13.0)	5 (10.4)	3 (21.4)	1 (10.0)	4 (16.7)	9 (12.5)
IGF-1/ULN Value at Diagnosis	n	21	22	43	12	10	22	65
	Mean (SD)	2.961 (0.996)	3.111 (1.622)	3.038 (1.339)	2.904 (1.178)	2.616 (0.889)	2.773 (1.043)	2.948 (1.245)
	Min - Max	1.47 - 5.04	1.04 -7.06	1.04 -7.06	1.08 - 4.42	1.32 - 4.01	1.08 - 4.42	1.04 - 7.06
Tumor Size at Diagnosis [mm]	n	14	15	29	6	4	10	39
	Mean (SD)	17.4 (8.9)	13.3 (5.8)	15.2 (7.6)	20.8 (10.5)	19.0 (8.4)	20.1 (9.3)	16.5 (8.2)
	Min - Max	5 - 34	3 - 25	3 - 34	13 - 40	10 - 30	10 - 40	3 - 40
Method of Pituitary Tumor Confirmation	MRI/CT, n (%)	24 (96.0)	22 (95.7)	46 (95.8)	14 (100)	9 (90.0)	23 (95.8)	69 (95.8)
	Surgical pathology, n (%)	5 (20.0)	3 (13.0)	8 (16.7)	3 (21.4)	3 (30.0)	6 (25.0)	14 (19.4)
	Other, n (%)	1 (4.0)	0	1 (2.1)	0	0	0	1 (1.4)
Pituitary Surgery	Yes, n (%)	23 (92.0)	19 (82.6)	42 (87.5)	12 (85.7)	9 (90.0)	21 (87.5)	63 (87.5)
	No, n (%)	2 (8.0)	4 (17.4)	6 (12.5)	2 (14.3)	1 (10.0)	3 (12.5)	9 (12.5)

		CAM2029			Placebo			Overall
Parameter [unit]	**Statistics**	**Octreotide LAR (N=25)**	**Lanreotide ATG (N=23)**	**Overall (N=48)**	**Octreotide LAR (N=14)**	**Lanreotide ATG (N=10)**	**Overall (N=24)**	**(N=72)**
IGF-1/ULN Value after Surgery	N	21	19	40	12	9	21	61
	Mean (SD)	1.924 (0.883)	1.607 (0.568)	1.773 (0.758)	1.651 (0.694)	1.902 (0.779)	1.758 (0.724)	1.768 (0.740)
	Min - Max	1.09 - 4.30	1.01 - 2.90	1.01 - 4.30	1.08 - 3.45	1.28 - 3.47	1.08 - 3.47	1.01 - 4.30
GH Nadir after GTT [µg/L]	n	6	9	15	5	2	7	22
	Mean (SD)	12.05 (11.46)	8.16 (7.98)	9.72 (9.34)	11.53 (11.28)	1.67 (0.18)	8.71 (10.39)	9.40 (9.44)
	Min - Max	2.0 - 33.5	1.4 - 22.4	1.4 - 33.5	2.7 - 30.0	1.5 - 1.8	1.5 - 30.0	1.4 - 33.5
Mean GH Concentration [µg/L]	n	6	2	8	1	1	2	10
	Mean (SD)	30.60 (28.14)	3.12 (0.03)	23.73 (26.97)	19.20 (NC)	2.52 (NC)	10.86 (11.79)	21.15 (24.71)
	Min - Max	3.1 - 84.1	3.1 - 3.1	3.1 - 84.1	19.2 - 19.2	2.5 - 2.5	2.5 - 19.2	2.5 - 84.1

CT: computerized tomography; GH: growth hormone; GTT: glucose tolerance test; IGF-1: insulin-like growth factor-1; Max: maximum; Min: minimum; MRI: magnetic resonance imaging; n: number of patients within category; N: number of patients in the analysis set; NC: not calculable; ULN: upper limit of normal; %: percentage of patients
If ULN value was not defined for IGF-1, then the IGF-1 value was excluded from the analysis.
Time since diagnosis was calculated as: (date of diagnosis – start date of the first treatment)/365.25, therefore if a patient was not treated in the trial, no time since diagnosis was calculated.
Source: Table 14.1.6.2

Medical History and Concurrent Illnesses

69 patients (95.8%) in the ITT analysis set had at least one medical history recorded (CAM2029: 97.9%; placebo: 95.8%).

Table 17 Reported medical history (cut-off ≥10% overall at PT level) by SOC, PT, treatment arm and previous treatment (ITT analysis set)

	CAM2029			Placebo			Overall
System Organ Class Preferred Term	Octreotide LAR (N=25) n (%)	Lanreotide ATG (N=23) n (%)	Overall (N=48) n (%)	Octreotide LAR (N=14) n (%)	Lanreotide ATG (N=10) n (%)	Overall (N=24) n (%)	(N=72) n (%)
Any Medical History	24 (96.0)	23 (100)	47 (97.9)	12 (85.7)	10 (100)	22 (91.7)	69 (95.8)
Metabolism and nutrition disorders							
Obesity	8 (32.0)	6 (26.1)	14 (29.2)	4 (28.6)	1 (10.0)	5 (20.8)	19 (26.4)
Type 2 diabetes mellitus	4 (16.0)	6 (26.1)	10 (20.8)	2 (14.3)	3 (30.0)	5 (20.8)	15 (20.8)
Vitamin D deficiency	1 (4.0)	6 (26.1)	7 (14.6)	1 (7.1)	4 (40.0)	5 (20.8)	12 (16.7)
Dyslipidaemia	5 (20.0)	4 (17.4)	9 (18.8)	2 (14.3)	0	2 (8.3)	11 (15.3)
Glucose tolerance impaired	4 (16.0)	5 (21.7)	9 (18.8)	1 (7.1)	0	1 (4.2)	10 (13.9)
Diabetes mellitus	5 (20.0)	2 (8.7)	7 (14.6)	2 (14.3)	0	2 (8.3)	9 (12.5)
Vascular disorders							
Hypertension	16 (64.0)	12 (52.2)	28 (58.3)	2 (14.3)	5 (50.0)	7 (29.2)	35 (48.6)
Endocrine disorders							
Goitre	5 (20.0)	8 (34.8)	13 (27.1)	5 (35.7)	2 (20.0)	7 (29.2)	20 (27.8)
Hypothyroidism	2 (8.0)	6 (26.1)	8 (16.7)	4 (28.6)	1 (10.0)	5 (20.8)	13 (18.1)
Hepatobiliary disorders							
Cholelithiasis	6 (24.0)	2 (8.7)	8 (16.7)	6 (42.9)	1 (10.0)	7 (29.2)	15 (20.8)
Surgical and medical procedures							
Cholecystectomy	5 (20.0)	5 (21.7)	10 (20.8)	1 (7.1)	0	1 (4.2)	11 (15.3)
Gastrointestinal disorders							
Chronic gastritis	4 (16.0)	3 (13.0)	7 (14.6)	1 (7.1)	1 (10.0)	2 (8.3)	9 (12.5)
Haemorrhoids	4 (16.0)	3 (13.0)	7 (14.6)	1 (7.1)	1 (10.0)	2 (8.3)	9 (12.5)
Musculoskeletal and connective tissue disorders							
Osteoarthritis	4 (16.0)	5 (21.7)	9 (18.8)	0	1 (10.0)	1 (4.2)	10 (13.9)
Osteoporosis	1 (4.0)	5 (21.7)	6 (12.5)	1 (7.1)	1 (10.0)	2 (8.3)	8 (11.1)
Eye disorders							
Cataract	2 (8.0)	4 (17.4)	6 (12.5)	1 (7.1)	1 (10.0)	2 (8.3)	8 (11.1)
Renal and urinary disorders							
Renal cyst	3 (12.0)	1 (4.3)	4 (8.3)	2 (14.3)	2 (20.0)	4 (16.7)	8 (11.1)

ITT: intention-to-treat; n: number of patients within category; N: number of patients in the analysis set; PT: preferred term; SOC: system organ class; %: percentage of patients
Source: Table 14.1.7.2

Prior Medications/Treatments for Acromegaly

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

39/72 (54.2%) patients were receiving octreotide LAR at screening and 33/72 (45.8%) patients were receiving lanreotide ATG.
Most patients (76.4%) were on mid-high doses of octreotide LAR (20, 30, or 40 mg) or lanreotide ATG (90 or 120 mg) when they entered the trial [HS 18-633].
The other patients (23.6%) were on low doses of octreotide LAR (10 mg) or lanreotide ATG (60 mg).

- **Numbers analysed**

Table 18 Patient disposition by treatment arm and previous treatment (ITT analysis set)

	CAM2029			Placebo			Overall
Category/Analysis Set	Octreotide LAR (N=25) n (%)	Lanreotide ATG (N=23) n (%)	Overall (N=48) n (%)	Octreotide LAR (N=14) n (%)	Lanreotide ATG (N=10) n (%)	Overall (N=24) n (%)	(N=72) n (%)
Safety analysis set	25 (100)	22 (95.7)	47 (97.9)	14 (100)	10 (100)	24 (100)	71 (98.6)
FAS	25 (100)	22 (95.7)	47 (97.9)	14 (100)	10 (100)	24 (100)	71 (98.6)
ITT analysis set	25 (100)	23 (100)	48 (100)	14 (100)	10 (100)	24 (100)	72 (100)
mITT analysis set	25 (100)	23 (100)	48 (100)	14 (100)	10 (100)	24 (100)	72 (100)
PP analysis set	22 (88.0)	20 (87.0)	42 (87.5)	12 (85.7)	9 (90.0)	21 (87.5)	63 (87.5)

FAS: full analysis set: ITT: intention-to-treat; mITT: modified intention-to-treat; n: number of patients within category;
N: number of patients in the analysis set; PP: per protocol; % percentage of patients

- **Outcomes and estimation**

Primary and Key Secondary Efficacy Endpoints

The primary efficacy endpoint and both key secondary efficacy endpoints were met, with one-sided p-values below the pre-defined significance level of 0.025.

Table 19 Overview of the closed testing procedure in HS-18-633 (ITT analysis set)

Endpoint	Upper-tailed p-value for Difference in Proportions	Outcome
Primary efficacy endpoint – Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24	0.0018	Success
First key secondary efficacy endpoint – Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24, including patients with IMP dose reduction	0.0018	Success
Second key secondary efficacy endpoint – Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 and mean GH cycle <2.5 µg/L at Week 24	0.0035	Success

GH: growth hormone; IGF 1: insulin-like growth factor-1; IMP: investigational medicinal product; ITT: intention-to-treat; ULN: upper limit of normal
In the closed testing procedure, a comparison was eligible for superiority testing only if all previous comparisons, if any, had established superiority at the one-sided significance level of p<0.025

Primary Efficacy Endpoint – "Proportion of Patients with Mean IGF-1 ≤1×ULN at Week 22 and Week 24"

The proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 (average of the two measurements) was statistically significantly higher in the CAM2029 treatment arm (72.2%) than in the placebo treatment arm (37.5%).

The difference in proportions (CAM2029-placebo) was 34.6% (95% CI: 11.3%, 57.9%), p=0.0018, and the odds ratio (CAM2029/placebo) was 4.31 (95% CI: 1.52, 12.27).

Of note, in the Table 20, n= mean number of responders (average of the two measurements at week 22 and week 24).

Table 20 Primary efficacy endpoint analysis – proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 by treatment arm in HS-18-633 (ITT analysis set)

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

ATG: autogel; CI: confidence interval; EOT: end of trial; IGF-1: insulin-like growth factor-1; ITT: intention-to-treat; LAR: long-acting repeatable; n: mean number of responders; N: number of patients in the analysis; ULN: upper limit of normal

a Mantel-Haenszel-type common difference in proportions across strata, stratified by prior treatment (octreotide LAR or lanreotide ATG)

b Upper-tailed p-value of the common risk difference test using Mantel-Haenszel stratum weights (octreotide LAR or lanreotide ATG). The significance level was 0.025

c Mantel-Haenszel-type common odds ratio across strata, stratified by prior treatment (octreotide LAR or lanreotide ATG)

Patients with intercurrent events were regarded as non-responders independently of their (missing or non-missing) Week 22 and Week 24/EOT data.

Overall proportions of responders were not weighted.

Seven patients (CAM2029: 5; placebo: 2) had intercurrent events during the trial. These patients were set to non-responders in the primary and key secondary efficacy analyses.

Very few patients had missing data for IGF-1 and GH during the trial, including at the Week 22 and Week 24 visits when the primary and key secondary efficacy endpoints were assessed.

At Week 22, 4 patients (8.3%) in the CAM2029 treatment arm and 1 patient (4.2%) in the placebo treatment arm had missing data for IGF-1 and GH. At Week 24, 2 patients (4.2%) in the CAM2029 treatment arm (the 2 withdrawn patients) and no patients in the placebo treatment arm had missing data for IGF-1 and GH.

34 patients in the CAM2029 treatment arm and 9 patients in the placebo treatment arm were classified as responders in the main analysis of the primary efficacy endpoint based on their IGF-1 values, and 8 patients in the CAM2029 treatment arm and 13 patients in the placebo treatment arm were classified as non-responders.

Five patients in the CAM2029 treatment arm and 2 patients in the placebo treatment arm were classified as non-responders due to intercurrent events. Data were imputed for 1 patient in the CAM2029 treatment arm since the patient was randomized but not treated.

Table 21 Responder status for the main analysis of the primary efficacy endpoint by treatment arm, and previous treatment (ITT analysis set)

	CAM2029			Placebo		
Responder Status	**Octreotide LAR (N=25) n (%)**	**Lanreotide ATG (N=23) n (%)**	**Overall (N=48) n (%)**	**Octreotide LAR (N=14) n (%)**	**Lanreotide ATG (N=10) n (%)**	**Overall (N=24) n (%)**
True Responder	18 (72.0)	16 (69.6)	34 (70.8)	5 (35.7)	4 (40.0)	9 (37.5)
True Non-Responder	4 (16.0)	4 (17.4)	8 (16.7)	7 (50.0)	6 (60.0)	13 (54.2)
Intercurrent Event Non-Responder	3 (12.0)	2 (8.7)	5 (10.4)	2 (14.3)	0	2 (8.3)
Missing Data Imputed as Non-Responder	0	0	0	0	0	0
Imputed MAR	0	1 (4.3)	1 (2.1)	0	0	0

ITT: intention-to-treat; MAR: missing at random.

In line with the inclusion criteria of the trial, all patients had IGF-1 levels ≤1×ULN at screening. At baseline (mean of the values at Week -2 and pre-dose on Day 1), the proportion of patients with IGF-1 levels ≤1×ULN was 91.7% in both treatment arms, i.e., not all patients were responders at baseline.

The proportions then varied in the interval between 68.8% and 85.4% from Week 4 to Week 24 in the CAM2029 treatment arm and was 70.8% at the end of the Double-Blind Treatment Phase (mean of the values at Week 22 and Week 24).

In the placebo treatment arm, there was a consistent decrease in proportion of patients with IGF-1 levels ≤1×ULN over time to 37.5% at the end of the Double-Blind Treatment Phase.

23 patients (47.9%) in the CAM2029 treatment arm and 2 patients (8.3%) in the placebo treatment arm had mean IGF-1 levels at Week 22 and Week 24 that were below or equal to their IGF-1 levels at baseline.

Table 22 Number of patients with IGF-1 levels ≤1×ULN by visit, time point, treatment arm and previous treatment (ITT analysis set)

		CAM2029			Placebo		
Visit	Time Point	Octreotide LAR (N=25) n (%)	Lanreotide ATG (N=23) n (%)	Overall (N=48) n (%)	Octreotide LAR (N=14) n (%)	Lanreotide ATG (N=10) n (%)	Overall (N=24) n (%)
Week -8 to -4	Regular	24 (96.0)	23 (100)	47 (97.9)	14 (100)	10 (100)	24 (100)
Week -2	Regular	24 (96.0)	21 (91.3)	45 (93.8)	14 (100)	9 (90.0)	23 (95.8)
Mean of Screening		25 (100)	23 (100)	48 (100)	14 (100)	10 (100)	24 (100)
Day 1	Pre-Dose	21 (84.0)	20 (87.0)	41 (85.4)	12 (85.7)	10 (100)	22 (91.7)
Baseline		23 (92.0)	21 (91.3)	44 (91.7)	12 (85.7)	10 (100)	22 (91.7)
Week 4	Pre-Dose	21 (84.0)	20 (87.0)	41 (85.4)	9 (64.3)	7 (70.0)	16 (66.7)
Week 8	Pre-Dose	19 (76.0)	18 (78.3)	37 (77.1)	5 (35.7)	5 (50.0)	10 (41.7)
Week 12	Pre-Dose	22 (88.0)	18 (78.3)	40 (83.3)	5 (35.7)	5 (50.0)	10 (41.7)
Week 16	Pre-Dose	20 (80.0)	16 (69.6)	36 (75.0)	3 (21.4)	3 (30.0)	6 (25.0)
Week 20	Pre-Dose	20 (80.0)	17 (73.9)	37 (77.1)	2 (14.3)	4 (40.0)	6 (25.0)
	2 h Post-Dose	19 (76.0)	16 (69.6)	35 (72.9)	2 (14.3)	4 (40.0)	6 (25.0)
	5 h Post-Dose	19 (76.0)	16 (69.6)	35 (72.9)	2 (14.3)	4 (40.0)	6 (25.0)
	8 h Post-Dose	18 (72.0)	17 (73.9)	35 (72.9)	2 (14.3)	4 (40.0)	6 (25.0)
	24 h Post-Dose	20 (80.0)	18 (78.3)	38 (79.2)	2 (14.3)	3 (30.0)	5 (20.8)
	96 h Post-Dose	20 (80.0)	17 (73.9)	37 (77.1)	1 (7.1)	3 (30.0)	4 (16.7)
Week 22	Post-Dose	21 (84.0)	16 (69.6)	37 (77.1)	5 (35.7)	4 (40.0)	9 (37.5)
Week 24/EOT	Post-Dose	17 (68.0)	16 (69.6)	33 (68.8)	5 (35.7)	3 (30.0)	8 (33.3)
Mean of Week 22-24		18 (72.0)	16 (69.6)	34 (70.8)	5 (35.7)	4 (40.0)	9 (37.5)

EOT: end of trial; IGF-1: insulin-like growth factor-1; ITT: intention-to-treat; n: number of patients within category; N: number of patients in the analysis set; %: percentage of patients; ULN: upper limit of normal
Mean of Screening was calculated as the mean of values at Week -8 to -4 and Week -2
Baseline was calculated as the mean of values at Week -2 and Day 1
Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing for other reasons
Source: Table 14.2.6.1

Sensitivity Analyses of the Primary Efficacy Endpoint

All the sensitivity analyses of the primary efficacy endpoint supported the results from the main analysis, with p-values of 0.0025 or below. Patients with intercurrent events were regarded as non-responders in all sensitivity analyses.

Six supportive analyses were performed on the primary efficacy endpoint, in which the responder rates by treatment arm at Week 22 and Week 24 and the difference in responder rates between the treatment arms were estimated together with their respective two-sided 95% CI.

The supportive analyses all reinforced the robustness of the results from the main analysis.

Secondary Efficacy Analyses

Main Analysis of the Key Secondary Efficacy Endpoint I "Proportion of Patients with Mean IGF-1 Levels ≤1×ULN at Week 22 and Week 24, Irrespective of IMP Dose"

- The results for the first key secondary efficacy endpoint (including the sensitivity analyses) were the same as for the primary efficacy endpoint since no patients had their dose decreased in the trial.

- The second key secondary efficacy endpoint of the trial was met, and the proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 and mean GH <2.5 µg/L at Week 24 was statistically significantly higher in the CAM2029 treatment arm (70.0%) than in the placebo treatment arm (37.5%).

The difference in proportions (CAM2029-placebo) was 32.3% (95% CI: 8.8%, 55.7%), p=0.0035, and the odds ratio (CAM2029/placebo) was 3.86 (95% CI: 1.37, 10.90).

Sensitivity analysis of the key secondary efficacy endpoints

As for the primary efficacy endpoint, the sensitivity analysis I of the second key secondary efficacy endpoints could not be performed.

The other sensitivity analyses only showed small differences compared to the main analysis of the endpoint, with p-values of 0.0040 or below in all analyses.

Other Secondary Efficacy Endpoints

1) Time to Loss of Response

Time to Loss of Response: IGF-1 levels >1×ULN

The time to loss of response, defined as the earliest time when the IGF-1 levels of two consecutive measurements were >1×ULN, was statistically significantly longer in the CAM2029 treatment arm than in the placebo treatment arm, p<0.0001.

The median time to loss of response was not reached in the CAM2029 treatment arm, whereas it was 8.4 weeks in the placebo treatment arm [HS-18-633]. The hazard ratio (CAM2029/placebo) was 0.10 (95% CI: 0.04, 0.28; p<0.0001) [HS-18-633]

Time to Loss of Response: IGF-1 levels >1.3×ULN

The time to loss of response in the CAM2029 treatment arm was also compared to the time to loss of response in the placebo treatment arm using the stratified log-rank test, stratified by stratum (p=0.0007).

2) IGF-1 Levels over Time and Change from Baseline to Week 24 in IGF-1 Levels

The mean IGF-1/ULN remained stable and below 1×ULN in the CAM2029 treatment arm throughout the 24-week treatment period [HS-18-633].

In the placebo treatment arm, the mean values increased above 1×ULN at Week 8 and remained above ULN up to Week 24. The analysis of change from baseline to Week 24 in IGF-1/ULN showed a significant increase in mean IGF-1/ULN in patients receiving placebo and stable values in patients receiving CAM2029, with a mean difference between the treatment arms of -0.47 in favour of CAM2029 (95% CI: 0.72, -0.21; two-sided p=0.0004) [HS-18-633].

Of note, at baseline, the proportion of patients with IGF-1 levels ≤1×ULN was 91.3% in the CAM2029 treatment arm. This decreased to 70.8% at Week 22/Week 24, with a difference in proportions (Week 22/Week 24-baseline) of -20.5% (95% CI: -33.7%, -7.3%).

In patients in the placebo treatment arm, the proportion of patients with IGF-1 levels ≤1×ULN was 93.4% at baseline, which decreased to 37.8% at Week 22/Week 24. The difference in proportions (Week 22/Week 24-baseline) was -55.6% (95% CI: -77.8%, -33.4%).

3) GH Levels over Time and Change from Baseline to Week 24 in GH Levels

The mean GH levels remained around or below 1.0 µg/L throughout the 24-week treatment period in the CAM2029 treatment arm and increased to around 1.0 to 2.1 µg/L in the placebo treatment arm.

The analysis of change from baseline to Week 24 in mean GH levels showed a significant increase in the placebo treatment arm and stable values in the CAM2029 treatment arm, with a mean difference of -0.5393 µg/L in favour of CAM2029 (95% CI: 0.9882 µg/L, -0.0905 µg/L; two-sided p=0.0185).

The mean GH levels remained low and around or below 1.0 µg/L throughout the 24-week treatment phase in the CAM2029 treatment arm, whereas they increased to around 1 to 2 µg/L in the placebo treatment arm.

4) Proportions of Patients with Biochemical Response based on GH <1.0 µg/L and <2.5 µg/L

The proportions of patients with mean GH <1.0 µg/L at Week 24 were 59.9% in the CAM2029 treatment arm and 37.5% in the placebo treatment arm [HS-18-633, Table 14.2.8.2]. The difference in proportions between the treatment arms was 21.3% (95% CI: -2.6%, 45.1%); one sided p=0.0404 (not significant).

The proportions of patients with mean GH <2.5 µg/L at Week 24 were 87.5% in the CAM2029 treatment arm and 83.3% in the placebo treatment arm [HS-18-633, Table 14.2.8.1]. The difference in proportions between the treatment arms was 3.2% (95% CI: -13.9%, 20.4%); one sided p=0.3559 (not significant).

Of note, in line with the exclusion criteria of the trial, all patients had mean GH levels <2.5 µg/L at screening. On Day 1, 95.8% of the patients in each treatment arm had mean GH levels <2.5 µg/L. The proportion of patients with GH levels <2.5 µg/L then varied between 72.9% and 89.6% in the CAM2029 treatment arm and between 66.7% and 87.5% in the placebo treatment arm during Week 4 to Week 22.

The proportions of patients with mean GH levels <1.0 µg/L were similar between the treatment arms at screening (CAM2029: 83.3%; placebo: 87.5%) and on Day 1 (CAM2029: 83.3%; placebo: 79.2%).

The proportions of responders then decreased in both treatment arms, with a smaller decrease in the CAM2029 treatment arm. From Week 4 to Week 22, the proportions of patients with GH levels <1.0 µg/L varied between 59.9% and 68.8% in the CAM2029 treatment arm and between 37.5% and 70.8% in the placebo treatment arm.

5) Proportion of Patients who Received Rescue Medication with Standard of Care

One patient in the placebo treatment arm discontinued treatment with IMP due to worsening of clinical signs and symptoms of acromegaly in combination with increased IGF-1 levels. This patient was switched to rescue medication with SoC. No patients in the CAM2029 treatment arm were switched to rescue medication with SoC.

6) Change from Baseline to Week 24 in Tumour Size

The median change in tumour size from screening to Week 24 was 0 mm3 in both treatment arms, suggesting that the tumour size remained unchanged throughout the trial.

7) Clinical Signs and Symptoms of Acromegaly over Time

<u>AIS score (Acromegaly Index of Severity)</u>

The AIS Overall Score was calculated as the sum of the score of all 6 symptoms of acromegaly (headache, sweating, fatigue, joint pain, paraesthesia, and soft tissue swelling), with individual symptoms scores of 0 to 3 depending on intensity (none, mild, moderate, severe). The AIS Overall Score, therefore, ranged from 0 (no symptoms) to 18 (severe symptoms).

The mean AIS Overall Score at baseline (on treatment with SoC) were lower in the placebo treatment arm (mean [SD]: 2.4 [2.5]) than in the CAM2029 treatment arm (mean [SD]: 4.7 [3.3]) [HS-18-633]. During the treatment with IMP, the acromegaly symptoms were well controlled over time, with a tendency of decreased AIS Overall Score from baseline in the CAM2029 treatment arm . There were no differences in the change in AIS Overall Score from baseline to Week 24 between the treatment arms in the ANCOVA analysis.

The change from baseline to the Week 24/EOT in LS Mean AIS Overall Score was -0.3 in the CAM2029 treatment arm and -0.8 in the placebo treatment arm based on the ANCOVA analysis. The mean difference between the

treatment arms (CAM2029-placebo) was 0.5 (95% CI: -0.8, 1.7), and the difference was not statistically significant (p=0.4506).

Ring Size over Time

The LS Mean change from baseline to Week 24/EOT in ring size (circumference) was -0.47 mm in the CAM2029 treatment arm and -0.62 mm in the placebo treatment arm. The mean difference between the treatment arms (CAM2029-placebo) was 0.15 mm (95% CI: -0.95 mm, 1.24 mm), and the difference was not statistically significant (p=0.7941).

8) TSQM (Treatment Satisfaction Questionnaire for Medication)

The TSQM domain scores range from 0 to 100, where higher scores indicate better satisfaction. In the ANCOVA analysis of change from baseline to Week 24/EOT, the baseline TSQM scores represent the patients' satisfaction with their previous treatment with SoC (octreotide LAR or lanreotide ATG).

There was a significant increase from baseline (i.e., while on treatment with SoC) to Week 24 in the TSQM convenience domain in both treatment arms, with an LS Mean change of 13.85 (95% CI: 9.45, 18.25) in the CAM2029 treatment arm and 9.90 (95% CI: 4.06, 15.75) in the placebo treatment arm . The improvement seen in both treatment arms may be related to the improved administration. There were no apparent differences between the treatment arms for this domain. There were no meaningful changes from baseline within or between the treatment arms for the other TSQM domains.

For the effectiveness domain, there were no relevant treatment differences. The LS Mean scores decreased with 2.72 from baseline to Week 24/EOT in the CAM2029 treatment arm (95%CI: -9.94, 4.51) and with 3.11 in the placebo treatment arm (95%CI: -12.09, 5.86). The mean difference between the treatment arms (CAM2029-placebo) was 0.40 (95% CI: -10.80, 11.60).

There were also no treatment differences in the global satisfaction domain. The LS Mean scores increased slightly with 0.10 from baseline to Week 24/EOT in the CAM2029 treatment arm (95%CI: -7.00, 7.20), whereas they decreased with 2.77 in the placebo treatment arm (95%CI: - 11.60, 6.06). The mean difference between the treatment arms was 2.87 (95% CI: -8.23, 13.97).

For the side effects domain (where an increase in scores means a decrease in side effects), the LS Mean scores increased with 3.37 from baseline to Week 24/EOT in the CAM2029 treatment arm (95%CI: -1.95, 8.69), whereas they decreased with 3.70 in the placebo treatment arm (95%CI: -10.77, 3.38). The mean difference between the groups (CAM2029-placebo) was 7.07 (95% CI: -1.63, 15.76).

9) Patient Satisfaction Scale Scores at Week 24

At Week 24, patients were asked to complete a patient satisfaction scale questionnaire and rate their overall experience with treatment with CAM2029/placebo compared to their previous treatment with octreotide LAR or lanreotide ATG. The patient satisfaction scale scores ranged from 1 "much worse" to 5 "much better", where higher score indicated higher patient satisfaction.

44 of 48 patients in the CAM2029 treatment arm and all patients in the placebo treatment arm completed the patient satisfaction scale.

Patients receiving CAM2029 reported high satisfaction with the treatment compared to their previous treatment with SoC.

29.2% of the patients receiving CAM2029 rated the treatment as "much better" compared to 12,5% with placebo, 18.8% as "slightly better" compared to 33.3% with placebo, 29.2% as "about the same" compared

to 25% with placebo, 4.2% as "slightly worse" compared to 16.7% with placebo than their previous treatment with SoC.

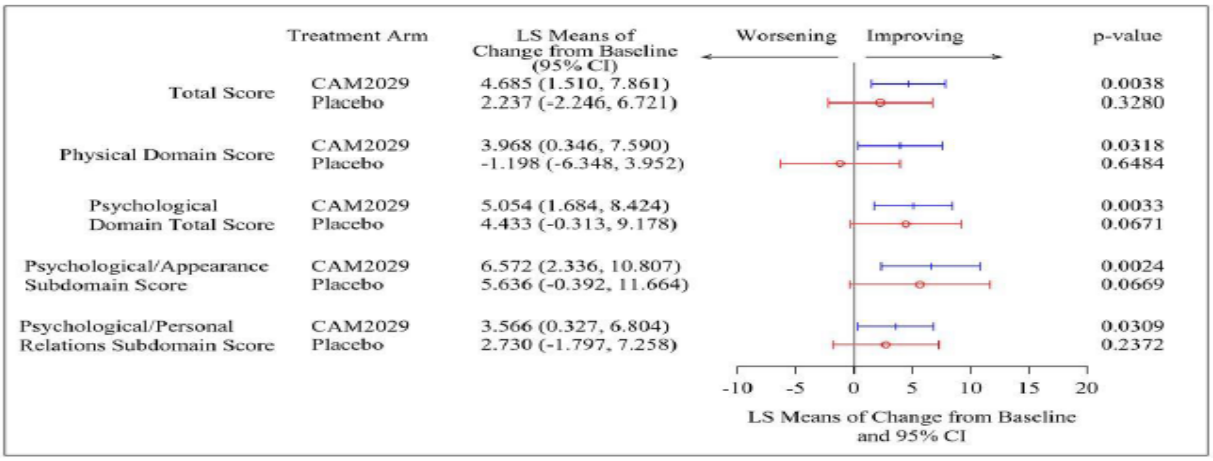
The mean scores at Week 24/EOT were 3.9 (95% CI: 3.6, 4.2) in the CAM2029 treatment arm and 3.4 (95% CI: 2.9, 3.8) in the placebo treatment arm.

10) Change from Baseline in AcroQoL and EQ-5D-5L Scores

AcroQoL

The AcroQoL domain scores range from 0 to 100, where higher scores indicate better satisfaction. In the ANCOVA analysis of change from baseline to Week 24/EOT, the baseline AcroQoL scores represent the patients' quality of life while on treatment with SoC (octreotide LAR or lanreotide ATG). An overview of the results is shown in Figure 4.

Figure 4 Forest plot of LS Means for change from baseline to Week 24/EOT in AcroQoL scores by treatment arm (ITT analysis set)



AcroQoL: Acromegaly Quality of Life Questionnaire; CI: confidence interval; EOT: end of trial; ITT: intention-to-treat; LS: least square
ANCOVA model with treatment arm and prior treatment as factors and baseline AcroQoL domain/scale scores as covariate.
Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing for other reasons. Missing data were imputed.

There was an increase in AcroQoL Total Score from baseline to Week 24/EOT in the CAM2029 treatment arm, with an LS Mean change of 4.685 (95% CI: 1.510, 7.861). There was also an increase in the LS Mean Total Score of 2.237 in the placebo treatment arm (95% CI: -2.246, 6.721).

The mean difference between the treatment arms was 2.448 (95% CI: -2.958, 7.853).

EQ-5D-5L Scores (EuroQoL5-dimension 5-level)
An EQ-5D-5L index value of 0 represents death and 1 represents full health. Values below 0 can occur. The EQ-5D-5L VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

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

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

The SIAQ domain scores range from 0 to 10, where higher scores indicate better patient experience. The SIAQ PRE module ('pre-treatment') was completed by the patients before their first self-administration of IMP. Most patients who chose to self-administer the IMP completed the PRE module on Day 1 in connection with their first self-administration (CAM2029: 23/28; placebo: 12/17). A few patients performed their first self-administration at Week 4 or Week 8.

The SIAQ POST module was completed 20 to 40 minutes after the first self-administration ('post-treatment 1') and after the last self-administration at Week 20 ('post-treatment 2').

Overall, 45 patients (62.5%) and caregivers of 3 patients (4.2%) administered the IMP at least once during the trial.

The 45 patients who self-administered the IMP also completed the SIAQ. The mean scores (score range: 1 to 10) in the SIAQ domains 'feelings about injections', 'satisfaction with current way of taking medication' and 'self-confidence' at baseline (pre-treatment) were 6.4 to 8.0 in the CAM2029 treatment arm and 5.9 to 6.7 in the placebo treatment arm.

There was a general increase in the scores for these domains from baseline to post-treatment 1 (after the first injection) and post-treatment 2 (after the last injection at Week 20), indicating improvements in all three domains. The increases from pre-treatment to post-treatment 2 were also in general higher than the increases from pre-treatment to post-treatment 1.

For the domains with only post-treatment measurements (self-image, injection site reactions, ease of use and satisfaction with self-injection), mean scores for the different SIAQ domains were in the higher interval, ranging from about 6.5 to 9.2 for the CAM2029 treatment arm, where the highest scores (best results) were for the domains 'injection site reactions' and 'self-image'.

Feasibility of Self-Administration

Overall, 57 patients/partners (79.2%) stated that they were willing to self-administer the IMP during the trial. The proportion of patients/partner opting for self-administration was higher in the placebo treatment arm (91.7%) than in the CAM2029 treatment arm (72.9%). 52 of the 57 patients/partners (91.2%) who underwent training in self-administration were declared competent to self-administer the IMP (CAM2029: 91.4%, placebo: 90.9%).

42 patients (58.3%) had the IMP administered by the trial personnel at least once during the trial, whereas 45 patients (62.5%) and 3 partners (4.2%) administered the IMP themselves at least once.

Very few patients and partners had any difficulties while performing the injections during the trial (Week 4: 1 patient, Week 8: 1 partner, Week 12: 1 patient, Week 16: 3 patients).

Subgroup analysis

Exploratory subgroup analyses were performed on the primary and key secondary efficacy endpoints by sex, race, age, and prior treatment with octreotide LAR or lanreotide ATG.

Subgroup analyses were also performed on the subgroups of patients who had baseline IGF-1 levels ≤1×ULN and baseline GH levels ≤ or <1.0 µg/L.

1) Subgroup Analyses of the Primary Efficacy Endpoint

- The proportions of responders were similar between men (75.0%) and women (67.9%) in the CAM2029 treatment arm, but higher in patients aged 18 to 64 years (76.5%) than in patients aged ≥65 years (57.1%). In the placebo treatment arm, the proportions of responders were similar between men (33.3%) and women (41.7%), and between patients aged 18 to 64 years (36.8%) and patients aged ≥65 years (40.0%).

- In the subgroup of patients who had baseline IGF-1 levels ≤1×ULN,

The proportion of patients who also had IGF levels ⩽1×ULN at Week 22 and Week 24 was statistically significantly higher in the CAM2029 treatment arm (75.0%) than in the placebo treatment arm (36.4%). The difference in proportions (CAM2029-placebo) was 38.7% (95%: CI: 14.8%, 62.6%), one-sided p=0.0008, and the odds ratio (CAM2029/placebo) was 5.22 (1.73, 15.71),

- Subgroup of patients who had GH levels <1.0 µg/L at baseline

In the subgroup of patients who had mean GH levels <1.0 µg/L at baseline, the proportions of patients who also had mean GH levels <1.0 µg/L at Week 24 were 66.7% in the CAM2029 treatment arm and 47.4% in the placebo treatment arm

The difference in proportions between the treatment arms (19.5% [95% CI: -7.5%, 46.5%]) was not statistically significant (one-sided p=0.0782).

2) Subgroup analysis of the key secondary endpoints

- Subgroup Analyses of Key Secondary Efficacy Endpoint I ("Proportion of Patients with Mean IGF-1 Levels ≤1×ULN at Week 22 and Week 24, Irrespective of IMP Dose")

The results of the exploratory subgroup analyses performed on the key secondary endpoint I were also the same as the results of the subgroup analyses of the primary efficacy endpoint.

- Subgroup Analyses of Key Secondary Efficacy Endpoint II ("Proportion of Patients with Mean IGF-1 levels ≤1×ULN at Week 22 and Week 24 and Mean GH Levels <2.5 µg/L at Week 24")

Exploratory subgroup analyses were performed on the key secondary efficacy endpoint II by sex,race, age and prior treatment with octreotide LAR or lanreotide ATG.

The proportions of responders were similar between men (75.0%) and women (64.3%) in the CAM2029 treatment arm, but higher in patients aged 18 to 64 years (73.5%) than in patients aged ⩾65 years (57.1%). In the placebo treatment arm, the proportions of responders were similar between men (33.3%) and women (41.7%), and also between patients aged 18 to 64 years (36.8%) and patients aged ⩾65 years (40.0%).

- **Ancillary analyses**

Post-Hoc Analysis of the Primary Efficacy Endpoint

When PK data were available after database lock, it was discovered that 2 patients in the placebo treatment arm showed presence of octreotide in several samples taken at time points potentially affecting the primary endpoint. Therefore, a post-hoc analysis of the primary efficacy endpoint was performed excluding these 2 patients. The results were consistent with the results from the main analysis.

The proportion of responders was statistically significantly higher in the CAM2029 treatment arm (71.7%) than in the placebo treatment arm (31.8%). The difference in proportions (CAM2029-placebo) was 39.8% (95% CI: 16.4%; 63.2%), p=0.0004, and the odds ratio (CAM2029/placebo) of 5.41 (95% CI: 1.80; 16.25).

Phase 3 Trial [HS-19-647] = Supportive study

A phase 3, open-label, single arm, multi-centre trial to assess the long-term safety of octreotide subcutaneous depot (CAM2029) in patients with acromegaly

Methods

HS-19-647 was an open-label, single–arm, multi-centre, Phase 3 trial that assessed the long-term safety (primary objective) and efficacy (secondary objective) of CAM2029 in patients with acromegaly.

Enrolment in the trial has been completed, and the trial is still ongoing to allow patients who completed treatment with CAM2029 in study [HS-18-633] and derived benefit to continue treatment with CAM2029 in this long-term study. An interim report with a data cut-off of 23 May 2023 has been submitted initially and the CTR with main part data with a data cut-off 30 April 2024 was submitted during the review process.

[HS-19-647] enrolled both patients who were directly recruited into the trial ('new patients') and patients who completed participation in the preceding trial [HS-18-633] ("roll-over patients").

Main part of trial

"New patients" enrolled in HS-19-647 were on stable doses of octreotide LAR (10, 20, 30, or 40 mg) or lanreotide ATG (60, 90, or 120 mg) once monthly for at least 3 months before screening. They also had either of the following:

- IGF-1 >1×ULN and ≤2×ULN at screening (average of the assessments at screening and Week -2) with or without radiotherapy, or

- IGF-1 ≤1×ULN at screening (average of the assessments at screening and Week -2) with or without prior pituitary radiotherapy at least 3 years before screening and confirmed disease activity, defined as IGF-1 >1×ULN during the period from 3 to 9 months before screening.

"Roll over patients" included patients who were randomised to CAM2029 ('CAM2029 roll-over patients') or to placebo ('placebo roll-over patients') in study [HS-18-633]. The treatment allocation in [HS-18-633] was kept blinded also after patients had rolled over to [HS-19-647], until the blind in [HS-18-633] was broken at the time of the primary analysis.

- "Placebo roll-over patients" included patients who had been "pharmacologically washed out" during participation in [HS-18-633]. These patients are regarded as "non-pharmacologically treated" for acromegaly as they remained untreated for 6 months during the previous trial.

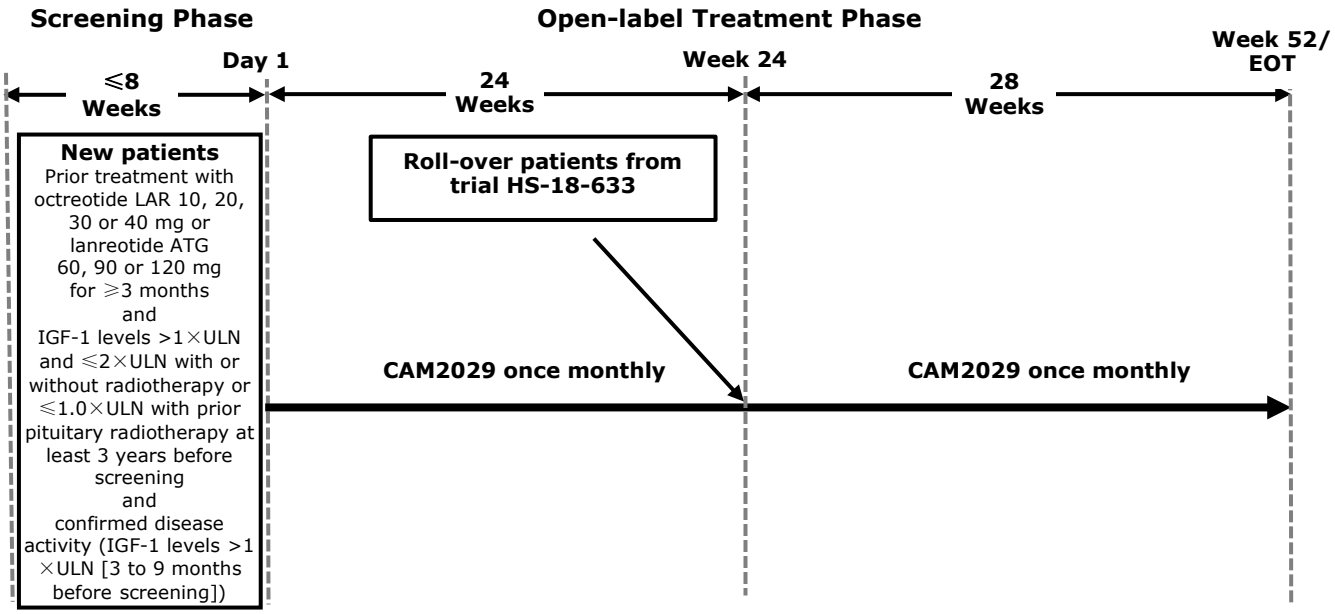
The trial was conducted at multiple clinical trial centres in Europe and the US. The trial consisted of a main part and an extension part. The overall duration of participation for a patient in this trial was up to 116 weeks, with open-label treatment for up to 104 weeks.

This interim clinical trial report of trial [HS-19-647] includes all data available up to, and including, the data cut-off date (23-May-2023) for the planned interim analysis. The cut-off date for the interim analysis was chosen to obtain a sufficient number of patients exposed to CAM2029 for 52 weeks to document long-term safety and tolerability of CAM2029.
Trial Initiation Date (first patient first visit): 10-Oct-2019
Data Cut-off Date of Interim Report: 23-May-2023
Main Part Completion date: 30 April 2024

The main part of the trial consisted of 2 phases: the Screening Phase and the Open-label Treatment Phase (which included the Double-blind Treatment Phase in [HS-18-633] for roll-over patients).

The duration of participation for a patient in the main part of the trial was up to 60 weeks for "new patients" (up to 8 weeks Screening Phase and 52 weeks Open-label Treatment Phase), and up to 28 weeks for "roll-over patients from [HS-18-633]" (participation in Open-label Treatment Phase only).

Figure 5 Trial Design - Main part of the Trial



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

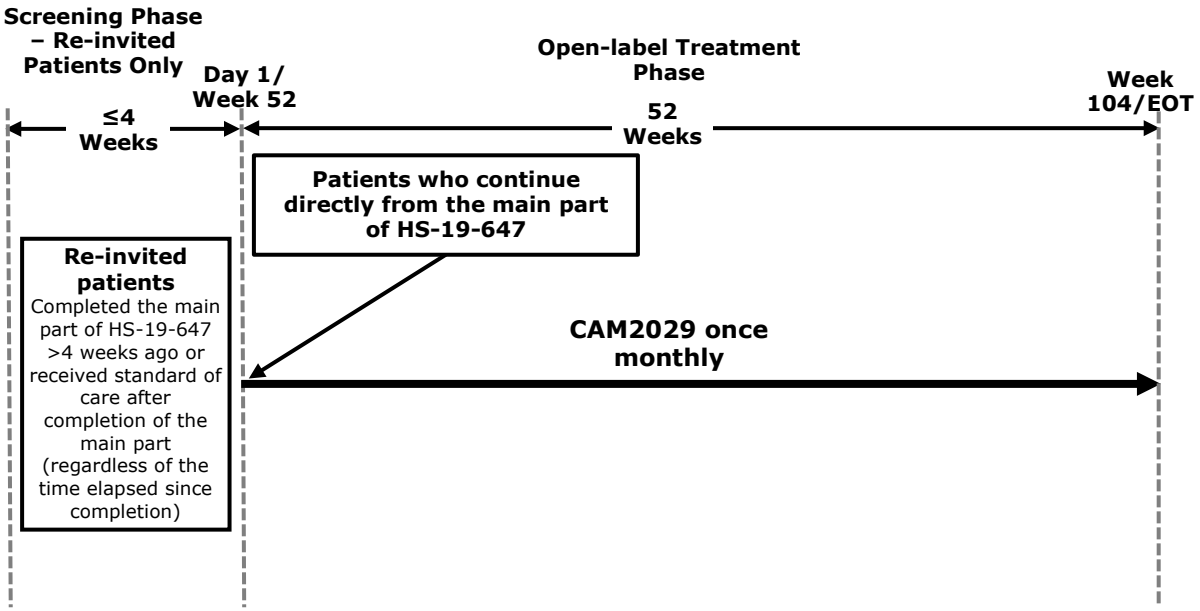
Extension Part of the Trial

The 52-week extension part of the trial was added in protocol amendment 4 to enable further collection of long-term safety, efficacy, and PRO data on CAM2029, and to provide an opportunity for patients who completed treatment with CAM2029 in the main part of the trial to continue treatment with CAM2029.

The extension part included both patients who continued directly from the main part of the trial, and re-invited patients who had previously completed the main part of [HS-19-647] trial more than 4 weeks back or were treated with SoC in between the 2 parts.
For re-invited patients there were no restrictions on the type (e.g., monotherapy or combination therapy), dose levels, dosing frequencies, or how long they received SoC in the period between the 2 parts of the trial.

The extension part of the trial consisted of 2 phases; the Screening Phase (up to 4 weeks, and applicable for re-invited patients only) and the Open-label Treatment Phase (up to 52 weeks, for all patients enrolled in the extension part of the trial).

Figure 6 Trial Design – Extension Part of the Trial



EOT: End of Trial
The duration of participation for any patient in the extension part of the trial was up to 52 weeks for patients who continued directly from the main part of the trial, and up to 56 weeks for re-invited patients from main part of the trial (up to 4 weeks Screening Phase and 52 weeks Open-label Treatment Phase).

Patients who participated in the extension part of the trial were treated with 20 mg CAM2029, or 10 mg CAM2029 (depending on the dose they received at the end of the main part of the trial), using the pre-filled pen throughout the 52-week treatment period. Patients/partners who used the pre-filled syringe in the main part of the trial were trained on using the pre-filled pen if needed on Day 1/Week 52. Patients or partners who used the pre-filled pen in the main part of the trial were also re-trained, if needed.

At Week 104 (or 4 weeks after the last dose in case of premature withdrawal from the trial), the patients came to the trial site for an EOT visit. All patients who completed the extension part of the trial were then continued to be treated for their acromegaly according to the Investigator's discretion.

- **Study Participants**

Diagnosis and Main Criteria for Inclusion: Main Part of the Trial

For New Patients

1. Diagnosis of acromegaly by historical evidence of (persistent or recurrent) acromegaly as documented by:
   a. IGF-1 levels >1×ULN

   b. Pituitary adenoma on magnetic resonance imaging (MRI) or pathology report. Computerized tomography was accepted if MRI could not be performed

   c. IGF-1 levels >1×ULN measured at least 3 months after the surgery for patients who have undergone pituitary surgery

2. Treatment with a stable dose of octreotide LAR (10, 20, 30, or 40 mg) or lanreotide ATG (60, 90, or 120 mg) for at least 3 months as monotherapy prior to screening

3. IGF-1 levels >1×ULN and ≤2.0×ULN at screening (adjusted for age and sex; mean value of the first measurement at screening and the second measurement at 2 weeks before Day 1) with or without prior pituitary radiotherapy (at least 3 years prior to screening),

or

IGF-1 levels ≤1×ULN at screening (adjusted for age and sex; value of the first measurement at screening and the second measurement at 2 weeks before Day 1) either without prior pituitary radiotherapy or with prior pituitary radiotherapy at least 3 years prior to screening and confirmed disease activity defined as IGF-1 levels >1×ULN during the period from 3 to 9 months prior to screening.

4. Adequate liver, pancreatic, renal, and bone marrow functions

5. Normal ECG

For Roll-Over Patients from Trial HS-18-633

1. Patients who attended the Week 24 visit of the preceding trial (HS-18-633) and were willing to continue their participation in this trial.

Main Exclusion Criteria: Main Part of the Trial

For New Patients

1. Had received medical treatment for acromegaly with pasireotide (within 6 months prior to screening), pegvisomant (within 3 months prior to screening), dopamine agonists (within 3 months prior to screening) or other investigational agents (within 30 days or 5 half-lives prior to screening [whichever is longer])

2. Patients who usually took octreotide LAR or lanreotide ATG less frequently than every 4 weeks (e.g. every 6 weeks or 8 weeks)

3. Compression of the optic chiasm causing any visual field defect for whom surgical intervention was indicated

4. Patients who had undergone major surgery/surgical therapy for any cause within 1 month prior to screening

5. Patients who underwent pituitary surgery within 6 months prior to screening

6. Patients who had received prior pituitary irradiation within 3 years prior to screening

7. Patients with poorly controlled diabetes mellitus (hemoglobin A1c [HbA1c] >8.0%)

For Roll-Over Patients from Trial HS-18-633

1. Unresolved, drug-related serious adverse event (SAE) from the preceding trial (HS-18-633)

2. Patients who had a clinically significant or unstable medical or surgical condition that could precluded safe and complete trial participation.

Continuation Criteria for Patients who continue Directly into the Extension Part of the Trial

Patients who continue directly from the main part of the trial had to have completed treatment with CAM2029 in the main part of the trial, attended the Week 52 visit, and provided written informed consent to continue treatment in the extension part of the trial before treatment could be continued.

Main Inclusion Criteria for Re-Invited Patients – Extension Part of the Trial

1. Completed treatment with CAM2029 in the main part of the trial and attended the Week 52 visit

2. Adequate liver, pancreatic and renal functions

3. Normal ECG

Main Exclusion Criteria for Re-invited Patients – Extension Part of the Trial

1. Receiving treatments (other than treatments for acromegaly) known to affect GH or IGF-1 concentration

2. Patients who had undergone major surgery/surgical therapy (including pituitary surgery) for any cause within 1 month prior to screening

3. Patients who had received pituitary irradiation since the end of the main part of the trial

4. Patients with poorly controlled diabetes mellitus (HbA1c >8.0%)

- **Treatments**

Test Product, Dose and Mode of Administration:

CAM2029 20 mg (1.0 mL, pre-filled syringes or pre-filled pens) or 10 mg (0.5 mL, pre-filled syringes or pre-filled pens) was administered through SC injections in the abdomen or thigh once monthly (28 days±7 days).

Table 23 Trial treatments

Treatment	CAM2029 pre-filled syringe	CAM2029 pre-filled pen
Treatment name	CAM2029 (octreotide subcutaneous depot)	CAM2029 (octreotide subcutaneous depot)
Manufacturer		
Dosage formulation	Solution for injection in a ready-to-use pre-filled syringe	Solution for injection in a pre-filled pen
Unit dose strengths	10 mg/0.5 mL for 10 mg 20 mg/1.0 mL for 20 mg	10 mg/0.5 mL for 10 mg 20 mg/1.0 mL for 20 mg
Dosage levels	10 mg 20 mg	10 mg 20 mg
Route of administration	SC injection	SC injection
Packaging and labeling	CAM2029 was provided in pre-filled syringes. Each pre-filled syringe was labeled in line with country requirements	CAM2029 was provided in pre-filled pens. Each pre-filled pen was labeled in line with country requirements

Abbreviations: SC=subcutaneous

In the main part of the trial, the administration of CAM2029 was performed in the morning and as close as possible to the time point of the first dose. Patients could self-administer CAM2029 (or have CAM2029 administered by their partner) at home at the visits.

Main Part of the Trial

- CAM2029 was administered as an SC injection in the abdomen, thigh and/or buttock, regardless of who gave the injection (trial personnel, patient, or partner). CAM2029 was administered once monthly (every 28 days±7 days).

Self- or partner-administration of CAM2029 in the abdomen, thigh or buttock was allowed after appropriate training and under the supervision of adequately trained trial personnel. The first self- or partner-administration was preferably performed on Day 1. Re-training was performed for patients and/or partners switching from injections with pre-filled syringe to injections with pre-filled pen.

If the patients or their partners were considered competent to administer CAM2029, they continued with the self- or partner-administration. If patients (or their partners) were not able or confident to self-administer the treatment at home, they had to visit the site and perform the administration there.

- Doses and Dose Adjustments:

New Patients

New patients were treated with 20 mg CAM2029 on Day 1, regardless of their previous dose of octreotide LAR (10, 20, 30, or 40 mg) or lanreotide ATG (60, 90, or 120 mg). The first dose of 20 mg CAM2029 was administered 4 weeks (±3 days) after the last dose of octreotide LAR or lanreotide ATG.

Roll-over Patients from [HS-18-633]

Roll-over patients from [HS-18-633] received 20 mg or 10 mg CAM2029 at Week 24, depending on the CAM2029 dose (or corresponding volume of placebo) [HS-18-633]. Patients who were switched to SoC during [HS-18-633] due to worsening of the acromegaly symptoms were treated with 20 mg CAM2029 at Week 24 in [HS-19-647].

All Patients

In the Open-label Treatment Phase, doses of CAM2029 could be down titrated from 20 mg to 10 mg once monthly for safety/tolerability reasons where applicable. After down-titration, the patient could return to the previous dose if the safety issue was resolved, and the benefit-risk evaluation allowed it. If the patient was on the lowest permitted dose (10 mg) and a further dose reduction for safety reasons was required, the patient was discontinued from treatment but continued to be followed in the trial.

Extension Part of the Trial

- CAM2029 was administered every 28 days±7 days as an SC injection in the abdomen, thigh and/or buttock, regardless of who gave the injection. The timing of each dose had to be in relation to the date of the previous dose. Only the pre-filled pen was used in the extension part of the trial.

Training in how to administer CAM2029 with the pre-filled pen was performed in connection with the first dose in the extension part of the trial (Day 1/Week 52) for patients/partners who used the pre-filled syringe in the main part of the trial. Patients or partners who used the prefilled pen in the main part of the trial could be re-trained, if needed.

- *Doses and Dose Adjustments*: the first dose on Day 1/Week 52 of the extension part of the trial was the same dose as the last dose the patient received in the main part of the trial (i.e., 20 mg or 10 mg CAM2029), both for patients who continued directly and for re-invited patients. Down-titration from 20 mg to 10 mg CAM2029 for safety/tolerability reasons could be performed.

Rescue therapy = standard of care

Patients participating in the main part of the trial could be discontinued from treatment with the CAM2029 and switched to SoC in case they experienced worsening of signs and symptoms of acromegaly and after discussion with the Medical Monitor.

For roll-over patients, the worsening of symptoms had to be accompanied by an increase in the levels of IGF-1 to $\geq 1.3 \times$ ULN at 2 consecutive visits.

- **Objectives and Outcomes/endpoints**

- Primary objective and primary endpoint (main and extension part of the trial)

Table 24 Primary objective and primary endpoint (main and extension part of the trial)

Objectives	Endpoints
Primary Objective	***Primary Endpoint***
• To assess the overall safety and tolerability of CAM2029	• Characterization of AEs

- Secondary objective

- **Main part**

Table 25 Secondary objectives and secondary endpoints (main part)

Secondary Objectives	***Secondary Endpoints[a]***
• To assess the efficacy of CAM2029 in biochemical response for IGF-1	• Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 50 and Week 52 (average of the 2 measurements) • Proportion of patients with mean IGF-1 levels <1.3×ULN at Week 50 and Week 52 (average of the 2 measurements)
• To assess the efficacy of CAM2029 in biochemical response for GH	• Proportion of patients with mean GH cycle levels <1.0 µg/L at Week 52[b] • Proportion of patients with mean GH cycle levels <2.5 µg/L at Week 52 • Proportion of patients with mean GH cycle levels <5.0 µg/L at Week 52
• To assess the efficacy of CAM2029 in biochemical response for IGF-1 and GH	• Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 50 and Week 52 and mean GH cycle levels <2.5 µg/L at Week 52
• To assess the efficacy of CAM2029 for IGF-1 levels over time	• Change from baseline in IGF-1 levels
• To assess the efficacy of CAM2029 for GH levels over time	• Change from baseline in GH levels
• To assess time to loss of response of CAM2029	• Time to IGF-1 levels >1×ULN • Time to IGF-1 levels ≥1.3×ULN
• To assess retention in treatment	• Proportion of patients retained in treatment at Week 52
• To evaluate the effects of CAM2029 on tumor size	• Change from baseline in tumor size
• To assess the effects of CAM2029 on clinical signs and symptoms of acromegaly	• Severity scores of clinical signs and symptoms of acromegaly over time • Ring size over time
• To measure patients' satisfaction with CAM2029	• TSQM scores over time using all 4 domains of TSQM (effectiveness, side effects, convenience and satisfaction) • Patient satisfaction scale scores at Week 24 and Week 52
• To measure the effects of CAM2029 on QoL	• Change from baseline in AcroQoL and EQ-5D-5L scores
• To measure patients' satisfaction with self-administration of CAM2029	• Change from PRE module to the POST module in SIAQ scores
• To assess supervised self- or partner-administration of CAM2029	• Proportion of patients/partners declared competent by a healthcare professional to administer CAM2029 out of those trying

Secondary Objectives	***Secondary Endpoints[a]***
• To evaluate solicited safety assessments after treatment with CAM2029	• Changes in laboratory values, vital signs, ECG readings and gallbladder imaging • Incidence of injection site reactions (erythema and swelling) and level of injection site pain
• To assess the plasma concentrations of octreotide after administration of CAM2029 in patients with acromegaly	• Octreotide plasma concentrations over time

Abbreviations: AcroQoL=Acromegaly Quality of Life Questionnaire; AE=adverse event; ECG=electrocardiogram; EQ-5D-5L=EuroQoL 5-dimension 5-level; GH=growth hormone; IGF-1=insulin-like growth factor-1; QoL=quality of life; SAP=statistical analysis plan; SIAQ=Self-Injection Assessment Questionnaire; TSQM=Treatment Satisfaction Questionnaire for Medication; ULN=upper limit of normal

[a] In protocol amendment 2, the GH cycle assessment at Week 50 was replaced with a single GH (GH random) sample and the secondary endpoints based on GH cycle levels at Week 50 and Week 52 were subsequently revised to only include the Week 52 cycle. In protocol amendment 4, the patient satisfaction and QoL endpoints in the main part of the trial were upgraded from being exploratory objectives/endpoints to being secondary objectives/endpoints.

[b] This endpoint was added in the SAP.

- **Extension part**

Table 26 Table secondary objectives and secondary endpoints (extension part)

Secondary Objectives	***Secondary Endpoints***
• To assess the efficacy of CAM2029 in biochemical response for IGF-1	• IGF-1 levels over time
• To assess the efficacy of CAM2029 in biochemical response for GH	• GH levels over time
• To evaluate the effects of CAM2029 on tumor size	• Tumor size over time
• To assess the effects of CAM2029 on clinical signs and symptoms of acromegaly	• Severity scores of clinical signs and symptoms of acromegaly over time • Ring size over time
• To evaluate patients' satisfaction with CAM2029	• TSQM scores over time using all 4 domains of TSQM (effectiveness, side effects, convenience and satisfaction)
• To evaluate the effects of CAM2029 on QoL	• AcroQoL, EQ-5D-5L and SF-36 scores over time
• To evaluate the effects of CAM2029 on health economic outcomes	• WPAI scores over time
• To evaluate solicited safety assessments after treatment with CAM2029	• Laboratory values, vital signs, ECG readings and gallbladder imaging over time

AcroQoL: Acromegaly Quality of Life Questionnaire; AE: adverse event; ECG: electrocardiogram; EQ-5D-5L: EuroQoL 5-dimension 5-level; GH: growth hormone; IGF-1: insulin-like growth factor-1; QoL: quality of life; SF-36: Short Form-36; TSQM: Treatment Satisfaction Questionnaire for Medication; WPAI: Work Productivity and Activity Impairment.

The 52-week extension part of the trial was added in protocol amendment 4, and the objectives and endpoints corresponding to this extension part of the trial were included.

- **Sample size**

Sample size estimation was not based on a statistical power analysis. With approximately 140 patients in the safety analysis set, a sufficient number of patients were obtained to document the long-term safety and tolerability of CAM2029 during at least 52 weeks of treatment.

Patients who completed treatment in the main part of the trial could proceed to the extension part of the trial, either directly or as re-invited patients.

- **Randomisation and blinding (masking)**

No randomization and no blinding as this is an open-label and single arm-study.

- **Statistical methods**

The following analysis populations were defined:

- The ITT analysis set, which included all patients treated with CAM2029 in [HS-19-647] (N=135)

- The PP analysis set, which included all patients in the ITT analysis set with no major protocol deviations that had an impact on the efficacy assessment. This analysis set also excluded patients who had been withdrawn from the trial or who had discontinued treatment with CAM2029, and patients who still were ongoing in the main part of the trial at the data cut-off (N=100).). At the completion date for the main part, N= 123.

- The safety analysis set, which comprised all patients who were administered at least one dose of IMP in either [HS-18-633] (roll-over patients) or [HS-19-647] (new patients) (N=135)

All efficacy analyses were based on the ITT analysis set.

A subgroup of the ITT analysis set included the roll over patients who completed treatment with placebo in [HS 18 633] without being switched to rescue medication due to lack of efficacy (N=17). These patients were regarded as being "pharmacologically washed-out" from their previous SRL treatment.

Indeed, 18 patients had received placebo before rolling over to [HS-19-647] but one of the patients who previously received placebo had switched to SoC in HS-18-633 before enrolling in HS-19-647.

Baselines

Two baselines were defined in the trial.

1) The SoC baseline (or cumulative baseline) represented the baseline on SoC before receiving the first IMP dose in [HS 18 633] for roll-over patients and before receiving the first CAM2029 dose in [HS 19 647] for new patients (i.e., pre-dose Day 1 or the mean of Week -2 and pre dose Day 1, depending on the efficacy variable).

Additionally, another baseline was defined as the last measurement prior to the start of treatment with CAM2029. For new patients and CAM2029 roll-over patients, this baseline coincided with the SoC baseline.

2) For placebo roll-over patients, the active baseline (referred to as the placebo baseline hereafter) was the closest measurement before receiving the first CAM2029 dose in the [HS 19-647 trial](i.e., pre-dose Week 24 or the mean of Week 22 and pre-dose Week 24, depending on the efficacy variable).

<u>Two types of baseline values were defined</u>:

• Cumulative baseline (or SoC baseline): the closest measurement before the first dose of IMP (i.e., CAM2029 or placebo), with the following exceptions:

  o **For IGF-1**: the mean value of pre-treatment measurements, i.e., the measurement at Week -2 and the pre-dose measurement on Day 1, was used. If one of the IGF-1 values at Week -2 or Day 1 was missing, the other value was used

  o **For GH:** the pre-dose mean value from GH cycle value on Day 1 was used. If that value was missing, the screening value was used

  o **For ECG**: the mean of triplicate ECG measurements was used

• Active baseline (or placebo baseline): the closest measurement before the first dose of CAM2029

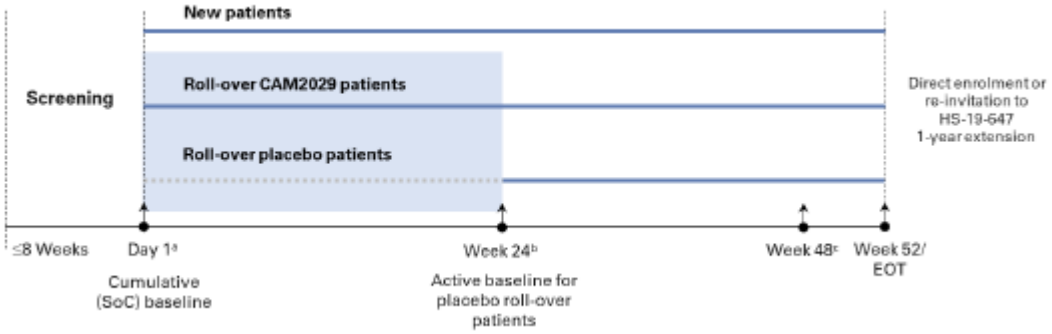
  o **For IGF-1**: the mean value of the measurement at Week -2 and the pre-dose measurement on Day 1 was used for patients in groups Prior CAM2029 in 633 and New in 647, and the mean value of the measurement at Week 22 and the pre-dose measurement at Week 24 was used for patients in the

group Prior Placebo in 633. If one of the IGF-1 values was missing, the other value was used as baseline value

o **For GH**: the pre-dose mean GH cycle value on Day 1 was used as baseline for patients in groups Prior CAM2029 in 633 and New in 647, and the pre-dose mean GH cycle value at Week 24 was used for patients in the group Prior Placebo in 633. If this value was missing, the preceding value (screening for Prior CAM2029 in 633 and New in 647, or Week 22 for Prior Placebo in 633) was used as baseline value

o **For ECG:** the mean of triplicate ECG measurements was used.

Figure 7 SoC and placebo baselines in HS-19-647



EOT: End of Trial in the main part; SoC: standard of care.
Blue, solid line refers to the period when patients were treated with CAM2029.
Grey, dotted line refers to the period when patients received placebo in HS-18-633.
a Day 1 in HS-18-633 for roll-over patients, and Day 1 in HS-19-647 for new patients.
b At Week 24, patients from HS-18-633 rolled over to HS-19-647.
c At Week 48, patients received the last CAM2029 dose in the main part of the trial.
The treatment allocation in HS-18-633 was kept blinded after patients had rolled over to HS-19-647 and until the blinds in HS-18-633 were broken.

Efficacy Analyses

- Two different definitions for biochemical response based on IGF-1 were applied:

- Mean IGF-1 ≤1×ULN at Week 50 and Week 52 (average of the two measurements, adjusted for age and sex at screening)

- Mean IGF-1 <1.3×ULN at Week 50 and Week 52 (average of the two measurements, adjusted for age and sex at screening)

All efficacy analyses were based on the ITT analysis set. For the endpoint related to proportion of patients with biochemical response based on IGF-1, the efficacy analysis was performed on the PP analysis set as well.

For the endpoints related to proportion of patients with biochemical response based on IGF-1 and GH levels (alone or combined) and change from baseline in IGF-1 and GH levels over time, efficacy analyses were performed separately for the "pharmacologically washed-out placebo roll-over patients".

For "roll-over patients", efficacy data obtained in [HS-18-633] were included and presented by patient group and overall, and by prior treatment.

Data from retrieved dropouts (i.e., following switch to SoC or dose reduction) were included in the evaluation of all efficacy endpoints. At the time of the interim analysis, the retrieved dropouts included 2 patients who were switched to SoC and 1 patient with CAM2029 dose reduction. One of the patients who was switched to SoC was still ongoing in the main part of the trial and did not contribute to all efficacy analyses. In the analyses of main part data, there were 3 retrieved dropouts, which included 2 new patients who discontinued CAM2029 treatment due to AEs and were switched to SoC, and 1 roll-over placebo patient who had the CAM2029 dose reduced during the trial.

Patients who were switched to SoC continued participation in the trial until Week 52 and followed all planned visits and assessments, (except post-dose assessments at Week 20 and Week 48) and trial drug related assessments.

Planned subgroup analyses

Data for all efficacy endpoints were split by prior treatment in all patient groups and overall.

A subgroup of the ITT analysis set included roll-over patients who completed treatment with placebo in [HS-18-633] without being switched to SoC due to lack of efficacy. These patients were regarded as "being washed-out of SRL treatment", and their IGF-1 and GH responses were evaluated separately.

These subgroup analyses were exploratory.

Interim Analyses and Data Monitoring

This clinical trial report provides the results from the planned interim analysis. No safety monitoring committee was set for the trial; however, safety data were regularly monitored and reviewed during meetings with the Medical Monitor from the CRO and the Sponsor.

At Day 121, the applicant provided the results of the full report of the main part of the study.

Results

- **Participant flow**

Disposition of Patients in the Main Part of the Trial

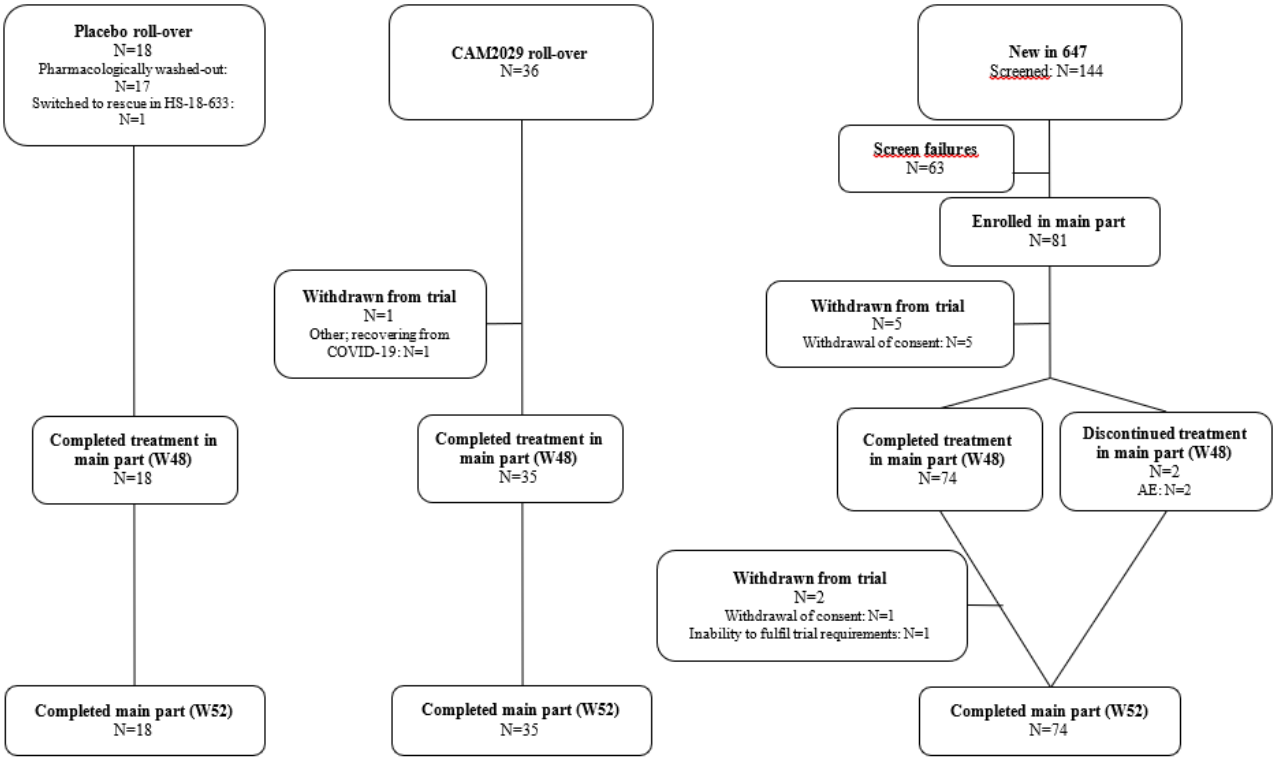
A total of 144 patients were screened for enrolment directly in the main part of [HS-19-647], of whom 81 patients were enrolled in the New in 647 group and 63 patients were screen failures. The most frequently reported reasons for screen failure included failure to fulfil inclusion criterion 6 (IGF-1 value at screening, 30/144 patients), inclusion criterion 4a (historical IGF-1 as evidence of acromegaly diagnosis, 10/144 patients), and inclusion criterion 2 (willingness and ability to comply with the requirements of the trial, 8/144 patients).
A total of 135 patients were enrolled in the trial at multiple trial sites in the United States (US) and Europe, of which 81 were new patients, 36 were CAM2029 roll-over patients, and 18 were placebo roll-over patients.
17 of the 18 placebo roll-over patients were considered "pharmacologically washed-out", because 1 placebo roll-over patient was switched to rescue medication with SoC in [HS-18-633] before rolling over to [HS-19 647].
At the main part completion date 127 patients (74 new patients, 35 CAM2029 roll-over patients and 18 placebo roll-over patients) had completed treatment with CAM2029 (i.e., received the Week 48 dose) in the main part of the trial.

Eight patients (5.9%) had discontinued treatment with CAM2029 and withdrew from the main part of (whom 7 New patients and 1 CAM2029 roll-over patient) since they withdrew from trial before they completed the main trial (see below).

Two new patients withdrew from the trial after receiving the last CAM2029 dose at Week 48, i.e., they completed treatment with CAM2029 as planned but did not attend the Week 52 visit. One of the patients withdrew consent, and the other patient was withdrawn due to inability to fulfil the last two visits.

In this trial, patients who discontinue treatment with CAM2029 and are switched to SoC, are followed up until completion of the main part of the trial but are not invited to enroll in the extension part. Two patients (both new patients) discontinued treatment with CAM2029 due to AEs assessed as related to CAM2029 and were switched to treatment SoC. Both patients remained in the trial until Week 52 visit (end of the main part).

Figure 8 Patient disposition in the main part of the trial HS-19-647 by patient group (full CTR main part)



Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; IGF-1=insulin-like growth factor-1; IMP=investigational medicinal product; N=number of patients; SoC=standard of care; W=Week

CAM2029/Placebo roll-over refers to patients who received either CAM2029 or placebo in HS-18-633 before enrolling at Week 24 in HS-19-647.

New in 647 refers to patients who were enrolled on Day 1 in HS-19-647.

Pharmacologically washed-out: placebo roll-over patients who are regarded as non-pharmacologically treated for acromegaly as they remained untreated for 24 weeks during participation in HS-18-633.

Switched to rescue: patients who were discontinued from IMP treatment and switched to SoC due to worsening of acromegaly symptoms in combination with increased IGF-1 levels during participation in HS-18-633.

Treatment in the main part of the trial was considered completed if patients received CAM2029 at Week 48.

The main part of the trial was considered completed at Week 52.

- **Recruitment**

Trial Initiation Date (first patient first visit): 10-Oct-2019

Completion date of the main part: 30 April 2024.

- **Conduct of the study**

The initial trial protocol version 1.0, issued on 20-May-2019, was the version submitted to the US FDA and approved by subsequent authorities. Protocol version 1.0 was in effect when the first patient's first visit in the trial took place.

After the first patient had been recruited, there were 4 global amendments, and 3 country-specific amendments issued to the protocol.

To accommodate patient and physician requests, the 52-week extension part of the trial was introduced to provide an opportunity for patients who completed treatment with CAM2029 in the main part of the trial to continue treatment with CAM2029. The extension part of the trial was added to the protocol 3 years after inclusion of the first patient in the main part of the trial when a considerable number of patients had already completed their participation in the main trial. Thus, it is estimated that the number of enrolled patients in the extension part of the trial will be much lower than those who completed the main part of the trial. Patients who were switched to SoC before Week 20 or Week 40 did not need to perform the post-dose assessments at Week 20 (2 to 96 hours after the dose) and/or Week 40 (2 to 24 hours after the dose).

Baseline data

Demographic and Baseline Disease Characteristics

The patients in the trial were aged 20 to 82 years, with an overall mean age of 52.9 years [HS 19-647]. Overall, 21 patients (15.6%) were 65 years or older (new patients: 11.1%, CAM2029 roll-over patients: 25.0%; placebo roll-over patients: 16.7%) [HS-19-647].

The overall mean BMI was 29.9 kg/m2 (range: 21 to 51 kg/m2).

Overall, 43.7% of the enrolled patients were men. Most patients (95.6%) were categorised as "White". 122 patients (90.4%) were enrolled in countries in Europe and 13 patients (9.6%) were enrolled in the US [HS-19-647, Table 14.1.5.7].

Baseline Disease Characteristics

The overall mean (SD) time since diagnosis was 11.1 (7.9) years (New in 647: 10.7 years; Prior CAM2029: 11.1 years; Prior Placebo: 12.3 years), and approximately half of the patients (51.9%) were diagnosed with acromegaly less than 10 years before screening [HS 19 647].

Most patients (119/135 = 88.1%) had undergone previous pituitary surgery.

Prior pituitary radiotherapy was reported in 12 of the 81 new patients (14.8%), 1 CAM2029 roll-over patient (2.8%), and 1 placebo roll-over patient (5.6%).

Among the "new patients", 76/81 (93.8%) have elevated IGF-1 at time of diagnosis.

At diagnosis, mean (SD) tumor size was 15.2 (8.3) mm.

The presence of a pituitary tumor was confirmed by MRI/CT in 130 patients (96.3%) and the histopathologic confirmation of a GH-staining adenoma was recorded in 24 patients (17.8%) who had prior pituitary surgery.

Table 27 History of acromegaly by patient group and previous treatment (safety analysis set)

		Placebo roll-over			CAM2029 roll-over			New in 647			Overall
Parameter	**Category/ Statistics**	**Oct LAR (N=11)**	**Lan ATG (N=7)**	**Overall (N=18)**	**Oct LAR (N=18)**	**Lan ATG (N=18)**	**Overall (N=36)**	**Oct LAR (N=59)**	**Lan ATG (N=22)**	**Overall (N=81)**	**Overall (N=135)**
Diagnosis Documented by	Confirmed pituitary tumor, n (%)	11 (100)	7 (100)	18 (100)	18 (100)	18 (100)	36 (100)	59 (100)	22 (100)	81 (100)	135 (100)
	Elevated IGF-1, n (%)	10 (90.9)	7 (100)	17 (94.4)	15 (83.3)	17 (94.4)	32 (88.9)	55 (93.2)	21 (95.5)	76 (93.8)	125 (92.6)
	GH nadir after GTT, n (%)	4 (36.4)	1 (14.3)	5 (27.8)	2 (11.1)	6 (33.3)	8 (22.2)	0	0	0	13 (9.6)
	Mean GH concentration, n (%)	1 (9.1)	1 (14.3)	2 (11.1)	5 (27.8)	2 (11.1)	7 (19.4)	0	0	0	9 (6.7)
Time since Diagnosis [years]	n	11	7	18	18	18	36	59	22	81	135
	Mean (SD)	15.1 (12.9)	7.9 (4.6)	12.3 (10.9)	11.1 (6.2)	11.1 (8.3)	11.1 (7.2)	11.0 (7.3)	10.2 (7.9)	10.7 (7.4)	11.1 (7.9)
	Min – Max	2 – 37	3 – 14	2 – 37	3 – 26	2 – 32	2 – 32	1 – 28	2 – 26	1 – 28	1 – 37
Time since Diagnosis	<10 years, n (%)	5 (45.5)	4 (57.1)	9 (50.0)	8 (44.4)	11 (61.1)	19 (52.8)	29 (49.2)	13 (59.1)	42 (51.9)	70 (51.9)
	≥10 to <20 years, n (%)	3 (27.3)	3 (42.9)	6 (33.3)	8 (44.4)	4 (22.2)	12 (33.3)	20 (33.9)	6 (27.3)	26 (32.1)	44 (32.6)
	≥20 years, n (%)	3 (27.3)	0	3 (16.7)	2 (11.1)	3 (16.7)	5 (13.9)	10 (16.9)	3 (13.6)	13 (16.0)	21 (15.6)
IGF-1/ULN value at Diagnosis	n	9	7	16	15	17	32	54	20	74	122
	Mean (SD)	2.681 (1.214)	2.690 (0.991)	2.685 (1.085)	2.987 (1.066)	3.457 (1.651)	3.237 (1.406)	3.030 (1.266)	2.474 (0.946)	2.880 (1.208)	2.948 (1.252)
	Min – Max	1.08 – 4.05	1.32 – 4.01	1.08 – 4.05	1.47 – 5.04	1.04 – 7.06	1.04 – 7.06	1.11 – 7.30	1.05 – 4.01	1.05 – 7.30	1.04 – 7.30
Tumor Size at Diagnosis [mm]	n	4	3	7	10	13	23	38	15	53	83
	Mean (SD)	18.0 (5.6)	15.3 (5.0)	16.9 (5.1)	18.5 (9.9)	13.3 (5.9)	15.6 (8.2)	14.4 (8.0)	15.9 (10.8)	14.9 (8.8)	15.2 (8.3)
	Min - Max	13 – 25	10 – 20	10 – 25	5 – 34	3 – 25	3 – 34	5 – 40	1 – 36	1 – 40	1 – 40
Method of Pituitary Tumor Confirmation	MRI/CT, n (%)	11 (100)	6 (85.7)	17 (94.4)	17 (94.4)	18 (100)	35 (97.2)	57 (96.6)	21 (95.5)	78 (96.3)	130 (96.3)
	Surgical pathology, n (%)	2 (18.2)	3 (42.9)	5 (27.8)	3 (16.7)	2 (11.1)	5 (13.9)	10 (16.9)	4 (18.2)	14 (17.3)	24 (17.8)
	Other, n (%)	0	0	0	1 (5.6)	0	1 (2.8)	0	0	0	1 (0.7)
Pituitary Surgery	Yes, n (%)	10 (90.9)	7 (100)	17 (94.4)	17 (94.4)	15 (83.3)	32 (88.9)	53 (89.8)	17 (77.3)	70 (86.4)	119 (88.1)
	No, n (%)	1 (9.1)	0	1 (5.6)	1 (5.6)	3 (16.7)	4 (11.1)	6 (10.2)	5 (22.7)	11 (13.6)	16 (11.9)
IGF-1/ULN value after Surgery	n	10	7	17	16	15	31	50	16	66	114
	Mean (SD)	1.752 (0.722)	1.784 (0.770)	1.765 (0.718)	2.037 (0.965)	1.700 (0.572)	1.874 (0.805)	1.765 (0.635)	1.582 (0.356)	1.721 (0.583)	1.769 (0.667)
	Min – Max	1.08 – 3.45	1.28 – 3.47	1.08 – 3.47	1.09 – 4.30	1.04 – 2.90	1.04 – 4.30	1.03 – 3.46	1.10 – 2.45	1.03 – 3.46	1.03 – 4.30
	Yes, n (%)	0	0	0 [a]	0	0	0 [a]	9 (15.3)	3 (13.6)	12 (14.8)	12 (8.9) [a]

		Placebo roll-over			CAM2029 roll-over			New in 647			Overall
Parameter	**Category/ Statistics**	**Oct LAR (N=11)**	**Lan ATG (N=7)**	**Overall (N=18)**	**Oct LAR (N=18)**	**Lan ATG (N=18)**	**Overall (N=36)**	**Oct LAR (N=59)**	**Lan ATG (N=22)**	**Overall (N=81)**	**Overall (N=135)**
Prior Pituitary Radiotherapy	No, n (%)	0	0	0	0	0	0	50 (84.7)	19 (86.4)	69 (85.2)	69 (51.1)
	Not Recorded, n (%)	11 (100)	7 (100)	18 (100)	18 (100)	18 (100)	36 (100)	0	0	0	54 (40.0)

Abbreviations: CT=computerized tomography; GH=growth hormone; GTT=glucose tolerance test; IGF-1=insulin-like growth factor-1; Lan ATG=lanreotide autogel; Max=maximum; Min=minimum; MRI=magnetic resonance imaging; n=number of patients within category; N=number of patients in the analysis set; Oct LAR=octreotide long-acting repeatable; SD=standard deviation; ULN=upper limit of normal; %=percentage of patients

Time since diagnosis was calculated as: (start date of the first treatment - date of diagnosis)/365.25.

If ULN value was not defined for IGF-1, then IGF-1 value was excluded from the analysis.

[a] One CAM2029 roll-over patient and one placebo roll-over patient had prior pituitary irradiation

Medical History and Concurrent Illnesses

132 patients (97.8%) in the safety analysis set had at least one medical history recorded.

Medical history was most frequently reported within the SOCs of 'Metabolism and nutrition disorders' (80.0%), 'Endocrine disorders' (63.7%), and 'Vascular disorders' (57.8%).

Table 28 Reported medical history (cut-off ≥10% overall for preferred term) by SOC, PT, patient group and previous treatment (safety analysis set)

	Placebo roll-over			CAM2029 roll-over			New in 647			Overall
System Organ Class Preferred Term	**Oct LAR (N=11) n (%)**	**Lan ATG (N=7) n (%)**	**Overall (N=18) n (%)**	**Oct LAR (N=18) n (%)**	**Lan ATG (N=18) n (%)**	**Overall (N=36) n (%)**	**Oct LAR (N=59) n (%)**	**Lan ATG (N=22) n (%)**	**Overall (N=81) n (%)**	**Overall (N=135) n (%)**
Any Medical History	11 (100)	7 (100)	18 (100)	17 (94.4)	18 (100)	35 (97.2)	58 (98.3)	21 (95.5)	79 (97.5)	132 (97.8)
Metabolism and nutrition disorders										
Obesity	4 (36.4)	1 (14.3)	5 (27.8)	6 (33.3)	6 (33.3)	12 (33.3)	20 (33.9)	3 (13.6)	23 (28.4)	40 (29.6)
Type 2 diabetes mellitus	2 (18.2)	1 (14.3)	3 (16.7)	3 (16.7)	4 (22.2)	7 (19.4)	11 (18.6)	8 (36.4)	19 (23.5)	29 (21.5)
Vitamin D deficiency	1 (9.1)	3 (42.9)	4 (22.2)	1 (5.6)	3 (16.7)	4 (11.1)	6 (10.2)	10 (45.5)	16 (19.8)	24 (17.8)
Dyslipidemia	2 (18.2)	0	2 (11.1)	5 (27.8)	4 (22.2)	9 (25.0)	10 (16.9)	1 (4.5)	11 (13.6)	22 (16.3)
Diabetes mellitus	2 (18.2)	0	2 (11.1)	3 (16.7)	2 (11.1)	5 (13.9)	9 (15.3)	1 (4.5)	10 (12.3)	17 (12.6)
Glucose tolerance impaired	1 (9.1)	0	1 (5.6)	3 (16.7)	4 (22.2)	7 (19.4)	3 (5.1)	3 (13.6)	6 (7.4)	14 (10.4)
Endocrine disorders										
Goiter	4 (36.4)	0	4 (22.2)	4 (22.2)	6 (33.3)	10 (27.8)	27 (45.8)	6 (27.3)	33 (40.7)	47 (34.8)
Hypothyroidism	4 (36.4)	0	4 (22.2)	2 (11.1)	4 (22.2)	6 (16.7)	3 (5.1)	5 (22.7)	8 (9.9)	18 (13.3)
Vascular disorders										
Hypertension	3 (27.3)	3 (42.9)	6 (33.3)	12 (66.7)	9 (50.0)	21 (58.3)	30 (50.8)	11 (50.0)	41 (50.6)	68 (50.4)
Hepatobiliary disorders										
Cholelithiasis	6 (54.5)	1 (14.3)	7 (38.9)	5 (27.8)	1 (5.6)	6 (16.7)	10 (16.9)	4 (18.2)	14 (17.3)	27 (20.0)
Surgical and medical procedures										
Cholecystectomy	1 (9.1)	0	1 (5.6)	3 (16.7)	4 (22.2)	7 (19.4)	10 (16.9)	0	10 (12.3)	18 (13.3)
Gastrointestinal disorders										
Chronic gastritis	1 (9.1)	0	1 (5.6)	3 (16.7)	2 (11.1)	5 (13.9)	10 (16.9)	1 (4.5)	11 (13.6)	17 (12.6)
Musculoskeletal and connective tissue disorders										
Osteoarthritis	0	1 (14.3)	1 (5.6)	4 (22.2)	3 (16.7)	7 (19.4)	6 (10.2)	2 (9.1)	8 (9.9)	16 (11.9)
Renal and urinary disorders										
Renal cyst	2 (18.2)	1 (14.3)	3 (16.7)	2 (11.1)	1 (5.6)	3 (8.3)	7 (11.9)	2 (9.1)	9 (11.1)	15 (11.1)

Abbreviations: Lan ATG=lanreotide autogel; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients within category; N=number of patients in the analysis set; Oct LAR=octreotide long-acting repeatable; PT=preferred term; SOC=system organ class; %=percentage of patients
Medical history was coded to system organ class and preferred term using MedDRA, version 25.0.
Medical history for roll-over patients was recorded at screening in HS-18-633.

Prior and Concomitant Medications/Treatments

Table 29 Prior medication for acromegaly by patient group and previous treatment (safety analysis set)

	Prior Placebo in 633			Prior CAM2029 in 633			New in 647			Overall
Drug Name	Oct LAR (N=11) n (%)	Lan ATG (N=7) n (%)	Overall (N=18) n (%)	Oct LAR (N=18) n (%)	Lan ATG (N=18) n (%)	Overall (N=36) n (%)	Oct LAR (N=59) n (%)	Lan ATG (N=22) n (%)	Overall (N=81) n (%)	(N=135) n (%)
Any Prior Medication	11 (100)	7 (100)	18 (100)	18 (100)	18 (100)	36 (100)	59 (100)	22 (100)	81 (100)	135 (100)
Octreotide	11 (100)	1 (14.3)	12 (66.7)	18 (100)	3 (16.7)	21 (58.3)	59 (100)	5 (22.7)	64 (79.0)	97 (71.9)
Lanreotide	0	7 (100)	7 (38.9)	0	18 (100)	18 (50.0)	3 (5.1)	22 (100)	25 (30.9)	50 (37.0)
Cabergoline	1 (9.1)	0	1 (5.6)	1 (5.6)	3 (16.7)	4 (11.1)	2 (3.4)	2 (9.1)	4 (4.9)	9 (6.7)
Bromocriptine	1 (9.1)	0	1 (5.6)	0	0	0	1 (1.7)	1 (4.5)	2 (2.5)	3 (2.2)
Pegvisomant	1 (9.1)	0	1 (5.6)	0	1 (5.6)	1 (2.8)	1 (1.7)	0	1 (1.2)	3 (2.2)
Pasireotide	0	0	0	0	1 (5.6)	1 (2.8)	0	1 (4.5)	1 (1.2)	2 (1.5)

Lan ATG: lanreotide autogel; n: number of patients within category; N: number of patients in the analysis set; Oct LAR: octreotide long-acting repeatable; %: percentage of patients
All octreotide and Sandostatin treatment categorized as octreotide, all lanreotide treatment categorized as lanreotide, somavert treatment categorized as pegvisomant, dostinex treatment categorized as Cabergoline
Table includes medications for acromegaly prior to enrollment in HS-18-633 for groups Prior Placebo and Prior CAM2029 in 633, and prior to enrollment in HS-19-647 for group New in 647

- **Numbers analysed**

All 135 enrolled patients were included in the safety and ITT analysis sets. 123 patients (91.1%) were included in the PP analysis set (New in 647 group: 72 patients; CAM2029 roll-over group: 35 patients; Placebo roll-over group:16 patients).

12 patients were excluded from the PP analysis set for the following reasons: 8 patients were withdrawn from the trial, 2 patients were discontinued from treatment, 1 patient missed 3 CAM2029 consecutive doses, and 1 patient received prohibited medication of ethinylestradiol; One patient was included in the PP analysis set, but the IGF-1 result at Week 52 was excluded from PP analyses.

Dose adjustments during the trial

Dose adjustments (i.e., dose reductions, return to previous dose, permanent discontinuations, and temporary interruptions) and missed doses are summarized for the whole trial in Table (safety analysis set).

Five patients (3.7%) had their CAM2029 doses adjusted (i.e., down-titrated, temporarily interrupted or discontinued) due to AEs.

One placebo roll-over patient (0.7%) had the dose down-titrated due to a related AE of diarrhea and received 6 injections at a dose of 10 mg (0.5 mL) of CAM2029. This patient did not return to the previous dose.

Three patients (2.2%) had their CAM2029 dose temporarily interrupted, and two patients (1.5%) had their CAM2029 dose permanently discontinued due to related AEs (one of them after having initially the dose temporarily interrupted)

Table 30 Dose adjustments and missed doses of CAM2029 by patient group and previous treatment – whole trial (safety analysis set)

	Placebo roll-over	CAM2029 roll-over	New in 647	Overall
Reason Action	**Overall (N=18) n (%)**	**Overall (N=36) n (%)**	**Overall (N=81) n (%)**	**(N=135) n (%)**
Adverse Event				
All	2 (11.1)	0	3 (3.7)	5 (3.7)
Dose down titrated	1 (5.6)	0	0	1 (0.7)
Returned to previous dose	0	0	0	0
Dose missed	0	0	0	0
Dose permanently discontinued	0	0	2 (2.5)	2 (1.5)
Dose temporarily interrupted	1 (5.6)	0	2 (2.5)	3 (2.2)
Other				
All	1 (5.6)	1 (2.8)	3 (3.7)	5 (3.7)
Dose down titrated	0	0	0	0
Returned to previous dose	0	0	0	0
Dose missed	1 (5.6)	1 (2.8)	3 (3.7)	5 (3.7)
Dose permanently discontinued	0	0	0	0
Dose temporarily interrupted	0	0	0	0

Abbreviations: n=number of patients within category; N=number of patients in the analysis set; %=percentage of patients

Only CAM2029 injections are presented in the above table.

Extent exposure

All 135 patients (100%) received at least one CAM2029 dose. 131 patients (97.0%) were exposed to CAM2029 for ≥24 weeks and 109 patients (80.7%) were exposed to CAM2029 for ≥52 weeks. The overall mean (SD) duration of exposure was 50.72 (11.22) weeks, ranging from 7.6 to 57.7 weeks.

- **Outcomes and estimation**

In general, the evaluations of efficacy parameters included data collected during HS-18-633 for roll-over patients, without imputations of missing data.

As mentioned before, two baselines were defined in the trial. The SoC baseline (or cumulative baseline) represented the baseline on SoC prior to receiving the first IMP dose in HS-18-633 for roll-over patients and prior to receiving the first CAM2029 dose in HS-19-647 for new patients (i.e., pre-dose Day 1 or the mean of values at Week -2 and pre-dose Day 1, depending on the efficacy variable). Additionally, an active baseline was defined as the last measurement prior to the start of treatment with CAM2029. For new patients and CAM2029 roll-over patients, the active baseline coincided with the SoC baseline.

For placebo roll-over patients, "the active baseline" (referred to as placebo baseline for placebo roll-over patients) was the closest measurement prior to receiving the first CAM2029 dose in the HS-19-647 trial (i.e.,

pre-dose Week 24 or the mean of values at Week 22 and pre-dose Week 24, depending on the efficacy variable).

Eight patients had their treatment discontinued (withdrawal from trial), these include 6 patients (4.4%) who withdrew from the trial before the last CAM2029 dose at Week 48 and 2 patients (1.5%) who remained in the trial after W48. One placebo roll-over patient (0.7%) had the CAM2029 dose reduced during the trial.

Data from retrieved dropouts were included in the evaluation of the efficacy endpoints. There were 3 retrieved dropouts, which included 2 new patients who discontinued CAM2029 treatment due to AEs and were switched to SoC, and 1 roll-over placebo patient who had the CAM2029 dose reduced during the trial.

Secondary Efficacy endpointsAll the data presented correspond to the main part of the study.

1) Proportion of Patients with Biochemical Response Based on IGF-1

Proportion of Patients with Biochemical Response Based on IGF-1 (Mean IGF-1 ≤1×ULN) – Patients with Evaluable Data

The observed proportions of patients with biochemical response based on IGF-1 levels at the "SoC (cumulative) baseline" (mean of values at Week -2 and Day 1), the placebo (active) baseline (mean of values at Week 22 and Week 24), and at the end of the main part of the trial (mean of values at Week 50 and Week 52) are provided.

In the overall population, all 135 patients who were enrolled in [HS-19-647] had IGF-1 data at the "SoC baseline". After 24 weeks with placebo in [HS-18-633], all 18 placebo roll-over patients had IGF-1 data at the placebo baseline. At the end of the 52-week treatment period, 127 patients (74 new patients, 35 CAM2029 roll-over patients, and 18 placebo roll-over patients) had evaluable IGF-1 data.

Proportion of Patients with Biochemical IGF-1 Response (Mean IGF-1 ≤1×ULN) – Patients with Evaluable Data

Of the 127 patients with evaluable IGF-1 data at Week 50 and/or Week 52 in the overall population, 59 patients (46.5%) were biochemically controlled with IGF 1 ≤1×ULN at the SoC baseline (mean of Week -2 and pre-dose Day 1). This proportion increased to 75 patients (59.1 %) at the end of the main part of the trial (mean of Week 50 and Week 52). This table includes only patients with evaluable results at Week 50 and/or Week 52.

For "new patients", the proportion of responders increased from 10 patients (13.5%) at the SoC baseline to 27 patients (36.5 %) at the end of the main part of the trial.

"CAM2029 roll-over patients" had a high proportion of responders at both SoC baseline (32/35 patients [91.4%]) and after 52 weeks of treatment with CAM2029 (31/35 patients [88.6%]).

For the "placebo roll-over patients", the proportion of responders decreased from 17 patients (94.4%) at the SoC baseline to 5 patients (27.8 %) at the placebo baseline (mean of Week 22 and Week 24) after receiving placebo for 24 weeks. 17/18 placebo roll-over patients (94.4%) showed adequate biochemical response after 28 weeks of treatment with CAM2029 at the end of the main part of the trial.

Estimated Difference in Proportion of Responders with Mean IGF-1 ≤1×ULN – Patients with Evaluable Data

In the analysis of change in the proportions of responders, estimated using a linear probability model based on a binomial distribution, the results were consistent with the observed proportions of responders. There was an

estimated increase in the proportions of responders at the end of main part of the trial (at 52 weeks) compared to the SoC baseline of 12.7% (95% CI: 5.5%; 19.9 %) in the overall population [HS-19-647].

For "new patients", the estimated increase was 22.8 % (95% CI: 11.6 %, 33.9%).

For "CAM2029 roll-over patients", there was an estimated decrease in the proportion of responders among the patients at W50/52 from SOC Baseline of -2% (95% CI: -13.3%, 9.2%).

-For the "placebo roll over patients", there was an estimated increase from the placebo baseline for placebo roll-over patients (68.5% [95% CI:47.4%, 89.5%]).

The differences in proportions of responders in the PP analysis set were similar to those in ITT analysis set.

Proportion of Patients with Mean IGF-1 <1.3×ULN – Patients with Evaluable Data at Week 50 and Week 52 (average of the 2 measurements)

Of the 127 patients with evaluable data overall, 99 patients (78.0%) had mean IGF-1 <1.3×ULN at the SoC baseline and 96 patients (75.6%) had mean IGF-1 <1.3×ULN at the end of the main part of the trial.

Of the 74 "new patients" with evaluable data, 46 patients (62.2%) at the SoC baseline and 44 patients (59.5%) at the end of the main part had mean IGF-1 <1.3×ULN.

Regarding the "new patients", the proportion of patients with mean IGF-1 <1.3×ULN decreased from baseline to W52 (62.2 % to 59.5%) All "CAM2029 and placebo roll-over patients "(100%) had mean IGF-1 <1.3×ULN at the SoC baseline. At the end of the main part of the trial, all placebo roll-over patients (100%) and 97.1% of the CAM2029 roll-over patients had mean IGF-1 <1.3×ULN.

Of note, at the placebo baseline, the proportion of "placebo roll-over patients" with mean IGF-1 <1.3×ULN decreased to 72.2 % (13/18 patients) and increase to 100 % at week 52.

Estimated Difference in Proportion of Responders with Mean IGF-1 <1.3×ULN – Patients with Evaluable Data

The estimated differences in proportions of patients with mean IGF-1 <1.3×ULN was - 2.5 % (95% CI: - 9.5%; 4.5 %) in the overall population.

The estimated differences could not be determined using the model in "roll-over patients", since the proportions of responders in both patient groups were approximately 100% both at baseline and at the end of the main part of the trial.

2) Proportions of Patients with Biochemical Response Based on GH

GH levels were determined as the mean of 5 GH samples taken pre-dose during a 2-hour period and as single (pre-dose) samples.

In the overall population, 134 of the 135 patients who were enrolled in [HS-19-647] had GH data at the SoC baseline. After 24 weeks with placebo in [HS-18-633], all 18 placebo roll-over patients had GH data at the placebo baseline.

At the end of the 52-week treatment period, 124 patients (74 new patients, 33 CAM2029 roll-over patients, and 17 placebo roll-over patients) had evaluable GH data.

Proportion of Patients with Mean GH <1.0 µg/L – Patients with Evaluable Data (N = 124) at week 52

Of the 124 patients with evaluable GH data at Week 52, 78 patients (62.9%) had mean GH <1.0 µg/L at the SoC baseline and 75 patients (60.5 %) had mean GH <1.0 µg/L at Week 52 .

For "new patients", the proportion of patients with mean GH <1.0 µg/L was approximately the same at the SoC baseline (48.6 %) and at Week 52 (45.9 %).

"CAM2029 roll-over patients" had a high proportion of patients with mean GH <1.0 µg/L both at the SoC baseline (87.9%) and at Week 52 (81.8%).

For the "placebo roll-over patients", the proportion of patients with mean GH <1.0 µg/L decreased from 13 patients (76.5%) at the SoC baseline to 5 patients (29.4%) at the "placebo baseline" after receiving placebo for 24 weeks. After 28 weeks of treatment with CAM2029, 14/17 (82.4%) of the patients had mean GH <1.0 µg/L at Week 52.

The estimated change in proportions of patients with mean GH <1.0 µg/L after treatment with CAM2029 at Week 52

The estimated differences were -3.9% (95% CI: -10.8%, 2.9%) in the overall population, -2.6% (95% CI: -11%, 5.7%) in "new patients", -8.8% (95% CI: -18.8%, 1.2 %) in "CAM2029 roll-over patients", and " -0.2%" (95% CI: - 27.1%, 26.6%) in placebo roll-over patients [HS-19-647].

The estimated difference from the "placebo baseline" to Week 52 in the placebo roll-over patients was + 50.9% (95% CI: 26.4%, 75.4 %) [HS-19-647].

Proportion of Patients with Mean GH <2.5 µg/L – Patients with Evaluable Data (N = 124) at Week 52

Overall, 111 of the 124 patients with evaluable GH data (89.5 %) at the SoC baseline and 110 patients (88.7%) at Week 52, had mean GH <2.5 µg/L.

For "new patients", the proportion is quite similar at SOC baseline and at W52 (82.4% at SOC baseline and 83.8% at W52).

For "CAM2029 roll over patients", the proportion at SOC baseline was 100% and 93.9% at W52.

For "placebo roll-over patients", the proportion is similar at SOC baseline and at week 52 (100%).

Estimated Difference in Proportion of Responders with Mean GH <2.5 µg/L – Patients with Evaluable Data

In the overall population, the difference in proportions of patients was unchanged, with an estimated difference from the SoC baseline to the end of the trial of -0.1 % (95% CI: -5.4%, 5.2%).

The estimated differences could not be determined using the model for the roll-over patients since the proportions of patients in both patient groups were approximately 100% both at baseline (SoC and placebo) and at Week 52.

3) Proportions of Patients with Biochemical Response Based on IGF-1 and GH

The proportions of patients with mean IGF-1 $\leq 1 \times$ ULN and mean GH <2.5 μg/L at each visit were similar to those seen for patients with mean IGF-1 $\leq 1 \times$ ULN only.

Overall, the observed proportion of patients was 45.9% (62/135 patients) at the SoC baseline and 54.8% (68/124 patients) at the end of main part of the trial.

The proportion of pharmacologically washed-out placebo roll-over patients with mean IGF-1 ≤1×ULN and mean GH <2.5 μg/L followed the same trend over time as observed for patients in this subgroup with mean IGF-1 ≤ 1×ULN only.

Estimated Difference in Proportion of Patients with Mean IGF-1 ≤1×ULN and Mean GH <2.5 µg/L – Patients with Evaluable Data

The estimated differences in proportions of patients at the end of main part of the trial compared to the SoC baseline were similar to those estimated for proportions of patients with mean IGF-1 ≤1×ULN only.

Similar results were seen both for the overall population and for each of the three patient groups. Overall, the estimated difference in proportions of patients at the end of main part of the trial compared to the SoC baseline was 9.7% (95% CI: 2.8%; 16.7%).

The estimated differences compared to the placebo baseline was 65.8% (95% CI: 43.7%; 87.9%) for the placebo roll-over patients.

4) Change from Baseline in IGF-1 and GH over time

IGF-1/ULN over Time and Change from SOC baseline in IGF-1/ULN

The different baseline values between "new" and "roll-over patients" reflect the different IGF-1 inclusion criteria in [HS-18-633] and [HS-19-647].

In [HS-18-633], eligible patients had to be biochemically controlled (IGF-1/ULN ≤1×ULN) at screening, while patients enrolled directly into [HS-19-647] (new patients) could have elevated IGF-1 values at screening, i.e., ≤2×ULN.

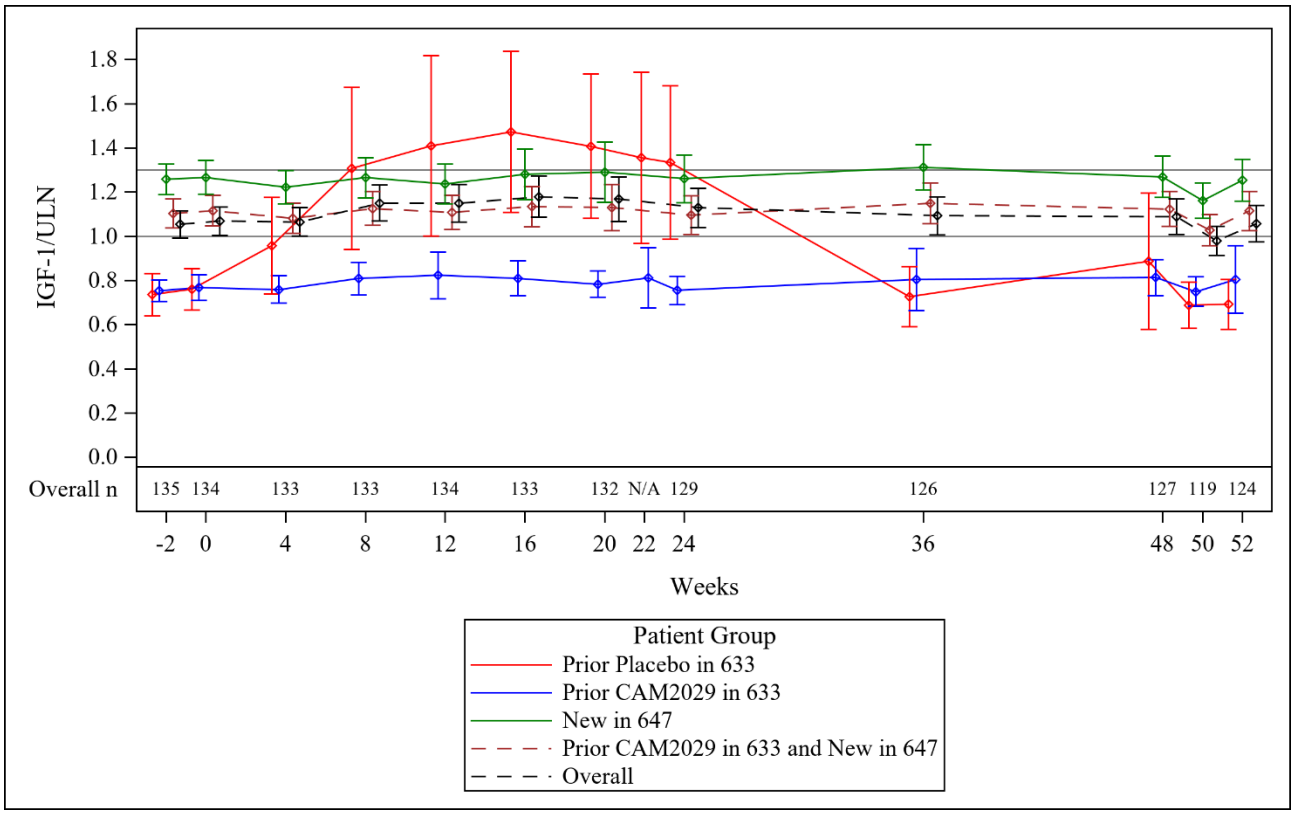
The mean IGF-1/ULN values were stable throughout the trial in both "new patients" and "CAM2029 roll-over patients", with an indication of lower IGF-1/ULN at the end of the 52-week treatment period than at the SoC baseline [HS-19-647].

Mean IGF-1/ULN values were stable throughout the trial in both new patients and CAM2029 roll-over patients, with a slight indication of lower IGF-1 values at the end of the treatment period with CAM2029 compared with the SoC baseline.

In the "placebo roll-over patients", the mean IGF-1/ULN increased markedly from 0.748 to 1.341 during the placebo period in [HS 18-633]and thereafter decreased to SoC baseline levels after treatment with CAM2029 in [HS-19-647]. The mean change in IGF 1/ULN from the placebo baseline to the end of the trial was a decrease of -0.652 (95% CI: - 0.968, -0.335) [HS 19 647].

A similar change was seen in the "pharmacologically washed-out placebo roll-over patients" [HS 19-647].

Figure 9 IGF-1/ULN values over time (mean, 95% CI) by patient group – main part (ITT analysis set)



Abbreviations: CI=confidence interval; IGF-1=insulin-like growth factor-1; ITT=intention-to-treat; n=number of patients with evaluable data at the certain visit; N/A=not applicable; ULN=upper limit of normal
ULN is based on sex and age at screening.
For Week 20 and Week 48 only the pre-dose values are displayed on the graph.
Figure includes the placebo period in HS-18-633 for patients in the Placebo roll-over group.
Figure includes data from retrieved dropouts.
Grey line represents the 1×ULN and 1.3×ULN responder limits.

GH Levels Over Time and Change from Baseline in GH Levels

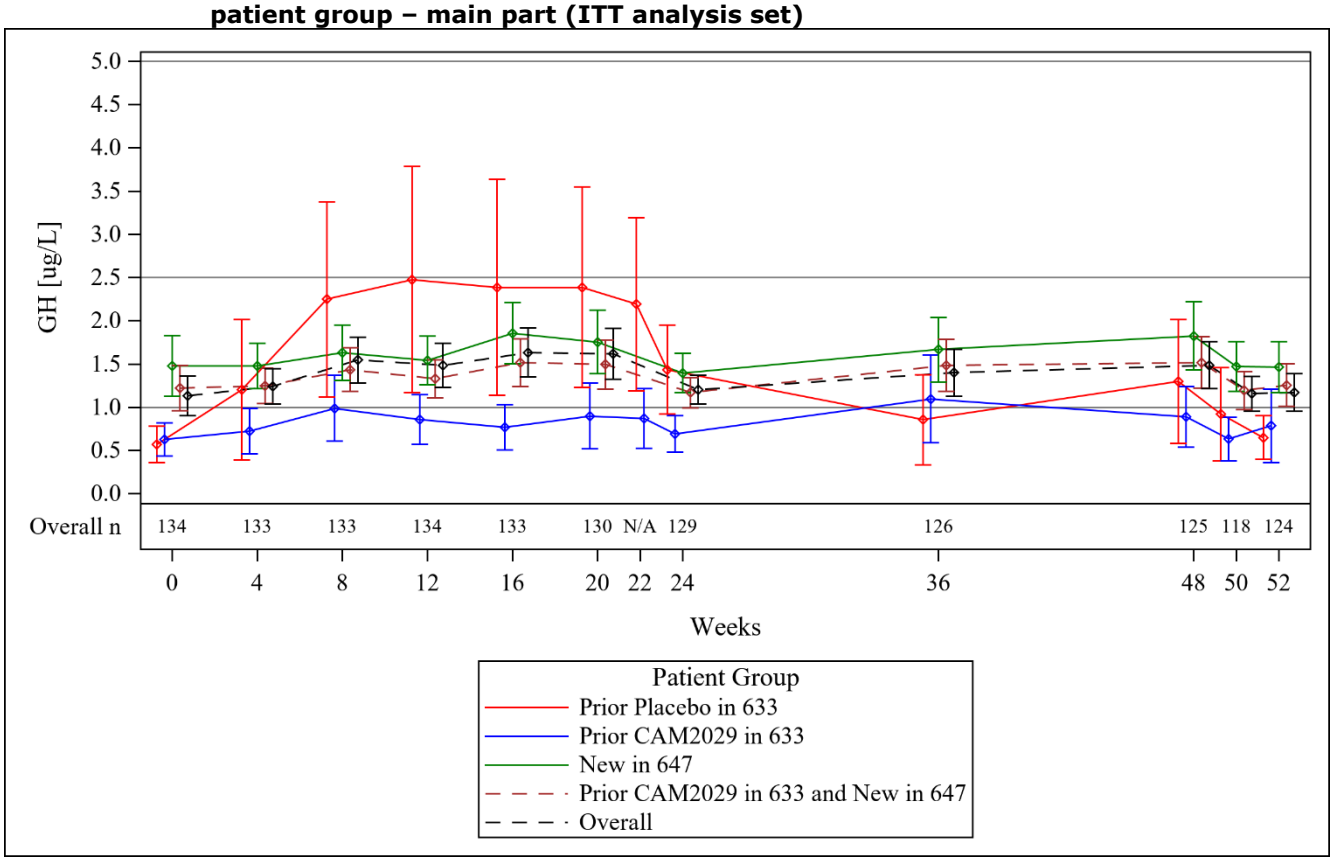
As shown in Figure , the mean GH levels (mean of 5 GH samples and single GH samples) remained stable throughout the trial in the overall population, in "new patients" (mean GH levels between 1.0 µg/L and 2.5 µg/L) and in "CAM2029 roll-over patients" (mean GH levels around and below 1.0 µg/L).

For "placebo roll-over patients", mean GH levels increased from below 1 µg/L at the SoC baseline to approximately 2.5 µg/L during the placebo period in [HS-18-633] and then returned to SoC baseline levels at week 52 after start of treatment with CAM2029 at Week 24. The same pattern was shown for the "pharmacologically washed-out roll-over placebo patients.

The changes in GH levels from the SoC baseline to Week 52 were small both in the overall population (mean of 0.0436 µg/L [95% CI: -0.1320 µg/L, 0.2193 µg/L]) and in the individual patient groups.

The only exception was the change in GH levels in "placebo roll-over patients" after start of treatment with CAM2029 at Week 24. In these patients, the observed GH levels decreased with a mean change of -0.8314 µg/L (95% CI: -1.4130 µg/L, -0.2498 µg/L) from mean of 1.4372 µg/L at Week 24 to 0.6504 µg/L at Week 52.

Figure 10 GH values (mean of 5 GH samples and single GH samples) over time (mean, 95%CI) by patient group – main part (ITT analysis set)



Abbreviations: CI=confidence interval; GH=growth hormone; ITT=intention-to-treat; n=number of patients with evaluable data at the certain visit; N/A=not applicable
The mean of 5 GH samples was assessed on Week -8, Day 1 (Week 0), Week 24 and Week 52; at all other visits single GH sample was assessed
Figure includes the placebo period in HS-18-633 for patients in the Placebo roll-over group.
Figure includes data from retrieved dropouts. Grey lines represent the 1.0 µg/L, 2.5 µg/L and 5.0 µg/L GH limits.

5) Time to loss of response

Time to loss of response was analyzed in roll-over patients who had IGF-1 ≤1×ULN at baseline.

Overall, 50 patients had IGF-1 ≤1×ULN at the SoC baseline (CAM2029 roll-over: 33 patients; Placebo roll-over: 17 patients)

Time to loss of response: IGF-1 >1×ULN

The estimated median time to loss of response from the SoC baseline was not analyzed for new patients and exceeded the trial duration for CAM2029 roll-over patients.

The median time to loss of response from the SoC baseline could not be estimated in "CAM2029 roll-over patients".

For placebo roll-over patients the estimated median time to loss of response from SoC baseline was 8.7 weeks (95% CI: 4.1, 16.1), within the 24-week placebo treatment before the first CAM2029 dose. The median time to loss of response from placebo baseline could not be estimated for placebo roll-over patients as too few of these patients had with IGF-1 ≤1×ULN at this baseline.

Time to Loss of Response: Time to IGF-1 ≥1.3×ULN

The median time to loss of response (IGF-1 ≥1.3×ULN) from the SoC baseline and from the placebo baseline could not be estimated for any of the patient groups.

6) Retention in Treatment

The treatment retention in the trial was high. Overall, 127 of the 135 patients (94.1%) were retained in treatment (i.e., had received CAM2029 at Week 48) [HS 19-647]. These 127 patients included 74 new patients (91.4%), 35 CAM2029 roll over patients (97.2%), and all 18 placebo roll over patients (100%).

7) Change from Baseline in Tumour Size

The median change from the SoC baseline to the end of the main part of the trial in tumour volume was 0 mm3 in all 3 patient groups.

The same result was seen for the change from the placebo baseline to the end of the main part of the trial.

These results suggest that tumor volume remained unchanged throughout the trial. None of the mean changes in tumour volume coincided with median changes values reflecting skewed distributions and large variations in tumour size data.

8) Clinical Signs and Symptoms of Acromegaly over Time

Overall, patients had mainly mild or moderate symptoms throughout the trial. At the SoC baseline, severe signs and symptoms were reported in the overall population as follows: joint pain in 15 patients (11.1%); headache, sweating, fatigue, and soft tissue swelling in 4 patients each (3.0%), paresthesia in 2 patients (1.5%). At the placebo baseline, severe signs and symptoms were reported for fatigue in 1 placebo roll-over patient (5.6%).

For most patients, severity of symptoms decreased or remained unchanged with time.

AIS overall scores

For the overall population, the mean (SD) AIS Overall Score was 4.3 (3.4) at the SoC baseline.

The mean change in AIS Overall Score from the SoC baseline to Week 52 was -1.2 (95% CI: -1.7, -0.6). There were significant decreases observed in "new patients" (-1.3 [95% CI: -2.1, -0.5]) and "CAM2029 roll-over patients" (-1.0 [95% CI: -1.9, -0.1]).

For "placebo roll-over patients", no notable change in AIS Overall Score from the SoC baseline to Week 52 was observed (mean: -0.9 [95% CI: -2.0, 0.2]) or the placebo baseline (mean of -0.6 [95% CI: -1.6, 0.5].

Change in proportion of patients with any clinical signs and symptoms of acromegaly

Table 31 AIS Overall Scores and change from SoC baseline to Week 52 by patient group – main part (ITT analysis set)

Visit	Statistics	Placebo roll-over (N=18)	CAM2029 roll-over (N=36)	New in 647 (N=81)	Overall (N=135)
SoC baseline	n	18	36	81	135
	Mean	3.0	4.8	4.4	4.3
	SD	2.6	3.0	3.6	3.4
Placebo baseline	n	18	-	-	-
	Mean	2.7	-	-	-
	SD	3.1	-	-	-
Week 52	n	18	33	73	124
	Mean	2.1	4.0	3.3	3.3
	SD	3.2	3.1	2.9	3.0
Change from SoC baseline to Week 52	n	18	33	73	124
	Mean	-0.9	-1.0	-1.3	-1.2
	95% CI of Mean	-2.0, 0.2	-1.9, -0.1	-2.1, -0.5	-1.7, -0.6

Abbreviations: AIS=Acromegaly Index of Severity; CI=confidence interval; ITT=intention-to-treat; n=number of patients within category; N=number of patients in the analysis set; SD=standard deviation; SoC=standard of care
The AIS Overall Score was calculated as the sum of the scores for the 6 symptoms of headache, sweating, fatigue, joint pain, paresthesia, and soft tissue swelling.
Table includes the placebo period in HS-18-633 for patients in the Placebo roll-over group.
Table includes data from retrieved dropouts.
Change from SoC baseline includes the placebo period in HS-18-633 for patients in the Placebo roll-over group.

Change in proportion of patients with any clinical signs and symptoms of acromegaly

At the SoC baseline, the estimated proportions of patients with any clinical sign or symptom were 89% in the overall population, 87.2% in "new patients", 96.7% in "CAM2029 roll-over patients" and 82.1% in "placebo roll-over patients".

The estimated proportion of patients in the overall population with any clinical signs and symptoms of acromegaly at Week 52 was lower than at the SoC baseline, with an estimated difference of - 10.9% (95% CI: -17.1 %, -4.7%).

The estimated differences in the individual patient groups were - 8.2% (95% CI: - 16.4%, 0.1%) in "new patients", -8.1% (95% CI: -17%, 0.7%) in "CAM2029 roll-over patients", and -27.2% (95% CI: -48.1%, -6.4%) in "placebo roll-over patients" and showed a tendency to decrease from the placebo baseline to Week 52 of -11.4% (95% CI: -32.3%, 9.6%). Of note, Placebo roll-over patients were treated with CAM2029 for the last 28 weeks.

Ring Size over Time

Overall, mean (SD) ring size was 65.1 (7.2) mm at the SoC baseline, ranging between 64.3 mm in "placebo roll-over patients" and 65.7 mm in "CAM2029 roll-over patients".

Changes from SoC baseline mean ring size were not significant in any of the patient groups, with a mean change from SoC baseline to Week 52 of -0.3 mm (95% CI: -1.0 mm, 0.4 mm) in the overall population.

9) Treatment Satisfaction (TSQM)

129 patients of the 130 patients who attended W24 visit completed the TSQM questionnaire at Week 24 and 126 on 127 patients who attended W52 visit completed the questionnaire at Week 52 [HS-19-647,].

In the overall population, significant increases in the TSQM scores were observed from the SoC baseline to Week 52 for the convenience, effectiveness, and global satisfaction domains [HS 19 647].

The largest improvement from SoC baseline was seen in the convenience domain score, with a mean change from SoC baseline to Week 52 of 15.38 (95% CI: 11.98, 18.77) in the overall population [HS-19-647,]. Significant increases in convenience score were shown in all three patient groups (CAM2029 roll-over patients:

17.78 [95% CI: 10.96, 24.59], placebo roll-over patients: 18.52 [95% CI: 6.79, 30.24], and new patients: 13.60 [95% CI: 9.35, 18.85]). The mean change in TSQM scores from the SoC baseline also tended to improve from Week 24 to Week 52 during which period the pre-filled pen device was available to all treatment groups. The mean convenience score improved from the last assessment using the pre-filled syringe to the last assessment while using the pre-filled pen, with apparent mean changes of 12.16 (95% CI: 7.83, 16.48) in the overall population and 11.67 (95% CI: 5.89, 17.44) in "new patients".

The effectiveness domain scores increased from SoC baseline to Week 52 in the overall population, with a mean change of 5.43 (95% CI: 2.12, 8.75). The mean increase from SoC baseline for this domain was highest in "the new patients" (mean change of 6.34 [95% CI: 1.66, 11.03]). In roll-over patients, there was a tendency for increased effectiveness scores with mean changes from SoC baseline to Week 52 of 3.33 (95% CI: -1.94, 8.60) in "CAM2029 roll-over patients" and 5.56 (95% CI: - 4.29, 15.40) in "placebo roll-over patients". The effectiveness scores also improved from the last assessment using the pre-filled syringe to the last assessment while using the pre-filled pen, with mean changes of 5.76 [2.26, 9.26] in the overall population and 6.02 [95% CI: 1.05, 10.98] in new patients. For the global satisfaction domain, the mean change from SoC baseline to Week 52 was 3.98 (95% CI: 0.78, 7.18) in the overall population, and the largest improvement was seen in the "CAM2029 roll-over patients" (mean change: 8.10 [95% CI: 1.07, 15.13]), 2.88 [95% CI: -0.80, 6.56) in new patients and 0.89 (95% CI: - 10.64, 12.43) in "placebo roll-over patients". The change in mean global satisfaction score in "placebo roll-over patients" showed a tendency for increase from the placebo baseline to Week 52 after start of CAM2029 treatment, with a mean change of 11.11 (95% CI: -0.78, 23.00). No change in global satisfaction score were seen from the assessment with the pre-filled syringe to the last assessment while using the pre-filled pen in any of the patient groups.

Overall, for the side effects domain, For the TSQM side effects domain, a tendency of improvement was seen from the SoC baseline to Week 52. Scores increased slightly from the SoC baseline to Week 24 and, then remained stable tothe end of the main part the trial, with a mean change from SoC baseline to Week 52 of 3.04 (95% CI: -0.67, 6.76). A tendency towards improved scores over time was observed in all patient groups except placebo roll-over treatments. The mean change from SoC baseline to Week 52 was 2.71 (95% CI: -2.48, 7.89) in "new patients"; 6.88 (95% CI: 0.50, 13.25) in "CAM2029 roll-over patients"; - 2.73 (95% CI: - 12.69, 7.22) in "placebo roll-over patients". The mean change in side effects scores from "placebo baseline" to Week 52 was 4.17 (95% CI: -4.02, 12.36).

There was a tendency towards improved scores over time in the side effect domain from the last assessment using the pre-filled syringe to the last assessment using the pre-filled pen in the overall population with a mean change of 3.17 (95% CI; -0.42, 6.76).

10) Patient Satisfaction Scale Scores

126 of the 130 patients who attended the site at Week 24 and 123 of the 127 patients at Week 52 had completed the patient satisfaction questionnaire.

High patient satisfaction scores were generally seen in all patient groups with mean overall scores of 3.9 (95% CI: 3.7, 4.1) at Week 24, and 4.1 (95% CI: 3.9, 4.3) at Week 52 (on a scale from 1 to 5) [HS-19-647].

The lowest observed mean patient satisfaction scale score was noted at Week 24 in placebo roll-over patients (3.4 [95% CI: 2.8, 4.0]) and the highest at Week 52 in CAM2029 roll-over patients (4.2 [95% CI: 3.9, 4.5]).

At Week 52, 87 of the 127 overall patients who had attended the visit answered that their experience with CAM2029 was 'Much better' (56 patients [41.5%]) or 'Slightly better' (31 patients [23.0%]) than with previous SoC treatment at baseline.

11) Acromegaly Quality of Life Questionnaire (AcroQoL)

The AcroQoL domain scores range from 0 to 100, where higher scores indicate better QoL.

Total scores

The AcroQoL Total Scores increased over time from the SoC baseline to Week 52 for the overall population and the CAM2029 roll-over patients. The mean increase was 2.989 (95% CI: 0.962, 5.015) in the overall population, and the largest increase was shown for the "CAM2029 roll-over patients" (mean: 6.785 [95% CI: 2.475, 11.095]) [HS-19-647]. The mean change from SoC baseline was 1.418 (95% CI: - 1.180, 4.016) in the "new patients" and 2.047 [95% CI -2.638, 6.732]) in "placebo roll-over patients"

Both the physical domain and the psychological domain scores have increased over time, in the overall population and CAM2029 roll-over patients.

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

Overall, 123 patients/partners (91.1%) stated that they were willing/opting to self-administer CAM2029. 116 of the 123 patients/partners (94.3%) opting for self-administration were declared competent by a healthcare professional to administer CAM2029.

Overall, 95 of the enrolled patients (70.4%) and caregivers of 18 patients (13.3%) administered CAM2029 themselves at least once during the trial.

The changes from pre-treatment to post-treatment in the domains 'feelings about injections' and 'self confidence' indicated improvements.

Few patients and partners had problems while performing the injections during the trial. All patients with reported problems while injecting were able to administer CAM2029.

Subgroup analyses

A subgroup of the ITT analysis set was defined, which consisted of "placebo roll-over patients" who completed treatment with CAM2029 in [HS-18-633] i.e., without being switched to SoC due to lack of efficacy. This subgroup analyses were exploratory. These patients were regarded as "pharmacologically washed-out placebo roll-over", and their IGF-1 and GH responses were evaluated separately.

The mean IGF-1/ULN in the "pharmacologically washed-out placebo roll-over patients" increased markedly during the 24-week placebo treatment period in [HS-18-633], from 0.733 at the SoC baseline to 1.353 at placebo baseline.

After start of treatment with CAM2029 at Week 24, the mean IGF-1/ULN decreased back to SoC baseline levels at the end of the main part of the trial (mean of Week 50 and Week 52: 0.068). The mean change from the SoC baseline was -0.065 (95% CI: -0.124, -0.006) and the mean change from the placebo baseline was -0.686 (95% CI: -1.014, -0.357).

Table 31 Mean IGF-1/ULN in pharmacologically washed-out placebo roll-over patients by previous treatment – main part (ITT analysis set)

		Placebo roll-over		
Visit	Statistics	Oct LAR (N=10)	Lan ATG (N=7)	Overall (N=17)
SoC baseline	n	10	7	17
	Mean	0.728	0.740	0.733
	SD	0.167	0.203	0.176
Placebo baseline	n	10	7	17
	Mean	1.489	1.160	1.353
	SD	0.838	0.548	0.732
Mean of Week 50 and Week 52	n	10	7	17
	Mean	0.674	0.660	0.668
	SD	0.202	0.165	0.182

Abbreviations: CI=confidence interval; IGF-1=insulin-like growth factor-1; ITT=intention-to-treat; Lan ATG=lanreotide autogel; n=number of patients within category; N=number of patients in the analysis set; Oct LAR=octreotide long-acting repeatable; SD=standard deviation; SoC=standard of care; ULN=upper limit of normal
ULN is based on sex and age at screening.
Table includes data from retrieved dropouts.
Table includes the placebo period in HS-18-633 for patients in the Placebo roll-over group.
The SoC baseline was calculated as the mean of Week -2 and Day 1 measurements.
The placebo baseline for placebo roll-over patients was calculated as the mean of values at Week 22 and Week 24 measurements.

Table 32 Change from baseline in IGF-1/ULN in pharmacologically washed-out placebo roll-over patients by previous treatment – main part (ITT analysis set)

		Placebo roll-over		
Visit	Statistics	Oct LAR (N=10)	Lan ATG (N=7)	Overall (N=17)
Change from SoC baseline to mean of Week 50 and Week 52	n	10	7	17
	Mean	-0.054	-0.080	-0.065
	95% CI of Mean	-0.140, 0.032	-0.186, 0.026	-0.124, -0.006
Change from placebo baseline (Placebo) to mean of Week 50 and Week 52	n	10	7	17
	Mean	-0.815	-0.501	-0.686
	95% CI of Mean	-1.344, -0.286	-0.916, -0.085	-1.014, -0.357

Abbreviations: CI=confidence interval; IGF-1=insulin-like growth factor-1; ITT=intention-to-treat; Lan ATG=lanreotide autogel; n=number of patients within category; N=number of patients in the analysis set; Oct LAR=octreotide long-acting repeatable; SoC=standard of care; ULN=upper limit of normal
ULN was based on sex and age at screening.
Table includes data from retrieved dropouts.
Change from the SoC baseline includes the placebo period in HS-18-633 for patients in the Placebo roll-over group.
The SoC baseline was calculated as the mean of Week -2 and Day 1 measurements.
The placebo baseline for placebo roll-over patients was calculated as the mean of values at Week 22 and Week 24 measurements.

- **Ancillary analyses**

No ancillary analysis was performed in this study.

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).

Table 33 Summary of efficacy for trial HS-18-633

Title: A Phase 3, randomized, double-blind, placebo-controlled, multi-center trial to assess efficacy and safety of octreotide subcutaneous depot (CAM2029) in patients with acromegaly			
Study identifier	HS-18-633 2019-001191-11 NCT04076462		
Design	Phase 3, randomized, double-blind, placebo-controlled, multi-centre trial assessing the efficacy and safety of CAM2029 in patients treated with octreotide long-acting repeatable (LAR) or lanreotide autogel (ATG) at time of enrolment.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		24 weeks Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	CAM2029		Octreotide subcutaneous depot (solution for injection in a ready-to-use pre-filled syringe), 20 mg (1.0 mL). 24 weeks (6 injections). 48 patients randomized
	Placebo		Placebo, 1.0 mL. 24 weeks (6 injections). 24 patients randomized
Endpoints and definitions	Primary endpoint	% of patients with mean IGF-1 ≤1×ULN (primary)	Proportion of patients with mean insulin-like growth factor-1 (IGF-1) ≤1×upper limit of normal (ULN) at Week 22 and Week 24 (average of the two measurements)
	Key secondary efficacy endpoint I	% of patients with mean IGF-1 ≤1×ULN (incl. dose reductions)	Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24, including patients who had their dose decreased to 10 mg CAM2029 (or 0.5 mL placebo)
	Key secondary efficacy endpoint II	% of patients with mean IGF-1 ≤1×ULN and GH <2.5 µg/L	Proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 and mean growth hormone (GH) <2.5 µg/L at Week 24
Database lock	05-Jun-2023		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	The intention-to-treat (ITT) analysis set, which included all patients randomized to a treatment arm Time point: Week 24		
	Treatment group	CAM2029	Placebo

Descriptive statistics and estimate variability	Number of subjects	48	24
	% of patients with mean IGF-1 ≤1×ULN (primary) (mean number of responders/number of patients in the analysis (%))	34.7/48 (72.2)	9.0/24 (37.5)
Effect estimate per comparison	Primary endpoint: % of patients with mean IGF-1 ≤1×ULN (primary)	Comparison groups	CAM2029–Placebo
		Difference in Proportions [%] (Mantel-Haenszel-type common difference in proportions across strata, stratified by prior treatment [octreotide LAR or lanreotide ATG])	34.6
		95% CI	11.3, 57.9
		P-value (Upper-tailed p-value of the common risk difference test using Mantel-Haenszel stratum weights (octreotide LAR or lanreotide ATG). The significance level was 0.025)	0.0018
Notes	Seven patients (CAM2029: 5; placebo: 2) had intercurrent events during the trial. These patients were set to non-responders in the primary efficacy analysis. Six of the 7 patients with intercurrent events continued in the trial: 5 patients discontinued treatment due to adverse drug reactions and 1 patient (placebo) switched to rescue medication with standard of care. One patient in the CAM2029 treatment arm was withdrawn after the first dose of investigational medicinal product (IMP). One patient who was randomized but never treated with IMP was not defined as having an intercurrent event, as these were defined as events occurring after a patient received treatment with the IMP. This patient was imputed under missing at random in the analysis of the primary efficacy endpoint.		
Analysis description	Key Secondary analysis I and II:		
Analysis population and time point description	The ITT analysis set, which included all patients randomized to a treatment arm Time point: Week 24		
	Treatment group	CAM2029	Placebo
	Number of subjects	48	24

Descriptive statistics and estimate variability	Key secondary endpoint I: % of patients with mean IGF-1 ≤1×ULN (incl. dose reductions) (mean number of responders/number of patients in the analysis (%))	34.7/48 (72.2)	9.0/24 (37.5)
	Key secondary endpoint II: % of patients with mean IGF-1 ≤1×ULN and GH <2.5 µg/L (mean number of responders/number of patients in the analysis (%))	33.6/48 (70.0)	9.0/24 (37.5)
Effect estimate per	Key secondary endpoint I:	Comparison groups	CAM2029–Placebo
		Difference in Proportions [%] (Mantel-Haenszel-type common difference in proportions across strata, stratified by prior treatment (octreotide LAR or lanreotide ATG)	34.6
		95% CI	11.3, 57.9
		P-value (Upper-tailed p-value of the common risk difference test using Mantel-Haenszel stratum weights (octreotide LAR or lanreotide ATG). The significance level was 0.025)	0.0018
	Key secondary endpoint II: % of patients with mean IGF-1 ≤1×ULN and GH <2.5 µg/L	Comparison groups	CAM2029-Placebo
		Difference in Proportions [%] (Mantel-Haenszel-type common difference in proportions across strata, stratified by prior treatment (octreotide LAR or lanreotide ATG)	32.3
		95% CI	8.8, 55.7
		P-value (Upper-tailed p-value of the common risk difference test using Mantel-Haenszel stratum weights (octreotide LAR or lanreotide ATG). The significance level was 0.025)	0.0035
Notes	The key secondary endpoints were analysed in a similar way as the primary endpoint.		

Table 34 Summary of efficacy for trial HS-19-647

Title: A Phase 3, open-label, single arm, multi-center trial to assess the long-term safety of octreotide subcutaneous depot (CAM2029) in patients with acromegaly			
Study identifier	HS-19-647 2019-002190-66 NCT04125836		
Design	Phase 3, open-label, single-arm, multi-centre trial assessing the long-term safety and efficacy of CAM2029 in patients treated with octreotide LAR or lanreotide ATG at time of enrolment. Enrolled patients included: new patients and patients rolling over from the Phase 3 trial HS-18-633 (see Table 1). All 3 patient groups received the same trial treatment with CAM2029. New patients were enrolled directly in HS-19-647 and received their first CAM2029 dose on Day 1 in the trial. Roll-over patients received their first CAM2029 dose in HS-19-647 at Week 24. For roll-overs previously treated with CAM2029 in HS-18-633, the first dose in HS-19-647 was their 7th dose of CAM2029. For roll-overs who received placebo in HS-18-633, the first dose in HS-19-647 was their 1st dose of CAM2029.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		52 weeks Not applicable 52 weeks
Hypothesis	Not applicable (N/A)		
Treatments groups	Overall		CAM2029 (in a ready-to-use pre-filled syringe or pre-filled pen), 20 mg (1.0 mL). 52 weeks (13 injections). 135 patients enrolled
	New patients		CAM2029 (in a ready-to-use pre-filled syringe or pre-filled pen), 20 mg (1.0 mL). 52 weeks (13 injections). 81 patients enrolled
	CAM2029 roll-overs		CAM2029 (in a ready-to-use pre-filled syringe or pre-filled pen), 20 mg (1.0 mL). 28 weeks (7 injections). 36 patients enrolled
	Placebo roll-overs		CAM2029 (in a ready-to-use pre-filled syringe or pre-filled pen), 20 mg (1.0 mL). 28 weeks (7 injections). 18 patients enrolled
Endpoints and definitions	Primary endpoint	N/A	N/A (safety is the primary endpoint)

	Main secondary efficacy endpoint	% of patients with mean IGF-1 ≤1×ULN	Proportion of patients with mean IGF-1 ≤1×ULN at SoC baseline, at placebo baseline and at Week 50 and Week 52 (average of the two measurements) Definitions: SoC baseline: the baseline on SoC before receiving the first IMP dose in HS-18-633 for roll-over patients and before receiving the first CAM2029 dose in HS-19-647 for new patients. Placebo baseline: the baseline before receiving the first CAM2029 dose in HS-19-647 for placebo roll-overs. Biochemical response based on IGF-1 (main efficacy analysis) was defined as mean IGF-1 ≤1×ULN at Week 50 and Week 52 (average of the two measurements, adjusted for age and sex at screening).
Database lock/ date of completion	30 April 2024		
Results and Analysis			
Analysis description	Main Secondary Analysis		
Analysis population and time point description	The ITT analysis set, which included all patients treated with CAM2029 in HS-19-647 (N=135) Time points: SoC baseline, placebo baseline, Week 50/52		

Descriptive statistics and estimate variability	Treatment group	Overall	New patients	CAM2029 roll-overs	Placebo roll-overs
	Number of subjects	135	81	36	18
	% of patients with mean IGF-1 ≤1×ULN (number of patients with biochemical response /number of patients with available IGF-1 data at the time point (%))	At SoC baseline: 62/135 (45.9) At Week 50/52: mean 75/127 (59.1)	At SoC baseline: 12/81 (14.8) At Week 50/52: mean 27/74 (36.5)	At SoC baseline: 33/36 (91.7) At Week 50/52: mean 31/35 (88.6)	At SoC baseline: 17/18 (94.4) At placebo baseline: 5/18 (27.8) At Week 50/52: mean 17/18 (94.4)

Effect estimate per comparison	Main secondary endpoint: % of patients with mean IGF-1 ≤1×ULN	Comparison groups	Overall

number of patients with biochemical response/number of patients with available IGF-1 data at Week 50/52 (%) (95% CI of % [by the Clopper-Pearson method])	At SoC baseline: 59/127 (46.5) (37.6, 55.5) At Week 50/52: 75/127 (59.1) (50.0, 67.7)
Comparison groups	New patients
number of patients with biochemical response/number of patients with available IGF-1 data at Week 50/52 (%) (95% CI of % [by the Clopper-Pearson method])	At SoC baseline: 10/74 (13.5) (6.7, 23.5) At Week 50/52: 27/74 (36.5) (25.6, 48.5)
Comparison groups	CAM2029 roll-overs
number of patients with biochemical response/number of patients with available IGF-1 data at Week 50/52 (%) (95% CI of % [by the Clopper-Pearson method])	At SoC baseline: 32/35 (91.4) 76.9, 98.2 At Week 50/52: 31/35 (88.6) (73.3, 96.8) 71.8, 97.7
Comparison groups	Placebo roll-overs
number of patients with biochemical response/number of patients with available IGF-1 data at Week 50/52 (%) (95% CI of % [by the Clopper-Pearson method])	At SoC baseline: 17/18 (94.4) 72.7, 99.9 At placebo baseline: 5/18 (27.8) (9.7, 53.5) At Week 50/52: 17/18 (94.4) 72.7, 99.9

Notes	In the analysis the proportions of responders were calculated based on the observed IGF-1 values at Week 50 and/or Week 52 (average of the two measurements). If one of the IGF-1 values at Week 50 or Week 52 was missing, the other value was used to define responders/non-responders in the analysis. No imputations were made. Data from retrieved dropouts (i.e., following switch to SoC or dose reduction) were included in the evaluation of the efficacy endpoint in this i analysis. There were 3 retrieved dropouts, which included 2 patients who discontinued CAM2029 treatment due to related AEs and were switched to SoC, and 1 patient who had the CAM2029 dose reduced during the trial.

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

Of note, these analyses were performed with the data of the interim analysis on 23 May 2023 and were not modified as not provided by the applicant.

Table 35 Comparison of patient populations and exposure across trials providing efficacy data

Trial	HS-12-455	HS-18-633	HS-19-647[a]
Population	Patients with acromegaly treated with a stable dose of octreotide LAR (10, 20 or 30 mg) for at least 2 months before screening[b]	Patients with acromegaly treated with a stable dose of octreotide LAR (10, 20, 30 or 40 mg) or lanreotide ATG (60, 90 or 120 mg) for at least 3 months before screening, and having IGF-1 ≤1×ULN (average of the assessments at screening and Week -2)	**Main Part:** New patients with acromegaly treated with a stable dose of octreotide LAR (10, 20, 30 or 40 mg) or lanreotide ATG (60, 90 or 120 mg) for at least 3 months before screening. Having either IGF-1 >1×ULN and ≤2.0×ULN (average of the assessments at screening and Week -2) with or without prior radiotherapy, or IGF-1 ≤1×ULN at screening with prior pituitary radiotherapy at least 3 years before screening and confirmed disease activity (IGF-1 >1×ULN) during the period from 3 to 9 months before screening[c] Roll-over patients from the CAM2029 and placebo treatment arms in HS-18-633 **Extension Part:** Patients continuing directly from the main part or re-invited patients who previously completed HS-19-647
Duration of CAM2029 treatment	3 months	24 weeks	**Main Part:** -New patients: 52 weeks -Roll-over patients: 28 weeks **Extension Part:** 52 weeks

Trial	HS-12-455	HS-18-633	HS-19-647[a]
Number of patients exposed to at least 1 dose of IMP	7	Total: 71 -CAM2029: 47 -Placebo: 24	**Main Part:** Total: 135 -New patients: 81 -CAM2029 roll-over patients: 36 -Placebo roll-over patients: 18 **Extension Part:** Total: 6 -New patients: 2 -CAM2029 roll-over patients: 3 -Placebo roll-over patients: 1
Number of patients included in the efficacy analyses	5	Total: 72[d] -CAM2029: 48 -Placebo: 24	**Main Part:** Total: 135 -New patients: 81 -CAM2029 roll-over patients: 36 -Placebo roll-over patients: 18 **Extension Part:** Total: 6 -New patients: 2 -CAM2029 roll-over patients: 3 -Placebo roll-over patients: 1
Number of patients discontinuing treatment with IMP (without withdrawing from trial) and reason for discontinuation (trial day)	0	Total: 6 (8.3%): CAM2029: 4 -4 due to AEs (Days 33, 79, 89, and 97) Placebo: 2 -1 due to AE (Day 86) -1 due to switch to rescue medication (Day 110)	**Main Part:** Total: 2 (1.5%) New patients: 2 -2 due to AEs (Days 30 and 59) **Extension Part:** Total: 0
Number of patients withdrawn from trial and reason for withdrawal (trial day)	0	Total: 2 (2.8%): CAM2029: 2 -1 due to withdrawal of consent before IMP administration (trial day N/A) -1 due to withdrawal of consent (Day 43)	**Main Part:** Total: 7 (5.2%) (whereof 2 completed treatment with IMP) New patients: 6 -5 due to withdrawal of consent (Days 106, 118, 167, 195, and 370) -1 due to inability to follow trial requirements and procedures – SAE (Day 350) CAM2029 roll-over patients: 1 -1 due to inability to follow trial requirements and procedures – not willing to come to site for fear of infection with COVID-19 (Day 382/213) **Extension Part:** Total: 0

Trial	HS-12-455	HS-18-633	HS-19-647[a]
Number of patients completing the trial	7 (100%)	Total: 70 (97.2%)	**Main Part:** Total: 103 (76.3%)[e] -New patients: 60 -CAM2029 roll-over patients: 28 -Placebo roll-over patients: 15 **Extension Part:** Total: 0[f]

ATG: autogel; IGF-1: insulin-like growth factor-1; IMP: investigational medicinal product; LAR: long-acting repeatable; N/A: not applicable; SAE: serious adverse event; ULN: upper limit of normal

[a] Data for HS-19-647 represent data at the time of data cut-off for the interim analysis

[b] The trial also enrolled 5 patients with neuroendocrine tumours

[c] From Protocol Amendment 4, patients with IGF-1 ≤1×ULN and without radiotherapy were also allowed to be enrolled, however, only 2 patients who fulfilled this criterion were enrolled

[d] 1 patient was randomised to CAM2029 and included in the intention-to-treat analysis set (and the efficacy analyses), but withdrew from the trial before being exposed to IMP

[e] 25 patients were still ongoing in the main part of the trial at the time of data cut-off for the interim analysis

[f] All patients were still ongoing in the extension part of the trial at the time of data cut-off for the interim analysis

Table 36 Comparison of demographic characteristics across trials in patients with acromegaly by trial and treatment arm/patient group (ITT/PK analysis sets)

Parameter	Category/Statistics	HS-12-455 (N=5)	HS-18-633		HS-19-647			Phase 3 Trials[a] (N=153)	Total[a] (N=158)
			CAM2029 (N=48)	Placebo (N=24)	New patients (N=81)	CAM2029 roll-over patients (N=36)	Placebo roll-over patients (N=18)		
Age (years)	n	5	48	24	81	36	18	153	158
	Mean (SD)	59.0 (10.8)	57.0 (11.2)	52.0 (15.1)	51.8 (11.4)	56.6 (10.5)	50.3 (15.4)	53.5 (12.2)	53.7 (12.1)
	Median	62.0	59.0	52.5	53.0	57.5	51.0	54.0	55.5
	Range	42; 70	29; 79	20; 82	25; 81	35; 79	20; 82	20; 82	20; 82
Age (years) grouped categories, n (%)	18-64 years	3 (60.0)	34 (70.8)	19 (79.2)	72 (88.9)	27 (75.0)	15 (83.3)	125 (81.7)	128 (81.0)
	≥65 years	2 (40.0)	14 (29.2)	5 (20.8)	9 (11.1)	9 (25.0)	3 (16.7)	28 (18.3)	30 (19.0)
Sex, n (%)	Female	2 (40.0)	28 (58.3)	12 (50.0)	48 (59.3)	18 (50.0)	10 (55.6)	88 (57.5)	90 (57.0)
	Male	3 (60.0)	20 (41.7)	12 (50.0)	33 (40.7)	18 (50.0)	8 (44.4)	65 (42.5)	68 (43.0)
Race, n (%)	Asian	0 (0.0)	2 (4.2)	0 (0.0)	3 (3.7)	2 (5.6)	0 (0.0)	5 (3.3)	5 (3.2)
	Black or African American	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (0.7)	1 (0.6)
	White	3 (60.0)	45 (93.8)	24 (100.0)	78 (96.3)	33 (91.7)	18 (100.0)	147 (96.1)	150 (94.9)
	Not reported	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
Weight (kg)	n	5	47	24	81	36	18	152	157
	Mean (SD)	83.2 (11.3)	85.1 (17.6)	87.1 (17.3)	87.6 (17.7)	85.4 (17.5)	88.2 (19.8)	86.7 (17.5)	86.6 (17.4)
	Median	83.0	82.0	85.1	85.2	83.7	85.3	84.6	84.2
	Range	67; 96	59; 140	55; 127	54; 143	59; 140	55; 127	54; 143	54; 143
BMI (kg/m^2)	n	5	47	24	81	36	18	152	157
	Mean (SD)	28.3 (4.4)	30.1 (5.6)	29.7 (5.8)	29.9 (4.7)	30.1 (5.6)	30.0 (6.5)	29.9 (5.1)	29.8 (5.1)
	Median	27.3	29.1	27.0	29.3	30.0	26.3	29.0	28.8
	Range	25; 36	22; 51	22; 40	21; 46	22; 51	22; 40	21; 51	21; 51

BMI: body mass index; ITT: intention-to-treat; PK: pharmacokinetic; SD: standard deviation

a Roll-over patients who participated in both HS-18-633 and HS-19-647 (i.e., the CAM2029 roll-over patients and the placebo roll-over patients) are counted only once in the 'Phase 3 Trials' and 'Total' columns

Table 37 Disease history and other background characteristics across trials in patients with acromegaly by trial and treatment arm/patient group (ITT/PK analysis sets)

Parameter	Category/Statistics	HS-12-455 (N=5)	HS-18-633		HS-19-647			Phase 3 Trials[a] (N=153)	Total[a] (N=158)
			CAM2029 (N=48)	Placebo (N=24)	New patients (N=81)	CAM2029 roll-over patients (N=36)	Placebo roll-over patients (N=18)		
Geographical region, n (%)	Europe	5 (100.0)	44 (91.7)	20 (83.3)	75 (92.6)	33 (91.7)	14 (77.8)	139 (90.8)	144 (91.1)
	US	0 (0.0)	4 (8.3)	4 (16.7)	6 (7.4)	3 (8.3)	4 (22.2)	14 (9.2)	14 (8.9)
Time since diagnosis (years)	n	5	47	24	81	36	18	152	157
	Mean (SD)	10.5 (10.9)	10.8 (6.8)	13.0 (10.7)	10.8 (7.4)	11.1 (7.2)	12.3 (10.9)	11.1 (7.8)	11.1 (7.9)
	Median	5.8	10.2	11.3	8.5	9.7	9.0	9.9	9.8
	Range	1; 27	2; 32	2; 37	1; 28	2; 32	2; 37	1; 37	1; 37
Time since diagnosis, n (%)	<10 years	3 (60.0)	23 (47.9)	11 (45.8)	42 (51.9)	19 (52.8)	9 (50.0)	76 (49.7)	79 (50.0)
	10 to <20 years	1 (20.0)	19 (39.6)	9 (37.5)	26 (32.1)	12 (33.3)	6 (33.3)	54 (35.3)	55 (34.8)
	≥20 years	1 (20.0)	5 (10.4)	4 (16.7)	13 (16.0)	5 (13.9)	3 (16.7)	22 (14.4)	23 (14.6)
Previous pituitary surgery, n (%)	Yes	2 (40.0)[b]	42 (87.5)	21 (87.5)	70 (86.4)	32 (88.9)	17 (94.4)	133 (86.9)	135 (85.4)
	No	0 (0.0)	6 (12.5)	3 (12.5)	11 (13.6)	4 (11.1)	1 (5.6)	20 (13.1)	20 (12.7)
	Not recorded	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)
Previous pituitary irradiation, n (%)	Yes	0 (0.0)	1 (2.1)[c]	1 (4.2)[c]	12 (14.8)	1 (2.8)	1 (5.6)	14 (9.2)	14 (8.9)
	No	0 (0.0)	0 (0.0)	0 (0.0)	69 (85.2)	0 (0.0)	0 (0.0)	69 (45.1)	69 (43.7)
	Not recorded	5 (100.0)[b]	47 (97.9)	23 (95.8)	0 (0.0)	35 (97.2)	17 (94.4)	70 (45.8)	75 (47.5)
Treatment at trial start, n (%)	Octreotide LAR	5 (100.0)	25 (52.1)	14 (58.3)	59 (72.8)	18 (50.0)	11 (61.1)	98 (64.1)	103 (65.2)
	Lanreotide ATG	0 (0.0)	23 (47.9)	10 (41.7)	22 (27.2)	18 (50.0)	7 (38.9)	55 (35.9)	55 (34.8)

ATG: autogel; ITT: intention-to-treat; LAR: long-acting repeatable; PK: pharmacokinetic; SD: standard deviation; US: United States

a Roll-over patients who participated in both HS-18-633 and HS-19-647 (i.e., the CAM2029 roll-over patients and the placebo roll-over patients) are counted only once in the 'Phase 3 Trials' and 'Total' columns

b There was no standardised collection of prior pituitary surgery or prior pituitary irradiation in HS-12-455, but 2 patients had prior pituitary surgery based on their medical history. No patients had prior pituitary irradiation based on their medical history

c Two patients in HS-18-633 were enrolled despite having prior pituitary irradiation (which was an exclusion criterion in the trial). These patients are discussed in HS-18-6

Table 38 Overall efficacy results based on IGF-1 and GH over time in [HS-18-633] and [HS 19-647] (ITT analysis sets)

		N		SoC Baseline[a] (Day 1)	Week 22/24 or Week 24[b]	Week 50/52[c] (HS-19-647)
IGF-1/ULN						
HS-18-633	CAM2029	48	Mean (SD)	0.760 (0.150)	0.798 (0.261)	N/A
	Placebo	24	Mean (SD)	0.775 (0.179)	1.235 (0.700)	N/A
HS-19-647	CAM2029 RO	36	Mean (SD)	0.759 (0.144)	0.756 (0.188)	0.729 (0.181)
	Placebo RO	18	Mean (SD)	0.748 (0.183)	1.341 (0.712)[d]	0.700 (0.168)
	New Patients	81	Mean (SD)	1.263 (0.289)	1.285 (0.476)	1.233 (0.367)
IGF-1 ≤1×ULN						
HS-18-633	CAM2029	48	n (%)	44 (91.7)	34 (70.8)	N/A
	Placebo	24	n (%)	22 (91.7)	9 (37.5)	N/A
HS-19-647	CAM2029 RO	36	n/N_{all} (%)	33/36 (91.7)	31/36 (86.1)	25/28 (89.3)
	Placebo RO	18	n/N_{all} (%)	17/18 (94.4)	5/18 (27.8)[d]	15/15 (100)
	New Patients	81	n/N_{all} (%)	12/81 (14.8)	23/69 (33.3)	20/60 (33.3)
GH (µg/L)						
HS-18-633	CAM2029	48	Mean (SD)	0.6188 (0.5262)	0.8011 (0.6535)	N/A
	Placebo	24	Mean (SD)	0.6534 (0.6700)	1.2853 (0.9956)	N/A
HS-19-647	CAM2029 RO	36	Mean (SD)	0.6222 (0.5517)	0.6930 (0.6288)	0.7623 (1.2779)
	Placebo RO	18	Mean (SD)	0.5696 (0.4420)	1.4372 (1.0333)[d]	0.6226 (0.5349)
	New Patients	81	Mean (SD)	1.4766 (1.5928)	1.3587 (0.9620)	1.4485 (1.2643)
GH <1.0 µg/L						
HS-18-633	CAM2029	48	n (%)	40 (83.3)	28 (58.3)	N/A
	Placebo	24	n (%)	19 (79.2)	9 (37.5)	N/A
HS-19-647	CAM2029 RO	36	n/N_{all} (%)	30/35 (85.7)	27/36 (75.0)	21/26 (80.8)
	Placebo RO	18	n/N_{all} (%)	14/18 (77.8)	6/18 (33.3)[d]	11/14 (78.6)
	New Patients	81	n/N_{all} (%)	40/81 (49.4)	30/69 (43.5)	27/60 (45.0)
GH <2.5 µg/L						
HS-18-633	CAM2029	48	n (%)	46 (95.8)	41 (85.4)	N/A
	Placebo	24	n (%)	23 (95.8)	20 (83.3)	N/A
HS-19-647	CAM2029 RO	36	n/N_{all} (%)	35/35 (100)	35/36 (97.2)	25/26 (96.2)
	Placebo RO	18	n/N_{all} (%)	18/18 (100)	16/18 (88.9)[d]	14/14 (100)
	New Patients	81	n/N_{all} (%)	67/81 (82.7)	63/69 (91.3)	51/60 (85.0)

GH: growth hormone: IGF-1: insulin-like growth factor-1; ITT: intention-to-treat; N: number of patients in the analysis set; n: number of responders; N_{all}: number of patients with available value at certain visit; N/A: not applicable; RO: roll-over patients

a Mean of Week -2 and pre-dose Day 1 for IGF-1 and mean values on Day 1 (pre-dose) for GH (or mean values at screening in HS-19-647 if the Day 1 value was missing)

b Mean of Week 22 and Week 24 for IGF-1 in HS-18-633 and placebo roll-over patients in HS-19-647, values at Week 24 for IGF-1 in new patients and CAM2029 roll-over patients in HS-19-647, and mean values at Week 24 for GH for patients in both trials.

c Mean of Week 50 and Week 52 for IGF-1 and mean values at Week 52 for GH.

d Placebo baseline for placebo roll-over patients in HS-19-647.

HS-18-633: Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing also for other reasons.

HS-19-647: The table includes data from all patients with data at the specific visit. Data from retrieved dropouts were included.

Table 39 Summary of AcroQoL and TSQM results over time in HS-18-633 and HS-19-647 (ITT analysis sets)

			SoC Baseline (Day 1)		Change from SoC Baseline to Week 24		Change from SoC Baseline to Week 52		Placebo Baseline (Week 24)		Change from Placebo Baseline to Week 52	
		N	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Acro QoL Total Score												
HS-18-633	CAM2029	48	48	62.689 (57.317, 68.062)	42	5.005 (1.127, 8.884)		N/A		N/A		N/A
	Placebo	24	24	63.039 (55.898, 70.180)	21	2.306 (-1.148, 5.760)		N/A		N/A		N/A
HS-19-647	CAM2029 RO	36	36	61.869 (55.282, 68.455)	36	4.672 (0.351, 8.992)	28	7.914 (3.377, 12.451)		N/A		N/A
	Placebo RO	18	18	60.378 (51.423, 69.333)	17	1.779 (-1.495, 5.054)	14	0.050 (-5.025, 5.126)	18	62.500 (52.209, 72.791)	15	-1.515 (-5.080, 2.050)
	New Patients	81	81	65.516 (61.122, 69.909)	68	0.168 (-2.618, 2.954)	58	2.192 (-0.611, 4.994)		N/A		N/A
	Overall	135	135	63.858 (60.539, 67.177)	121	1.734 (-0.325, 3.794)	100	3.494 (1.311, 5.677)		N/A		N/A
Acro QoL Physical Domain Score												
HS-18-633	CAM2029	48	48	57.747 (52.290, 63.205)	42	4.985 (0.292, 9.678)		N/A		N/A		N/A
	Placebo	24	24	61.849 (54.425, 69.273)	21	-1.190 (-4.830, 2.449)		N/A		N/A		N/A
HS-19-647	CAM2029 RO	36	36	58.160 (51.719, 64.600)	36	4.427 (-0.637, 9.491)	28	6.585 (1.612, 11.557)		N/A		N/A
	Placebo RO	18	18	59.201 (50.339, 68.064)	17	-1.287 (-4.927, 2.353)	14	-1.563 (-7.640, 4.515)	18	57.639 (48.220, 67.057)	15	0.625 (-3.724, 4.974)
	New Patients	81	81	64.275 (59.744, 68.806)	68	-2.390 (-5.620, 0.841)	58	0.539 (-2.536, 3.614)		N/A		N/A
	Overall	135	135	61.968 (58.590, 65.345)	121	-0.207 (-2.627, 2.214)	100	1.938 (-0.469, 4.344)		N/A		N/A
Acro QoL Psychological Domain Total Score												
HS-18-633	CAM2029	48	48	65.513 (59.745, 71.282)	42	5.017 (1.191, 8.843)		N/A		N/A		N/A
	Placebo	24	24	63.725 (55.705, 71.745)	21	4.297 (0.081, 8.514)		N/A		N/A		N/A
HS-19-647	CAM2029 RO	36	36	63.988 (56.857, 71.119)	36	4.812 (0.450, 9.173)	28	8.673 (3.771, 13.576)		N/A		N/A
	Placebo RO	18	18	61.058 (50.660, 71.455)	17	3.523 (-0.701, 7.747)	14	0.962 (-4.365, 6.288)	18	65.278 (53.872, 76.683)	15	-2.738 (-6.510, 1.034)
	New Patients	81	81	66.224 (61.539, 70.910)	68	1.630 (-1.420, 4.680)	58	3.138 (-0.056, 6.332)		N/A		N/A
	Overall	135	135	64.939 (61.357, 68.521)	121	2.843 (0.652, 5.034)	100	4.383 (1.974, 6.793)		N/A		N/A
TSQM Convenience Score												
HS-18-633	CAM2029	48	43	57.88 (53.03, 62.73)	37	14.71 (9.19, 20.24)		N/A		N/A		N/A
	Placebo	24	20	61.11 (51.09, 71.13)	20	8.06 (-1.76, 17.87)		N/A		N/A		N/A
HS-19-647	CAM2029 RO	36	31	59.14 (52.95, 65.33)	31	15.59 (9.25, 21.94)	24	18.06 (11.34, 24.77)		N/A		N/A
	Placebo RO	18	15	58.52 (45.17, 71.87)	15	13.33 (1.43, 25.24)	13	20.51 (7.20, 33.83)	18	68.52 (61.12, 75.92)	15	7.78 (-2.28, 17.83)
	New Patients	81	77	59.81 (56.43, 63.19)	63	9.79 (5.12, 14.46)	53	13.21 (8.28, 18.14)		N/A		N/A
	Overall	135	123	59.49 (56.52, 62.45)	109	11.93 (8.39, 15.47)	90	15.56 (11.77, 19.34)		N/A		N/A
TSQM Effectiveness Score												
HS-18-633	CAM2029	48	43	69.25 (64.30, 74.21)	37	-1.65 (-7.89, 4.58)		N/A		N/A		N/A
	Placebo	24	21	70.11 (62.17, 78.04)	21	-3.17 (-15.73, 9.38)		N/A		N/A		N/A
HS-19-647	CAM2029 RO	36	31	68.46 (61.96, 74.95)	31	-1.79 (-9.18, 5.60)	24	4.40 (-1.87, 10.66)		N/A		N/A
	Placebo RO	18	16	70.49 (60.30, 80.67)	16	-3.13 (-20.04, 13.79)	14	3.97 (-7.17, 15.11)	18	67.59 (54.98, 80.21)	15	7.41 (-5.52, 20.34)

			SoC Baseline (Day 1)		Change from SoC Baseline to Week 24		Change from SoC Baseline to Week 52		Placebo Baseline (Week 24)		Change from Placebo Baseline to Week 52	
		N	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
	New Patients	81	77	62.81 (59.49, 66.12)	63	3.04 (-2.35, 8.43)	53	7.81 (3.06, 12.56)		N/A		N/A
	Overall	135	124	65.21 (62.33, 68.09)	110	0.78 (-3.52, 5.08)	91	6.32 (2.80, 9.83)		N/A		N/A
TSQM Global Satisfaction Score												
HS-18-633	CAM2029	48	43	69.93 (65.08, 74.79)	37	2.90 (-2.29, 8.08)		N/A		N/A		N/A
	Placebo	24	21	76.19 (67.69, 84.69)	21	-6.12 (-19.81, 7.57)		N/A		N/A		N/A
HS-19-647	CAM2029 RO	36	31	68.43 (62.17, 74.70)	31	4.38 (-1.43, 10.18)	24	11.31 (3.82, 18.80)		N/A		N/A
	Placebo RO	18	16	77.23 (65.84, 88.63)	16	-6.70 (-24.84, 11.45)	14	0.00 (-12.94, 12.94)	18	67.06 (54.28, 79.85)	15	11.90 (-2.64, 26.45)
	New Patients	81	77	68.83 (65.27, 72.39)	63	0.68 (-3.80, 5.17)	53	2.96 (-1.29, 7.22)		N/A		N/A
	Overall	135	124	69.82 (66.80, 72.83)	110	0.65 (-3.23, 4.53)	91	4.71 (1.06, 8.36)		N/A		N/A
TSQM Side Effects Score												
HS-18-633	CAM2029	48	43	84.59 (77.82, 91.37)	37	6.42 (0.29, 12.54)		N/A		N/A		N/A
	Placebo	24	21	88.69 (78.69, 98.69)	21	-4.76 (-11.61, 2.08)		N/A		N/A		N/A
HS-19-647	CAM2029 RO	36	31	84.48 (76.19, 92.76)	31	4.64 (-1.74, 11.01)	24	6.25 (-1.53, 14.03)		N/A		N/A
	Placebo RO	18	16	85.16 (72.24, 98.08)	16	-4.69 (-13.41, 4.04)	14	-4.02 (-15.31, 7.27)	18	80.21 (67.49, 92.92)	15	5.00 (-4.98, 14.98)
	New Patients	81	77	89.04 (85.01, 93.08)	63	2.98 (-2.20, 8.15)	53	2.36 (-3.80, 8.52)		N/A		N/A
	Overall	135	124	87.40 (83.36, 90.94)	110	2.33 (-1.30, 5.96)	91	2.40 (-1.97, 6.78)		N/A		N/A

AcroQoL: Acromegaly Quality of Life Questionnaire; ITT: intention-to-treat; N: number of patients in the analysis set; n: number of patients with data; N/A: not applicable; RO: roll-over patients; SoC: standard of care; TSQM: Treatment Satisfaction Questionnaire for Medication
HS-18-633: Data from retrieved dropouts (i.e., following intercurrent events) (CAM2029: 4; placebo: 2) were set to missing, however, data could be missing also for other reasons.
HS-19-647: Data from retrieved dropouts were included

2.4.5.4. Supportive study

The long-term safety phase 3 study [HS-19-647] is considered as supportive given the design (open-label, single-arm). This study is not considered as supportive by the applicant and is described in the part of the main studies. As per the interim report with a cut-off data on the 23 May 2023, oly 6 patients have received at least one dose of CAM2029 (status: on-going).

2.4.5.5. Discussion on clinical efficacy

The efficacy of CAM2029 (Oczyesa) was evaluated in the 3 trials in patients with acromegaly: a phase 2 study [HS-12-455], 2 phase 3 studies [HS-18-633] and [HS-19-647].

The main trial for evaluating efficacy of CAM2029 was [HS-18-633], and long-term efficacy was evaluated as secondary endpoints in [HS-19-647].

Dose response studies

The choice of the dose for the phase 3 studies was mainly based on the results of a phase 1 study [HS-11-411] and the results of the phase 2 study [HS-12-455].

However, the clinical data from this phase 2 study are very limited as only 7 patients with acromegaly were included in this study. Therefore, the fixed dose of 20 mg was mainly evaluated in the phase 3 studies.

This choice was questionable due to uncertainties such as the extrapolation of the results from the clinical data of phase1 study to patients with acromegaly (subcutis changes in patients with acromegaly) which is not obvious and the higher bioavailability (4 to 5-fold) exposure and Cmax of CAM2029 compared to octreotide LAR which could have an impact on the long-term safety. Of note, the the bioavailability of octreotide for CAM2029 versus octreotide IR was determined to 92% to 98% and established a PK bridge between CAM2029 and the reference medicinal product Sandostatin IR.

According to the applicant, comparative PK and PD data do not appear to be sensitive to potential population effects relating to SC tissues differences or baseline IGF-1 levels based on data from a pop PK model and popPKPD model. However, these models used doses of octreotide IR which are recommended for maintenance of the treatment and not to start the treatment especially in treatment-naïve patients.

The higher biavailability of CAM2029 compared to octreotide LAR, and higher Cmax of CAM2029 compared to octreotide LAR which led to a higher exposure to octreotide, could have an impact in the short-term and long-term safety. However, the safety data seem reassuring for the well-controlled patients in the phase 3 studies but not in the healthy volunteers (in the phase 1 study) and pharmacologically washed-out patients (in study HS-19-647) as higher frequencies of gastro-intestinal events and cholelithiasis were highlighted in these patients.

Given there were no treatment-naïve patients in the 2 phase 3 studies, the safety of CAM2029 is not characterized in these patients and cannot be extrapolated from clinical data in healthy volunteers (phase 1 studies) and in the pharmacologically washed-out patients (study HS-19-647).Thus, the adequacy of the proposed dose (20 mg 4qw CAM2029) in relation to the proposed target population (adult patients in whom surgery is inappropriate or ineffective) was still not justified. Indeed, this choice was only considered as regards

to the indication "*long-term maintenance treatment of acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide*". In the phase 1 [HS-11-411], phase 2 [HS-12-455], in the PK Bridge phase 1 study [HS-19-664] and in poppk and popPKPD models, the doses of comparators (0.25 mg TID to 0.50 mg TID of octreotide IR and octreotide LAR 30 mg) are the doses recommended for the maintenance of treatment and not as starting doses for drug- naïve patients. Indeed, the results showed that the effects on the reduction of IGF-1 levels are comparable between 20 mg q4w CAM2029 and these comparators. The studies and popPK and popPKPD models and simulations have not been performed between 20 mg 4qw CAM2029 and comparators at starting doses nor with other doses of CAM2029 such as 10 mg 4qw.

At day 121, the applicant provided these simulations which have been performed with the starting dose and showed that the dose of 10 mg CAM2029 4 qw is similar to the starting dose of octreotide IR while the dose of 20 mg CAM2029 4qw is higher than the starting dose of octreotide IR. However, the applicant has not been performed the simulation between 20 mg 4qw and the starting doses nor with the optimal dose of octreotide IR. The applicant provided the simulations between 20 mg or and10 mg 4qw CAM2029 compared to the starting dose and optimal dose of octreotide IR (0.3 mg/ day) but no conclusion can be drawn from these simulations

Thus, the choice of the dose 20 mg every 4 weeks was questionable as starting dose especially for the treatment-naïve patients. A dose of CAM2029 10 mg every 4 weeks should have been investigated as starting dose especially in these patients. But the applicant accepted to restrict the indication of Oczyesa in the "maintenance treatment in adult patients with acromegaly who have responded and tolerated treatment with somatostatin analogues" and the dose of 20 mg/week is well adapted for these patients although there is still no possibility to reduce the dose to 10 mg/week in case of adverse events. Thus, there is no more issue as regards to the starting dose of Oczyesa in these patients.

Design and conduct of clinical phase 3 studies

- [HS-18-633] was a phase 3, randomized, double-blind, placebo-controlled, multi-center trial that assessed the efficacy and safety of CAM2029 versus placebo in patients with acromegaly. Eligible patients, who were biochemically controlled on stable doses of monotherapy treatment with long-acting SRLs (octreotide LAR 10, 20, 30, 40 mg or lanreotide Autogel 60, 90 or 120 mg) and who had prior evidence of active acromegaly disease, were randomized to treatment with either CAM2029 or placebo in a 24-week Double-blind Treatment Phase. Both patients with and without prior transsphenoidal surgery could be included in the trial, provided that at least 6 months had elapsed since surgery. Patients who had received prior pituitary irradiation were excluded. The diagnosis of acromegaly by historical evidence of (persistent or recurrent) acromegaly should have been performed. Patients should be well-controlled with IGF-1 levels $\leq 1 \times$ ULN (adjusted for age and sex).

63 of the 72 patients (87.5% in each treatment arm) had undergone previous pituitary surgery. This is in line with the acromegalic population as pituitary surgery is the first-line therapy proposed to most of the patients.

There were no treatment- naïve patients included in this phase 3 study, hence the approved indication only refers to the maintenance treatment in adult patients with acromegaly who have responded and tolerated treatment with somatostatin analogues, in line with the target population of the 2 phase 3 studies.

The applicant justified the possibility to use placebo in patients with acromegaly during 6 months as acromegaly is a slowly progressing disease and that the protocols included strict criteria for addressing worsening of signs and symptoms of acromegaly and elevations in IGF-1 above 1.3 times the upper limit of normal, including switch to rescue medication. The 6-month randomized treatment period was also selected to minimise the placebo treatment period in the trial.

All the patients should have an active acromegaly based on MRI or CT or OGTT to avoid patients with inactive disease due to the cumulative effect of past therapies (e.g., pituitary surgery, drugs, or a combination of these). This was to avoid inactive disease due to the cumulative effect of past therapies (e.g., pituitary surgery, drugs, or a combination of these).

The primary objective was to assess the superiority of CAM2029 compared to placebo in biochemical response for IGF-1 at 24 weeks. The primary endpoint was "Proportion of patients with mean IGF-1 levels $\leq 1 \times$ ULN at Week 22 and Week 24 (average of the 2 measurements)". This objective and endpoint are in line with the guidelines on treatment of acromegaly (Giustina et al 2010, Giustina et al 2024).

IGF-1 is considered as the most reliable biomarker to monitor the treatment efficacy. Indeed, random serum GH concentrations is uncertain because of the pulsatile secretion of GH, which occurs in normal individuals, in patients with active acromegaly, and in successfully treated patients with acromegaly. In contrast, plasma concentrations of IGF-1 are not pulsatile.

All efficacy analyses were based on the ITT analysis set. The efficacy analysis of the primary endpoint was repeated for the FAS and the PP analysis set as supportive analyses.

The key secondary objectives were to measure the superiority of CAM2029 compared to placebo in biochemical response for IGF-1 and GH.

The other secondary endpoints are time to loss of response of CAM2029 compared to placebo, assess efficacy of CAM2029 based on IGF-1 levels over time, GH levels over time, use of rescue medications, compare the efficacy of CAM2029 to placebo on tumor size, on clinical symptoms of acromegaly and on PROs such as "patients' satisfaction", QoL based on different scores (TSQM, ED-5D-5L, SIAQ), and compare the safety.

[HS-19-647] phase 3 study was an open-label, single - arm, multi-center, phase 3 trial that assessed the long-term safety (primary objective) and efficacy (secondary objective) of CAM2029 in patients with acromegaly.

As the study design is open-label and single-arm, the clinical data of this phase 3 study are considered as only supportive.

This study enrolled both patients who were directly recruited into the trial ('new patients') and patients who completed participation in the preceding trial [HS-18-633] ("roll-over patients").
There were also no treatment- naïve patients included in this study. However, there were patients exposed to placebo during the phase 3 study [HS-18-633] who were considered as "pharmacologically washed-out patients" in study [HS-19-647]. These patients are regarded as "non-pharmacologically treated" for acromegaly as they remained untreated for 6 months during the previous trial, but they cannot be considered as medically naïve patients. The applicant initially claimed that similar effects on GH and IGF-1 can be expected in treatment-naïve and SRL-experienced patients when administered CAM2029, but in the end theindication was restricted to the "maintenance treatment in adult patients with acromegaly who have responded and tolerated treatment with somatostatin analogues.
Most of the "new patients" (n = 69/81 (85%)) were uncontrolled (IGF-1 ≤ ULN) in this study following SOC or/and pituitary surgery and/or pituitary radiotherapy.
14.8% of the "new patients" had received prior pituitary irradiation more than 3 years before screening.

Of note, 86.4% of the "new patients" had already been treated with pituitary surgery.
There is also an extension part of 52 weeks which includes patients who continued directly from the main part of the trial, and re-invited patients who had previously completed the main part of [HS-19-647] trial more than 4 weeks back or were treated with SoC in between the 2 parts. For re-invited patients there were no restrictions

on the type (e.g., monotherapy or combination therapy), dose levels, dosing frequencies, or how long they received SoC in the period between the 2 parts of the trial.
Enrolment in the trial has been completed, and the trial is still on-going to allow patients who completed treatment with CAM2029 in study [HS-18-633] and derived benefit to continue treatment with CAM2029 in this long-term study. The results of the extension study will be provided in the post-marketing phase.

Efficacy data of the phase 3 studies and additional analyses

Overall, a total of 433 subjects (280 healthy volunteers and 153 patients with acromegaly) have received at least 1 dose of CAM2029 in the different studies (phase 1, phase 2 and phase 3 studies).

In the comparative, double-blind phase 3 study [HS-18-633], 72 well controlled patients (48 patients in the CAM2029 treatment arm and 24 patients in the placebo treatment arm) with IGF1 ≤ ULN at screening were enrolled. 70 patients completed the trial (46 patients in the CAM2029 arm and 24 patients in the placebo arm).

In the long-term, open-label, single-am phase 3 study [HS-19-647], 135 patients were enrolled, 81 "new patients" and "54 roll-over patients" (whereof 36 with prior CAM2029 treatment and 18 with prior placebo treatment) were included in the ITT analysis set and evaluated for efficacy.

At baseline, the demographic data were well balanced in the 2 groups in the study [HS-18-633] and in the 2 phase 3 studies were representative of the overall acromegalic population (mean age: 53.7 years), mean time since diagnosis was 11.1 years, slightly more women (57.0%) than men (43.0%).

As pituitary surgery is the first-line treatment option for most patients with acromegaly, 86.9% of the patients in the Phase 3 trials had undergone prior pituitary surgery.

In the 2 phase 3 studies, a fixed dose of 20 mg CAM2029 every 4 weeks was administered to the patients with acromegaly whatever the type of patients (well-controlled or uncontrolled) and whatever the previous dose of the other SLRs treatments with only the possibility to reduce the dose to 10 mg CAM2029 every 4 weeks in case of adverse events or a possibility to switch to a rescue therapy (SOC) in case of insufficient response (worsening of the signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3 ×ULN at 2 consecutive visits). The applicant clarified that the protocols for the two trials did not mandate a dose decrease for safety or tolerability reasons, except for ADRs of Grade ≥3 or electrocardiogram recordings showing QTcF prolongation.

The ADRs that led to discontinuation of CAM2029 treatment were either at injection site (4 cases) or migraine in (1 patient, grade 1), or depression i(1 patient, grade 1.In all 6 cases, either the Investigator or the patient decided to discontinue treatment with IMP.

The SmPC mentions in section 4.2 afixed dose of 20 mg every 4 weeks for the patients with acromegaly , but monitoring of IGF 1 levels and assessment of symptoms , are highlighted as well, so that the treatment could be adjusted by the clinician if needed.

The safety data of 20 mg 4qw CAM2029 in healthy volunteers never exposed to this product or patients pharmacologically washed-out from other SRLs showed higher frequencies of gastrointestinal adverse events and cholelithiasis during the first 3 months of treatment. This could be managed with a dose titration of the product as recommended and usually clinically necessary for the other SRLs. Still, it was accepted that the dose of 20 mg/month is more adapted for patients already exposed to somatostatin analogues who do need a dose titration.

Although the short-term safety seems in line with the safety of other SRL treatments in the phase 3 studies, the long-term safety will be better characterized in the on-going extension part of the study [HS-19-647]. This data will be provided in the frame of a MEA planned in the RMP in relation to the safety concern "long-term safety", which is considered as a missing information at this stage.

All the primary and key secondary endpoints were met in the pivotal study [HS-18-633] compared to placebo.

The proportion of patients with mean IGF-1 ≤1×ULN at Week 22 and Week 24 (average of the two measurements) was statistically significantly higher in the CAM2029 treatment arm (72.2%) than in the placebo treatment arm (37.5%).

The difference in proportions (CAM2029-placebo) was 34.6% (95% CI: 11.3%, 57.9%), p=0.0018,

The proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24 combined with mean GH levels <2.5 µg/L at Week 24 (key secondary efficacy endpoint II) was statistically significantly higher in the CAM2029 treatment arm (70.0%) than in the placebo treatment arm (37.5%), with a difference in proportions of 32.3% (95% CI: 8.8%, 55.7%), p=0.0035.

These results were expected as octreotide is a well-known substance with a relevant efficacy on IGF-1 levels in patients with acromegaly. However, CAM2029 was not compared directly to other SRL treatments in the phase 3 studies. Therefore, it is not known whether the efficacy of CAM2029 is superior or equivalent to the other SRL treatments. The comparisons with the other SRL treatments were only performed from baseline to W24 or W52.

However, in study [HS-18-633], although the mean IGF-1 levels was maintained below ULN from baseline to W24, when looking at the secondary objective "proportion of responders" in terms of "proportion of patients with mean IGF 1 ≤1×ULN over time", the proportion of responders at baseline was 91.7% in both treatment arms and 70.8% at the end of the trial in the CAM2029 treatment arm (mean of the values at Week 22 and Week 24). The estimated difference in proportions from baseline to W24 was -20.5% (95% CI: -33.7%, -7.3%) in the CAM2029 treatment arm. Of note, at 3 months, 4/44 = 9% of patients in this treatment arm were already uncontrolled after treatment with 20 mg 4qw CAM2029.

Moreover, in study [HS-18-633], although the mean GH levels remained around or below 1.0 µg/L throughout the 24-week treatment period in the treatment arm, the proportions of patients treated with CAM2029 with mean GH <1.0 µg/L and with mean GH <2.5 µg/L at Week 24 compared to placebo were not statistically significant. This also highlights that CAM2029 did not increase the proportion of patients well-controlled with mean GH <1.0 µg/L and with mean GH <2.5 µg/L compared to placebo.

Although there was a proportion of well controlled patients who were not maintained after 6 months of treatment in study [HS-18-633] and after 12 months of treatment in study [HS-19-647], this proportion seems not significant and seems to be due to the withdrawal of some patients and to the fluctuation of the IGF-1 levels.

However, the [HS-18-633] trial was not powered to show a difference in the proportions of patients with mean GH <1.0 µg/L or mean GH <2.5 µg/L between the CAM2029 and placebo treatment arms.

In case of inefficacy or reduced effectiveness of the treatment, this can be solved in stopping the treatment and switch to another somatostatin analogues. This information is reflected in the SmPC.

The results of the long-term extension study [HS-19-647] are not completed at this stage. During the extension part of the trial, there was a slight decrease in the mean IGF-1/ULN values in the directly enrolled patients and also an observed initial decrease in mean IGF-1/ULN values in the re-invited patients from the start of the

extension part (after returning to treatment with CAM2029) to Week 88 (at which time most of the patients had data at the data cut-off date), the proportion of patients with a mean IGF-1 ≤1×ULN at week 102/104 is increased among the re-invited patients and directly enrolled patients but all patients still do not have reached week 104.

Any potential overtime reduced effectiveness will be apparent only when the complete results of this extension study will be provided (no later than Q1 2026) and assessed in the frame of the above-mentioned MEA.

A subgroup analysis showed that from the uncontrolled patients with other SRLs included in study [HS-19-647] at baseline, 1/3 were well-controlled with 20 mg 4qw CAM2029 at W50/52. Therefore, it can be concluded that CAM2029 not effective for uncontrolled patients and is rather effective in the maintenance of the response in well-controlled patients with other somatostatin analogues. This was an additional argument to restrict the indication of Oczyesa to the maintenance treatment of well-controlled patients with SRLs and to add in the SmPC the option to stop the treatment and switch to another treatment in case of IGF-1 levels are not maintained**.**

In relation to PROs, the only domain which showed significant difference is the convenience domain in both arms reflecting a preference for treatment with CAM2029, including the injection with pre-filled syringe, over treatment with SoC.

In study [HS-19-647], the results cannot be compared as it is a single-arm study. Therefore, these results should be considered as only supportive.

Regarding the subgroup analysis, although men are more sensitive to CAM2029 (according to the popPKPD model), the proportion of responders are more or less similar between men and women. However, the proportion of responders is higher in patients aged 18 to 64 years (76.5%) than in patients aged ≥65 years (57.1%). Given the low number of old patients ≥ 65 years in study HS-18-633 and study HS-19-647, it is difficult to draw any conclusion as regards proportion of responders in this subgroup of patients. This difference was not observed in study HS-19-647 but this study is only supportive. Overall, the data do not reveal any concerns.

2.4.6. Clinical safety

2.4.6.1. Patient exposure

In phase 3 trials, 47 patients received CAM2029 in the pivotal study, and 135 patients in the open label phase study (81 new patients, 36 CAM2029 roll-over patients, and 18 placebo roll-over patients). The dosing in phase 3 trials was consistently 20 mg every 4 weeks.

Table 40 Trial HS-18-633: Duration of exposure by treatment arm (safety analysis set)

Duration of exposure	CAM2029 (N=47) n (%)	Placebo (N=24) n (%)	Overall (N=71) n (%)
≥4 weeks	47 (100)	24 (100)	71 (100)
≥8 weeks	46 (97.9)	24 (100)	70 (98.6)
≥12 weeks	45 (95.7)	24 (100)	69 (97.2)
≥16 weeks	43 (91.5)	23 (95.8)	66 (93.0)
≥20 weeks	42 (89.4)	23 (95.8)	65 (91.5)
≥24 weeks	42 (89.4)	22 (91.7)	64 (90.1)
Statistics [weeks]	(N=47)	(N=24)	(N=71)
n	47	24	71
Mean (SD)	26.09 (4.50)	27.11 (3.11)	26.43 (4.09)
Median	27.43	27.79	27.57
Min - Max	7.6 - 28.6	15.6 - 31.4	7.6 - 31.4

No treatment-naïve patients were included in the clinical development program of CAM2029. In the phase 3 trials, included patients with biochemically-controlled acromegaly who had been treated with octreotide LAR or lanreotide autogel (ATG) for at least 3 months at screening.

Considering adaptation period of the gastrointestinal and pancreatic effects of octreotide, GI-related events are expected in subjects exposed to octreotide for the first time. This explains the findings in healthy volunteer trials as compared with the ones in the trials in patients with acromegaly. Gastrointestinal-related adverse events were notably more common in subjects exposed to octreotide for the first time compared to patients on stable SRL doses (for example, 70% experienced diarrhoea in phase 1 trials, versus 8.9% in phase 3 open label trial). Furthermore, the difference between CAM2029 and octreotide LAR is explained by the approximate 10 to 14 days delay before reaching therapeutic octreotide levels after injection of octreotide LAR compared to the fast onset of CAM2029. This was also confirmed by the low frequencies of events within the SOC 'Gastrointestinal disorders' in the Phase 3 trials HS 18 633 (CAM2029: 17.0%; placebo: 12.5%), aligning with the stable SRL doses at enrolment.
These data suggested that GI adverse reactions would be more frequent in naive patients given the adaptation period of the GI and pancreatic effects of octreotide and then the safety profile in treatment-naïve patients would be different from that of controlled patients.

Therefore, the applicant was asked to discuss how safety data in treatment-naïve patients with acromegaly could be extrapolated from data in controlled patients included in phase 3 clinical trials to drug naïve patients with acromegaly.
It was claimed by the applicant that similar proportions of gastrointestinal adverse events and other safety outcomes between the washed-out placebo group and patients previously treated with somatostatin receptor ligands. However, this justification had critical limitations that refuted the argument for extrapolation to drug-naïve patients.

While the studies in healthy volunteers provided useful information on the pharmacokinetics and tolerability of CAM2029, they cannot be considered as drug-naïve patients with acromegaly. Healthy volunteers lack the underlying disease pathology, such as altered hormone levels and comorbidities that could significantly influence the safety profile of CAM2029 in treatment-naïve patients. Furthermore, the high frequency of CAM2029-related GI AEs observed in healthy volunteers (85.7% of GI disorders in healthy volunteers versus 10.6% in HS-18-633 and 13.3% in the main part of HS-19-647), confirms the higher frequency of GI adverse effects during initial exposure to CAM2029 compared to other somatostatin analogues. However, these findings

cannot be directly extrapolated to acromegaly patients, whose adaptation to the drug may differ substantially from the healthy volunteers.

The washed-out placebo roll-over patients included in study HS-19-647 are not an appropriate surrogate for treatment-naïve acromegaly patients. Indeed, these patients had prior exposure to SRLs, which likely conditioned their gastrointestinal and pancreatic systems, reducing their susceptibility to GI AEs upon reintroduction of octreotide. In contrast, treatment-naïve patients lack this prior adaptation, putting them at a higher risk of experiencing GI adverse events during the initial treatment period. Moreover, the small sample size of this subgroup (n=17) limits the statistical robustness of the conclusions, making it questionable to generalize these findings to the broader treatment-naïve population.

The applicant's data highlight, at some point, the higher risk of GI AEs in drug-naïve patients. In phase 1 trials, CAM2029 was associated with a significantly higher incidence of GI AEs compared to octreotide LAR and placebo. This aligns with the expectation that drug-naïve patients, who are being exposed to octreotide for the first time, would experience more frequent GI reactions. In contrast, the low incidence of GI AEs reported in the phase 3 trial (study HS-18-633) reflects a population of previously treated patients who had already adapted to the effects of SRLs. These findings further support the argument that after initiation of CAM2029, there is a higher frequency of gastro-intestinal adverse events compared to the other somatostatin analogues in drug naïve volunteers. As it is not possible to extrapolate safety data from healthy volunteers and pharmacologically washed-out patients to drug-naïve patients, the safety of CAM2029 is not characterized in these patients.

Furthermore, the washed-out placebo roll-over group in study HS-19-647 showed a notably higher incidence of cholelithiasis (22.2%) compared to previously treated patients (2.6%). The applicant was asked to explain why among the pharmacologically washed-out patients in study HS-19-647, there was a higher frequency of cholelithiasis than among the roll-over CAM2029 group of patients. Several literature data that addressed the higher incidence of cholelithiasis and gallstone-related complications after discontinuation of SRL treatment than during SRL treatment. This is attributed to SRLs impairing gallbladder motility and bile flow, leading to gallstone formation. Upon discontinuation, gallbladder motility resumes, which may trigger acute biliary complications. The higher frequency of cholelithiasis observed in pharmacologically washed-out patients, supports this hypothesis.

Regarding the fixed dose prefilled pen 20 mg, the applicant has acknowledged the use of a 10 mg pre-filled pen during the trial for dose reduction in one patient experiencing GI AEs (non-serious ADR of diarrhoea). It would have been relevant to provide this lower dose option to manage ADRs, particularly at the beginning of treatment to manage GI ADRs.

Overall, the applicant's response failed to adequately justify the extrapolation of safety data from healthy volunteers and pharmacologically washed-out placebo roll-over patients to drug-naïve acromegaly patients. Indeed, these patients cannot be considered as drug-naïve patients. Furthermore, the provided data indicated a higher risk of GI and pancreatic AEs in healthy volunteers and pharmacologically washed-out placebo roll-over patients (cholelithiasis). Therefore, it was considered that the safety of CAM2029 in drug-naïve patients was not characterized and could not be extrapolated from safety data of healthy volunteers and pharmacologically washed-out patients.

Thus, the indication was restricted to maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues.

On the other hand, two different devices were used during the clinical development: a pre-filled syringe and a pre-filled pen. The pre-filled pen was included in HS-19-647, 98 patients used the pre-filled pen device. Of the 135 patients in the trial (including the 37 patients who only used the syringe), 70.4% self-administered the

device, while 13.3% had the medication administered by their partner. No adverse events related to device use errors, including medication errors, were reported during the trial for either the pre-filled pen or syringe. The applicant was seeking approval for the pre-filled pen, which offers advantages in terms of convenience, ease of use, and patient adherence. However, it might also pose a potential higher risk of medication errors due to patient self-administration, lack of training, and possible pen malfunction, resulting in incorrect or incomplete drug delivery. Given the substantial difference with the reference medicinal product as regards to the device, as well as the fact that most other octreotide-containing products use syringe devices, the applicant was asked to provide a comprehensive analysis of potential risks in association with self-administration by patients using a pre-filled pen with a particular attention on the potential risk of inappropriate dosing (underdosing and overdosing) due to incorrect self-administration.

Indeed, the clinical trials did not report any adverse events related to device malfunctions, such as overdosing or underdosing. Underdosing could have more significant effects than suggested, especially in patients with complex medical conditions, where even small changes in dosage can impact disease management (worsening of disease symptoms, increased risk of CV complications, diabetes and metabolic issues, etc.). The importance of patient training was emphasised, and the product information leaflet includes detailed instructions and illustrations for proper use (IFU). In addition, medication errors (including underdosing cases) will be reviewed in each PSUR, accompanied by a discussion on the appropriateness of the established risk minimisation measures to prevent medication errors.

This approach was endorsed by the CHMP.

2.4.6.2. Adverse events

A total of 56 patients (78.9%) reported 267 AEs during the double-blind, placebo-controlled phase 3 trial, with an equal proportion of patients reporting ≥1 AE in the two treatment arms (CAM2029: 78.7%; placebo: 79.2%) regardless of trial drug relationship.

Table 41 Trial HS-18-633: Summary of proportion of patients with AEs by treatment arm (safety analysis set)

Proportion of patients with at least one	CAM2029 (N=47) n (%) E	Placebo (N=24) n (%) E	Overall (N=71) n (%) E	Difference in proportions [%][a] (CAM2029 - placebo) (95% CI)
AE	37 (78.7) 175	19 (79.2) 92	56 (78.9) 267	-0.7 (-20.7, 19.4)
IMP-related AE	24 (51.1) 98	15 (62.5) 56	39 (54.9) 154	-11.9 (-35.8, 12.1)
Grade 3 AE	5 (10.6) 5	2 (8.3) 2	7 (9.9) 7	2.6 (-11.3, 16.6)
SAE	4 (8.5) 4	2 (8.3) 2	6 (8.5) 6	0.4 (-13.2, 13.9)
IMP-related SAE	0	1 (4.2) 1	1 (1.4) 1	
AE leading to IMP discontinuation	4 (8.5) 5	1 (4.2) 1	5 (7.0) 6	4.4 (-6.8, 15.7)
AE leading to withdrawal from trial	0	0	0	
AE leading to dose reduction	0	0	0	
Fatal SAE	0	0	0	
AESI	23 (48.9) 76	15 (62.5) 49	38 (53.5) 125	-13.6 (-37.7, 10.6)
COVID-19-related AE	5 (10.6) 5	3 (12.5) 3	8 (11.3) 8	-1.4 (-17.3, 14.5)

The proportion of patients reporting AEs was almost similar between CAM2029 group and placebo group. However, the proportion of IMP-related AEs was higher in the placebo group (62.5% versus 51.1%). The pattern of the most reported AEs in acromegaly patients differed from that observed in healthy volunteers. In

acromegaly patients, injection site reactions were the most reported AEs (erythema, swelling, pruritus, etc.), with a slightly higher proportion in the CAM2029 group.

The most common ADRs were injection site reactions (erythema, swelling, and pruritus), followed by gastrointestinal ADRs (upper abdominal pain, diarrhoea, and nausea), musculoskeletal and connective tissue ADRs (arthralgia, joint swelling), nervous system ADRs (headache), hepatobiliary ADRs (chronic cholecystitis and hepatic cyst), and skin and subcutaneous tissue disorders (pruritus and erythema).

In the open-label phase 3 trial, when including events that occurred in HS-18-633 for CAM2029 roll-overs, 102 of the 135 patients (75.6%) had reported ≥1 AE regardless of trial drug relationship (placebo roll-overs: 66.7%; CAM2029 roll-overs: 94.4%; new patients: 69.1%). The 3 most common AEs, regardless of relationship to CAM2029, were injection site erythema (27.4%), injection site swelling (15.6%), and COVID-19 (14.8%).

Table 42 Trial HS-19-647: Summary of proportion of patients with AEs by patient group – whole trial (safety analysis set)

Proportion of patients with at least one	Placebo roll-overs (N=18) n (%)	CAM2029 roll-overs (N=36) n (%)	New patients (N=81) n (%)	Overall (N=135) n (%)
AE	12 (66.7)	34 (94.4)	56 (69.1)	102 (75.6)
Injection-site AE	9 (50.0)	19 (52.8)	33 (40.7)	61 (45.2)
Non-injection-site AE	8 (44.4)	33 (91.7)	49 (60.5)	90 (66.7)
IMP-related AE	12 (66.7)	24 (66.7)	40 (49.4)	76 (56.3)
IMP-related injection-site AE	9 (50.0)	19 (52.8)	33 (40.7)	61 (45.2)
IMP-related non-injection-site AE	5 (27.8)	12 (33.3)	24 (29.6)	41 (30.4)
Grade 3 AE	1 (5.6)	7 (19.4)	9 (11.1)	17 (12.6)
SAE	1 (5.6)	9 (25.0)	5 (6.2)	15 (11.1)
IMP-related SAE	1 (5.6)	1 (2.8)	0	2 (1.5)
AE leading to IMP discontinuation	0	0	2 (2.5)	2 (1.5)
AE leading to dose reduction	1 (5.6)	0	0	1 (0.7)
Fatal SAE	0	0	0	0
AESI	11 (61.1)	25 (69.4)	40 (49.4)	76 (56.3)
Injection-site AESI	9 (50.0)	19 (52.8)	33 (40.7)	61 (45.2)
Non-injection-site AESI	4 (22.2)	11 (30.6)	14 (17.3)	29 (21.5)
IMP-related AESI	11 (61.1)	22 (61.1)	37 (45.7)	70 (51.9)
IMP-related injection-site AESI	9 (50.0)	19 (52.8)	33 (40.7)	61 (45.2)
IMP-related non-injection-site AESI	3 (16.7)	4 (11.1)	7 (8.6)	14 (10.4)
Serious AESI	1 (5.6)	1 (2.8)	1 (1.2)	3 (2.2)
IMP-related serious AESI	1 (5.6)	1 (2.8)	0	2 (1.5)
AESI leading to IMP discontinuation	0	0	1 (1.2)	1 (0.7)
COVID-19-related AE	2 (11.1)	10 (27.8)	9 (11.1)	21 (15.6)

AEs assessed as related to CAM2029 occurred in 76 patients (56.3%). The most commonly reported AEs related to CAM2029 were injection site AEs. The most common non-injection site AEs related to CAM2029 were diarrhoea (8.9%), headache (7.4%), and cholelithiasis (4.4%).

IMP-related AEs were comparable between the roll-over groups (CAM2029 and placebo) and lower in the new patient group. The nature and distribution of reported ADRs were generally similar to the pivotal study, with slight frequency differences between the groups. Cholelithiasis was reported in six cases during the open label phase 3 trial, whereas it was not reported in the pivotal study. Cholelithiasis is a known ADR of octreotide and listed as a very common ADR in the product information. Octreotide can induce cholelithiasis by inhibiting gallbladder motility and reducing bile secretion, leading to bile stasis and stone formation.

IMP-related Adverse Events across the Phase 3 Trials (HS-18-633 and HS-19-647).

Table 43 IMP-related AEs by SOC, PT, and IMP – Phase 3 trials (safety analysis set)

SOC PT	CAM2029 (N=146) n (%) E	Placebo (N=24) n (%) E	Overall (N=152) n (%) E
Any IMP-related TEAE	83 (56.8) 344	15 (62.5) 56	88 (57.9) 400
General disorders and administration site conditions			
Any	68 (46.6) 251	15 (62.5) 45	75 (49.3) 296
Injection site erythema	41 (28.1) 77	5 (20.8) 7	45 (29.6) 84
Injection site swelling	24 (16.4) 45	2 (8.3) 2	26 (17.1) 47
Injection site pain	12 (8.2) 16	3 (12.5) 7	15 (9.9) 23
Injection site pruritus	15 (10.3) 18	1 (4.2) 1	15 (9.9) 19
Injection site mass	13 (8.9) 24	5 (20.8) 12	14 (9.2) 36
Injection site induration	10 (6.8) 15	3 (12.5) 4	13 (8.6) 19
Injection site nodule	13 (8.9) 21	1 (4.2) 4	13 (8.6) 25
Fatigue	4 (2.7) 5	0	4 (2.6) 5
Injection site bruising	4 (2.7) 4	1 (4.2) 1	4 (2.6) 5
Injection site haematoma	3 (2.1) 3	1 (4.2) 1	4 (2.6) 4
Injection site hypertrophy	3 (2.1) 3	0	3 (2.0) 3
Injection site oedema	2 (1.4) 2	1 (4.2) 1	3 (2.0) 3
Injection site discomfort	2 (1.4) 2	0	2 (1.3) 2
Injection site extravasation	2 (1.4) 3	0	2 (1.3) 3
Injection site inflammation	2 (1.4) 5	0	2 (1.3) 5
Injection site rash	0	2 (8.3) 5	2 (1.3) 5
Asthenia	1 (0.7) 1	0	1 (0.7) 1
Chest discomfort	1 (0.7) 1	0	1 (0.7) 1
Injection site dermatitis	1 (0.7) 2	0	1 (0.7) 2
Injection site haemorrhage	1 (0.7) 1	0	1 (0.7) 1
Injection site paraesthesia	1 (0.7) 1	0	1 (0.7) 1
Injection site reaction	1 (0.7) 1	0	1 (0.7) 1
Swelling face	1 (0.7) 1	0	1 (0.7) 1
Gastrointestinal disorders			
Any	19 (13.0) 35	0	19 (12.5) 35
Diarrhoea	12 (8.2) 14	0	12 (7.9) 14
Abdominal pain upper	5 (3.4) 7	0	5 (3.3) 7
Abdominal pain	3 (2.1) 3	0	3 (2.0) 3
Nausea	3 (2.1) 4	0	3 (2.0) 4
Abdominal distension	1 (0.7) 1	0	1 (0.7) 1
Aerophagia	1 (0.7) 1	0	1 (0.7) 1
Faeces discoloured	1 (0.7) 1	0	1 (0.7) 1
Faeces soft	1 (0.7) 1	0	1 (0.7) 1
Flatulence	1 (0.7) 1	0	1 (0.7) 1
Gastritis	1 (0.7) 1	0	1 (0.7) 1
Steatorrhoea	1 (0.7) 1	0	1 (0.7) 1
Nervous system disorders			
Any	11 (7.5) 16	1 (4.2) 4	12 (7.9) 20
Headache	10 (6.8) 11	0	10 (6.6) 11
Dizziness	1 (0.7) 1	0	1 (0.7) 1
Encephalopathy	1 (0.7) 1	0	1 (0.7) 1

SOC PT	CAM2029 (N=146) n (%) E	Placebo (N=24) n (%) E	Overall (N=152) n (%) E
Hypoaesthesia	0	1 (4.2) 1	1 (0.7) 1
Migraine	1 (0.7) 3	0	1 (0.7) 3
Paraesthesia	0	1 (4.2) 3	1 (0.7) 3
Hepatobiliary disorders			
Any	10 (6.8) 10	1 (4.2) 2	11 (7.2) 12
Cholelithiasis	6 (4.1) 6	0	6 (3.9) 6
Cholecystitis	1 (0.7) 1	1 (4.2) 1	2 (1.3) 2
Biliary colic	0	1 (4.2) 1	1 (0.7) 1
Cholecystitis acute	1 (0.7) 1	0	1 (0.7) 1
Cholecystitis chronic	1 (0.7) 1	0	1 (0.7) 1
Hepatic cyst	1 (0.7) 1	0	1 (0.7) 1
Musculoskeletal and connective tissue disorders			
Any	6 (4.1) 7	3 (12.5) 3	9 (5.9) 10
Arthralgia	5 (3.4) 6	1 (4.2) 1	6 (3.9) 7
Joint swelling	1 (0.7) 1	0	1 (0.7) 1
Muscle spasms	0	1 (4.2) 1	1 (0.7) 1
Soft tissue swelling	0	1 (4.2) 1	1 (0.7) 1
Investigations			
Any	4 (2.7) 4	1 (4.2) 1	5 (3.3) 5
Electrocardiogram T wave inversion	1 (0.7) 1	0	1 (0.7) 1
Glycosylated haemoglobin increased	1 (0.7) 1	0	1 (0.7) 1
High density lipoprotein decreased	1 (0.7) 1	0	1 (0.7) 1
Lipase increased	0	1 (4.2) 1	1 (0.7) 1
Weight decreased	1 (0.7) 1	0	1 (0.7) 1
Metabolism and nutrition disorders			
Any	5 (3.4) 5	0	5 (3.3) 5
Diabetes mellitus	1 (0.7) 1	0	1 (0.7) 1
Diabetes mellitus inadequate control	1 (0.7) 1	0	1 (0.7) 1
Glucose tolerance impaired	1 (0.7) 1	0	1 (0.7) 1
Hyperglycaemia	1 (0.7) 1	0	1 (0.7) 1
Vitamin B12 deficiency	1 (0.7) 1	0	1 (0.7) 1
Psychiatric disorders			
Any	3 (2.1) 3	0	3 (2.0) 3
Depression	1 (0.7) 1	0	1 (0.7) 1
Insomnia	1 (0.7) 1	0	1 (0.7) 1
Procedural anxiety	1 (0.7) 1	0	1 (0.7) 1
Skin and subcutaneous tissue disorders			
Any	3 (2.1) 4	0	3 (2.0) 4
Pruritus	2 (1.4) 2	0	2 (1.3) 2
Erythema	1 (0.7) 1	0	1 (0.7) 1
Erythema annulare	1 (0.7) 1	0	1 (0.7) 1
Reproductive system and breast disorders			
Any	2 (1.4) 3	0	2 (1.3) 3
Abnormal uterine bleeding	1 (0.7) 1	0	1 (0.7) 1
Breast mass	1 (0.7) 1	0	1 (0.7) 1
Postmenopausal haemorrhage	1 (0.7) 1	0	1 (0.7) 1

SOC PT	CAM2029 (N=146) n (%) E	Placebo (N=24) n (%) E	Overall (N=152) n (%) E
Vascular disorders			
Any	2 (1.4) 2	0	2 (1.3) 2
Haematoma	1 (0.7) 1	0	1 (0.7) 1
Hypotension	1 (0.7) 1	0	1 (0.7) 1
Blood and lymphatic system disorders			
Any	0	1 (4.2) 1	1 (0.7) 1
Anaemia	0	1 (4.2) 1	1 (0.7) 1
Cardiac disorders			
Any	1 (0.7) 1	0	1 (0.7) 1
Sinus tachycardia	1 (0.7) 1	0	1 (0.7) 1
Ear and labyrinth disorders			
Any	1 (0.7) 1	0	1 (0.7) 1
Vertigo	1 (0.7) 1	0	1 (0.7) 1
Infections and infestations			
Any	1 (0.7) 1	0	1 (0.7) 1
Furuncle	1 (0.7) 1	0	1 (0.7) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Any	1 (0.7) 1	0	1 (0.7) 1
Haemangioma of liver	1 (0.7) 1	0	1 (0.7) 1

For hepatic cysts, the applicant highlighted a pre-existing condition in some patients and the absence of evidence linking octreotide treatment to hepatic cyst formation, this is consistent with the reference product SmPC and other octreotide-based products such as Mycapssa.

Regarding increased glycosylated haemoglobin, the provided data aligns with known effects of octreotide on glucose regulation and is already addressed in the SmPC. In addition, the absence of literature evidence linking octreotide to decreased HDL or vertigo supports the conclusion to not update the SmPC.

Decreased weight and vitamin B12 deficiency are acknowledged as potential effects of octreotide, but these are already addressed in the SmPC under related categories (anorexia in section 4.8 and vitamin B12 deficiency in section 4.4 of the SmPC). This is in line with the reference product and other octreotide-based products such as Mycapssa.

In addition, the following CAM2029-related AEs not known to be related to somatostatin analogues were reported and were also discussed: *joint swelling, electrocardiogram T wave inversion, depression, insomnia, abnormal uterine bleeding, and breast mass, postmenopausal haemorrhage.* A thorough analysis was done for each reported ADR, emphasizing their limited occurrence (single cases) and lack of established association with octreotide or somatostatin analogues in the literature. Plausible alternative explanations were also provided, such as underlying medical histories or pre-existing conditions for most events.

Injection Site Adverse Events

- **Trial HS-18-633**

Overall, 34 patients (47.9%) had ≥1 injection site AE (CAM2029: 40.4%; placebo: 62.5%). It should be noted that each injection site was assessed/inspected for local tolerability after each injection and that CAM2029 forms a depot under the skin, which in some cases may be viewed as injection site swelling, injection site mass, or other injection site AE.
The most common injection site AEs (reported in ≥5% patients in any treatment arm) were injection site erythema (CAM2029: 25.5%; placebo: 20.8%), injection site swelling (CAM2029: 14.9%; placebo: 8.3%), injection site mass (CAM2029: 6.4%; placebo: 20.8%), injection site pruritus (CAM2029: 14.9%; placebo: 4.2%), injection site induration (CAM2029: 8.5%; placebo: 12.5%), injection site pain (CAM2029: 8.5%; placebo: 12.5%), and injection site nodule (CAM2029: 8.5%; placebo: 4.2%), and injection site rash (CAM2029: 0%; placebo: 8.3%)
All injection site AEs were assessed as related to the IMP by the Investigator.
All injection site AEs were of Grade 1 (CAM2029: 25.5%; placebo: 45.8%) or Grade 2 (CAM2029: 14.9%; placebo: 16.7%).

- **Trial HS-19-647**

When including events that occurred in HS-18-633 for CAM2029 roll-overs, injection site AEs occurred in 61 patients (45.2%) overall (placebo roll-overs: 50.0%; CAM2029 roll-overs: 52.8%; new patients: 40.7%). The most common injection site AEs (reported in ≥5% patients overall) were injection site erythema (27.4%), injection site swelling (15.6%), injection site pruritus (9.6%), injection site mass (8.9%), injection site nodule (8.9%), injection site pain (8.1%), and injection site induration (5.2%).
During assessment, a detailed analysis of injection site reactions across different injection sites (abdomen, thigh, and buttock) in diabetic patients versus non-diabetic patients during phase 3 clinical trials (HS-18-633 and HS-19-647) was provided. Overall, the data suggest no significant differences in ISRs incidence between the injection sites, particularly among diabetic patients.
Importantly, diabetic patients do not seem to be at a higher risk for ISRs compared to non-diabetic patients.
Regarding long-term safety, the applicant provided long-term safety data for CAM2029, focusing on results from study HS-19-647. Data for 109 patients treated for at least one year was presented, which demonstrate that the safety profile of CAM2029 is consistent with other injectable octreotide products.
The absence of new safety concerns, except for neoplasm cases particularly liver haemangioma, and the fact that the higher bioavailability of CAM2029 does not appear to result in additional safety risks further support this conclusion.
However, given the potential for rare or delayed adverse events, continued monitoring remains important. In this regard, the results of the ongoing 52-week extension study will be particularly relevant to further characterize long-term safety.
The final clinical trial report of the 52-week extension study (OLE phase of study HS-19-647) will be submitted no later than Q1 2026. in the frame of a MEA.
Some data from the 52-week extension part was provided during the procedure and assessed. Overall, 33 of the 43 enrolled patients had completed the extension part, 2 patients had discontinued IMP treatment/withdrawn from the trial during the extension part, and 8 patients were still ongoing.
Regarding AEs, 30 of 43 (69.8%) patients had experienced AEs (placebo roll-overs: 8 patients [100%]; CAM2029 roll-overs: 10 patients [66.7%]; new patients: 12 patients [60.0%]).
17 patients (39.5%) had experienced CAM2029-related AEs in the extension part (placebo roll-overs: 4 patients [50.0%]; CAM2029 roll-overs: 6 patients [40.0%]; new CAM2029 7 patients [35.0%]). The 3 most common CAM2029-related AEs were injection site swelling (11.6%), injection site erythema (9.3%), and injection site mass (9.3%). They are known ADRs of octreotide.

The frequency of ADRs during the extension part were slightly higher in the placebo roll-overs, compared to CAM2029 roll-overs, and new patients. This is potentially related to the low number of patients (8 patients). All ADRs reported in this subgroup were in the SOC « General disorders and administration site conditions ». No new safety data could be drawn from these results.
Regarding SAEs, one fatal SAE had occurred in the extension part. The patient (a reinvited new patient) died from suspected cardiac arrest. The event of death was assessed as not related to CAM2029, and not related to concurrent disease, medical history, concomitant medications, or trial participation.
Overall, the additional data on the fatal case do not provide any new safety information.
Amongst the remaining SAEs, only acute cholecystitis was assessed as related to CAM2029. This is a known ADR of octreotide and listed in the SmPC.
No patient discontinued the treatment due to inefficacy.

2.4.6.3. Serious adverse event/deaths/other significant events

In the pivotal study, the proportion of reported AESIs was lower in the treatment group compared to the placebo group (48.9 % vs. 62.5 %), with most AESIs related to the IMP.
In the phase 3 open label trial, more than half of patients experienced an AESI (56.3%), with injection site reactions being the most commonly reported AESI and all of them were assessed as treatment-related. The other treatment-related AESIs were cholelithiasis, hyperglycaemia, neoplasm, vitamin B12 deficiency, tachycardia, liver transaminase increased, thyroid function abnormality, and acute pancreatitis.

Table 44 Trial HS-19-647: Non-injection site AESIs by PT and patient group – whole trial (safety analysis set)

AESI PT	Placebo roll-overs (N=18) n (%)	CAM2029 roll-overs (N=36) n (%)	New patients (N=81) n (%)	Overall (N=135) n (%)
Any non-injection site AESI	5 (27.8)	12 (33.3)	16 (19.8)	33 (24.4)
Cholelithiasis				
Any	5 (27.8)	3 (8.3)	4 (4.9)	12 (8.9)
Cholelithiasis	4 (22.2)	1 (2.8)	3 (3.7)	8 (5.9)
Cholecystitis	0	0	1 (1.2)	1 (0.7)
Cholecystitis acute	0	1 (2.8)	0	1 (0.7)
Cholecystitis chronic	0	1 (2.8)	0	1 (0.7)
Gallbladder enlargement	1 (5.6)	0	0	1 (0.7)
Hyperglycaemia				
Any	0	2 (5.6)	6 (7.4)	8 (5.9)
Glucose tolerance impaired	0	1 (2.8)	5 (6.2)	6 (4.4)
Diabetes mellitus	0	0	1 (1.2)	1 (0.7)
Diabetes mellitus inadequate control	0	1 (2.8)	0	1 (0.7)
Glycosylated haemoglobin increased	0	0	1 (1.2)	1 (0.7)
Hyperglycaemia	0	0	1 (1.2)	1 (0.7)
Neoplasm				
Any	0	4 (11.1)	3 (3.7)	7 (5.2)
Haemangioma of liver	0	3 (8.3)	0	3 (2.2)
Breast neoplasm	0	1 (2.8)	0	1 (0.7)
Cervix carcinoma recurrent	0	0	1 (1.2)	1 (0.7)
Lipoma	0	0	1 (1.2)	1 (0.7)
Bowen's disease	0	0	1 (1.2)	1 (0.7)
Vitamin B12				
Any	0	2 (5.6)	4 (4.9)	6 (4.4)
Vitamin B12 deficiency	0	2 (5.6)	4 (4.9)	6 (4.4)
Tachycardia				
Any	0	1 (2.8)	3 (3.7)	4 (3.0)
Sinus tachycardia	0	0	2 (2.5)	2 (1.5)
Loss of consciousness	0	1 (2.8)	0	1 (0.7)
Atrial fibrillation	0	0	1 (1.2)	1 (0.7)
Liver transaminases				
Any	0	2 (5.6)	0	2 (1.5)
Gamma-glutamyltransferase increased	0	1 (2.8)	0	1 (0.7)
Liver function test increased	0	1 (2.8)	0	1 (0.7)
Ultrasound liver abnormal	0	1 (2.8)	0	1 (0.7)
Thyroid function abnormalities				
Any	0	1 (2.8)	1 (1.2)	2 (1.5)
Primary hypothyroidism	0	0	1 (1.2)	1 (0.7)
Thyroxine free decreased	0	1 (2.8)	0	1 (0.7)
Pancreatitis				
Any	0	1 (2.8)	0	1 (0.7)
Pancreatitis acute	0	1 (2.8)	0	1 (0.7)

The applicant reported seven cases of neoplasms during phase 3 trials, with one of three cases of liver haemangioma assessed as probably related to CAM2029 treatment.

The remaining cases of neoplasms were assessed by the applicant as not related to CAM2029. In addition, the applicant reported some literature data suggesting no increased risk of neoplasms with octreotide.

It is acknowledged that there is no evidence that octreotide specifically causes hepatic haemangioma (the most reported neoplasms). However, it can lead to hepatic toxicity, manifested by liver function test abnormalities,

hepatitis, and cholestasis. This hepatic toxicity could potentially contribute to vascular alterations in the liver, but a direct relationship with hepatic haemangioma has not been clearly established.
While the applicant highlights octreotide's antitumor effects, these findings primarily concern malignant tumours. The absence of specific data on benign neoplasms such as haemangioma does not exclude a potential association.
In summary, the available data do not allow for the exclusion of a causal relationship between CAM2029 and the occurrence of liver haemangioma. The clustering of cases in a relatively small trial population, the probable relationship in one case, coupled with the fact that the SmPC of Mycapssa include this ADR with a frequency "uncommon", and the mechanistic plausibility described above, indicated the need for updating the product information.
Liver haemangioma was included as ADR in the SmPC (section 4.8) with the frequency uncommon and neoplasm will be monitored in the future PSURs.
Regarding serious adverse events, in the phase 3 pivotal study, no IMP-related serious adverse events (SAEs) occurred in the CAM2029 treatment arm, while one SAE of cholecystitis in the placebo arm was assessed as IMP-related. In the open label phase 3 study, two SAEs were assessed as CAM2029 related: 1 patient with a Grade 2 SAE of cholelithiasis and another patient with a Grade 1 SAE of acute cholecystitis. Grade 3 SAEs occurred in 9 patients (6.7%) including 3 Grade 3 SAEs that occurred in CAM2029 roll-overs already in HS-18-633. The only Grade 3 SAE reported in >1 patient was COVID 19 (2 patients).
No deaths had occurred in the clinical trials with CAM2029 in the programme for treatment of acromegaly as of 21-Jan-2024.

2.4.6.4. Laboratory findings

The safety laboratory markers for these studies were the following: Clinical Chemistry, Clinical Haematology, Clinical Coagulation, Liver Enzymes (including ALT, Alkaline phosphatase, AST, Bilirubin and GGT), Prolactin, Thyroid Hormones, Glucose and Haemoglobin A1c Values.

The vital signs for physical examinations were the following: Supine Systolic and Diastolic Blood Pressure, Pulse Rate, Respiratory Rate and Electrocardiogram.

Summary of Laboratory Evaluations

No clinically meaningful trends in mean values of laboratory parameters over time or changes from baseline were observed for any laboratory parameter (including clinical chemistry, clinical haematology, clinical coagulation, prolactin, and thyroid hormones), in neither treatment arm in HS-18-633, nor in any patient group in HS-19-647.
Abnormal laboratory values assessed as clinically significant were reported as AEs. In HS-18-633, clinically significant laboratory abnormalities of CTCAE Grade 3 included high levels of amylase and lipase in 1 patient receiving CAM2029 (reported as a Grade 1 AE of acute pancreatitis; not IMP related), high levels of lipase in 1 patient receiving placebo (reported as an IMP-related Grade 1 AE), and high urate levels in 1 patient receiving placebo (reported as a Grade 1 AE; not related).
In HS-19-647, clinically significant laboratory values reported as AEs assessed as related to CAM2029 included 2 patients with hyperglycaemia-related AEs (of whom 1 patient had diabetes mellitus reported already as medical history), 1 patient with vitamin B12 deficiency, and 1 patient with decreased HDL. These AEs were all of Grade 1 or Grade 2.
No patients in any trial met the criteria for Hy's law (ALT or AST levels ≥3×ULN plus total bilirubin ≥2×ULN).
The applicant concluded that the laboratory findings were in line with the safety profile of octreotide. This is endorsed.

Summary of Vital Signs

There were no clinically relevant changes in mean values of vital signs parameters over time, neither in HS-18-633, nor in HS-19-647.

Clinically significant abnormal vital sign values reported as AEs included 1 patient in the CAM2029 treatment arm of HS-18-633 with an AE of hypertension and 2 patients in HS-19-647 (1 patient with a Grade 1 AE of sinus tachycardia assessed as possibly related to CAM2029 and 1 patient with a Grade 1 AE of decreased heart rate assessed as not related to CAM2029).

No clinically relevant changes in mean values of ECG parameters were observed over time, neither in HS-18-633, nor in HS-19-647.

No patients in HS-18-633 had any abnormal clinically significant ECG value during the trial. Further, no patients in the CAM2029 treatment group had any QTcF value >450 ms, while 1 patient in the placebo treatment arm had a post-baseline QTcF value in the interval >450 ms to ≤480 ms. The largest post-baseline increases in QTcF across all time points were in the interval >30 ms to ≤60 ms and were recorded in 1 patient in each treatment arm.

In HS-19-647, no patients had any QTcF value >480 ms. Across all time points, the highest increase in QTcF from the first dose of CAM2029 was between >30 ms and ≤60 ms (recorded in 12 patients [8.9%]).

No correlation was observed between octreotide concentrations and QTcF values or change in QTcF from active baseline for CAM2029, neither in HS-18-633, nor in HS-19-647.

In terms of QTcF intervals, the phase 3 trials demonstrated that CAM2029 does not significantly affect QTcF intervals, with no observed correlation between octreotide concentrations and QTcF values or changes.

The applicant confirmed with response to D-120 LoQ that laboratory parameters were not assessed at Cmax during the phase 3 trials. While safety monitoring was conducted throughout the trials and no laboratory values were linked to safety issues, the absence of assessments at Cmax preclude the evaluation of the maximum effect of octreotide on laboratory parameters.

For vital signs, the applicant highlighted that these were assessed at multiple time points, including at or near Cmax, in three phase 1 studies. However, this was not systematically done across the phase 3 trials, where vital sign measurements were less frequent and mostly pre-dose. This is acceptable given that no clinically meaningful trends in mean values of laboratory and vital signs parameters over time or changes from baseline were observed in phase 3 clinical trials.

2.4.6.5. In vitro biomarker test for patient selection for safety

N/A

2.4.6.6. Safety in special populations

- **Paediatric Population**

The safety of CAM2029 has not been evaluated in children since CAM2029 is not proposed to be indicated for the treatment of acromegaly in children (also called gigantism) as the prevalence is very low in this age group.

- **Elderly**

- **Trial HS-18-633**

At least one IMP-related AE was reported in 17 of the 34 patients (50.0%) aged 18 to 64 years and, similarly, in 7 of the 13 patients (53.8%) aged ≥65 years in the CAM2029 treatment arm. In the placebo treatment arm, ≥1 IMP-related AE was reported in 11 of the 19 patients (57.9%) aged 18 to 64 years and 4 of the 5 patients

(80.0%) aged ≥65 years. The small subset of patients aged ≥75 years included only 3 patients in the CAM2029 treatment arm and 1 patient in the placebo treatment arm.

- **Trial HS-19-647**

The proportion of patients with AEs within the different AE categories was overall similar in patients aged 18 to 64 years and patients aged ≥65 years. From the first dose of CAM2029, i.e., when including events that occurred in HS-18-633 for CAM2029 roll-overs, CAM2029-related AEs occurred in 64 of 114 patients (56.1%) aged 18 to 64 years and 12 of 21 patients (57.1%) aged ≥65 years. In the small subset of patients aged ≥75 years, 3 of 4 patients (75.0%) had ≥1 CAM2029-related AE.

Overall, in the clinical trials for CAM2029, a few elderly patients were included. Specifically, 13 patients aged ≥65 years in the pivotal study and 21 in the open label study. Reported IMP-related AEs were slightly higher in elderly patients across both trials. This suggests a potential increased sensitivity of CAM2029 in this age group.

Currently, there is no proposal for special dosage regimen for elderly population. The SmPC states that "there is no evidence of reduced tolerability or altered dose requirements in elderly patients treated with octreotide", and "Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out."

The applicant acknowledged the limited number of elderly patients in the trials (17.1%), they argued that this is reasonable given the rarity of acromegaly and the established safety profile of octreotide. This was accepted by the CHMP.

Cardiovascular AEs

The applicant discussed the cardiovascular risks in elderly patients with acromegaly and highlighted the benefits of octreotide in improving cardiac outcomes. The provided literature references support the notion that cardiovascular improvements occur with biochemical control. However, the data from the phase 3 trials show a slightly higher incidence of cardiac adverse events in elderly patients.

GI AEs

The applicant stated that GI AEs are similar between elderly and younger patients. Phase 3 trial data support this, showing comparable AE rates with no severe GI events or treatment discontinuations in elderly patients. This response is supported.

Glucose metabolism disorders

The applicant indicated that no hyperglycemia-related AEs were reported in elderly patients across phase 3 trials. While this suggests no strong safety signal, the small number of elderly participants limits the ability to detect rare but clinically relevant events.

Renal and hepatic impairment

The PopPK analysis suggested found no significant effect of creatinine clearance on the distribution and elimination of octreotide administered as CAM2029 in subjects with normal renal function or mild kidney impairment. However, only one patient with moderate renal impairment was included, limiting conclusions for this subgroup. A serious renal failure event was deemed unrelated to CAM2029, which is a reasonable assessment. For hepatic impairment, the applicant noted that no patients with moderate or severe dysfunction were studied, highlighting the need for further data.

Table 45 Summary of AEs by age category in HS-18-633 (safety analysis set)

Category	Age <65 (N=53) n (%)	Age 65-74 (N=14) n (%)	Age 75-84 (N=4) n (%)	Overall (N=71) n (%)

Any AE	40 (75.5)	13 (92.9)	3 (75.0)	56 (78.9)
Any SAE	4 (7.5)	1 (7.1)	1 (25.0)	6 (8.5)
- Fatal	0	0	0	0
- Hospitalization or prolongation of existing hospitalization	4 (7.5)	1 (7.1)	1 (25.0)	6 (8.5)
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	0	0	0	0
AE leading to IMP discontinuation	2 (3.8%)	3 (21.4%)	0	5 (7.0%)
AE leading to withdrawal from trial	0	0	0	0
Psychiatric disorders (SOC)	1 (1.9)	0	0	1 (1.4)
Nervous system disorders (SOC)	7 (13.2)	1 (7.1)	1 (25.0)	9 (12.7)
Accidents and injuries (SOC: Injury, poisoning and procedural complications)	2 (3.8)	1 (7.1)	0	3 (4.2)
Cardiac disorders (SOC)	1 (1.9)	0	1 (25.0)	2 (2.8)
Vascular disorders (SOC)	2 (3.8)	0	0	2 (2.8)
Cerebrovascular disorders (SOC)	0	0	0	0
Infections and infestations (SOC)	10 (18.9)	3 (21.4)	1 (25.0)	14 (19.7)
Anticholinergic syndrome (PT)	0	0	0	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, fall, black out, syncope, dizziness, ataxia, fracture (PTs)	3 (5.7)	0	0	3 (4.2)

Table 46 Summary of AEs by age category – HS-19-647 main part (safety analysis set)

Category	**Age <65 (N=114) n (%)**	**Age 65-74 (N=17) n (%)**	**Age 75-84 (N=4) n (%)**	**Overall (N=135) n (%)**
Any AE	85 (74.6)	13 (76.5)	4 (100)	102 (75.6)
Any SAE	9 (7.9)	4 (23.5)	2 (50.0)	15 (11.1)
- Fatal	0	0	0	0
- Hospitalization or prolongation of existing hospitalization	8 (7.0)	4 (23.5)	2 (50.0)	14 (10.4)
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	1 (0.9)	0	0	1 (0.7)
AE leading to IMP discontinuation	2 (1.8%)	0	0	2 (1.5%)
AE leading to withdrawal from trial	0	0	0	0
Psychiatric disorders (SOC)	4 (3.5)	0	0	4 (3.0)
Nervous system disorders (SOC)	25 (21.9)	1 (5.9)	1 (25.0)	27 (20.0)
Accidents and injuries (SOC: Injury, poisoning and procedural complications)	4 (3.5)	1 (5.9)	1 (25.0)	6 (4.4)

Cardiac disorders (SOC)	6 (5.3)	1 (5.9)	0	7 (5.2)
Vascular disorders (SOC)	4 (3.5)	1 (5.9)	0	5 (3.7)
Cerebrovascular disorders (SOC)	0	0	0	0
Infections and infestations (SOC)	34 (29.8)	5 (29.4)	4 (100)	43 (31.9)
Anticholinergic syndrome (PT)	0	0	0	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, fall, black out, syncope, dizziness, ataxia, fracture (PTs)	3 (2.6)	1 (5.9)	2 (50.0)	6 (4.4)

- **Sex**

The clinical trials for CAM2029 showed that the proportion of patients experiencing adverse events (AEs) was generally similar between men and women. This indicates that the overall safety profile of CAM2029 does not significantly differ between genders. Except of discontinuation of treatment in healthy volunteers which was higher in women, injection site AEs were also more commonly reported in women. Overall, subgroup analysis by gender showed similar trends to the safety analysis set.

- **Body Mass Index**

In the clinical trials for CAM2029, IMP-related AEs showed variability based on the BMI. Specifically, in the pivotal phase, patient with BMI of ≥18.5 to <25 experienced more IMP-related AEs in both treatment and placebo groups. Conversely, in the open label trial, the subgroup of patients with a BMI of ≥30 kg/ m^2 had a slightly higher proportion of IMP-related AEs. No consistent pattern in the distribution of patients with adverse events (AEs) across different AE categories when comparing various BMI categories.

- **Renal and Hepatic Impairment**

Octreotide did not show renal toxicity, and impaired renal function did not seem to affect the total exposure (AUC) of octreotide when administered as SC injection. The SmPC of Oczyesa indicates that the drug can be used in patients with mild, moderate, or severe renal impairment, and clinical response and tolerability should be monitored.

It is also mentioned in the SmPC that no significant effect of creatinine clearance (CLCR) on clearance of octreotide with Oczyesa was found analysing 191 study participants with normal renal function (CLCR ≥90 mL/min), 24 with mild renal impairment (CLCR 60-89 mL/min), and 1 subject with moderate renal impairment (CLCR 30-59 mL/min). Impaired renal function did not affect the total exposure (AUC) with subcutaneous short-acting octreotide.

Regarding patients with hepatic impairment, the SmPC indicates that patients with liver cirrhosis showed prolonged elimination of octreotide following subcutaneous administration of drug (but not patients with fatty liver disease). The SmPC does not currently recommend dose adjustments for these patients. This was accepted by the CHMP.

- **Use in Pregnancy and Lactation**

Non-clinical Reproduction Studies

According to the Sandostatin SmPC, reproduction studies in animals revealed no evidence of teratogenic, embryo/foetal, or other reproduction effects due to octreotide at parental doses of up to 1 mg/kg/day. Some retardation of physiological growth was noted in the offspring of rats, which was transient and attributable to GH inhibition brought about by excessive PD activity.

Furthermore, in the pre- and post-natal developmental studies, reduced growth and maturation were observed in the F1 offspring of dams given octreotide during the entire pregnancy and lactation period. Delayed descent of the testes was observed for male F1 offsprings, but fertility of the affected F1 male pups remained normal. Thus, the above-mentioned observations were transient and considered to be the consequence of GH inhibition.

Animal reproduction studies have not been conducted with CAM2029.

Data from use of octreotide in pregnant women are limited. Most reports were received after post-marketing use of octreotide and more than 50% of exposed pregnancies were reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100 to 1200 µg/day of Sandostatin or 10 to 40 mg/month of Sandostatin LAR. Congenital anomalies were reported in about 4% of pregnancy cases for which the outcome is known. No causal relationship to octreotide is suspected in these cases.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. According to the SmPC for Sandostatin, as a precautionary measure, it is preferable to avoid the use of Sandostatin during pregnancy.

Use of CAM2029 in Pregnancy in Clinical Trials

Two pregnancies, both in Phase 1 trials, have been reported in subjects exposed to CAM2029:

One subject receiving 10 mg CAM2029 SC in trial HS-07-291 became pregnant despite use of contraception. An induced abortion was performed, which was reported as an SAE (classified as an SAE due to being a medically important event) and was assessed as not related to the IMP.

One subject in trial HS-11-411 became pregnant and was withdrawn from the trial after the second injection of 10 mg CAM2029 and had an uncomplicated, spontaneous delivery at full-term. The child was healthy with no complications, malformations or illnesses reported.

Lactation

According to the Sandostatin SmPC, it is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breast-feed during Sandostatin treatment.

Although studies regarding octreotide use during breastfeeding are few, in various case reports with patients receiving the SC form of octreotide, there was a significant level of the drug found in breast milk, almost at similar concentrations as in serum. However, further studies showed that the oral absorption of octreotide was not very efficient.

No use of CAM2029 has been reported during lactation.

2.4.6.7. Immunological events

Samples were analysed for ADAs in HS-18-633 and HS-19-647. No samples were ADA-positive at any timepoint.

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

No dedicated studies were provided to assess safety related to drug-drug interactions but heart rate disorder such as tachycardia and bradycardia were reported as Oczyesa adverse events. Thus, caution should be exercised in case of co-administration with cardiovascular treatment.

2.4.6.9. Discontinuation due to adverse events

- **Trial HS-18-633**

Four patients (8.5%) in the CAM2029 treatment arm and 1 patient (4.2%) in the placebo treatment arm discontinued treatment due to ≥1 AE. The AEs that led to IMP discontinuation in the CAM2029 treatment arm included injection site induration (2 patients), injection site erythema (1 patient), and migraine (1 patient). The AE that led to IMP discontinuation in the placebo treatment arm was injection site erythema.

All AEs that lead to discontinuation of the IMP were Grade 1 or Grade 2 and assessed as related to IMP.

Of note, one additional patient in the placebo treatment arm was discontinued from treatment with placebo due to worsening of clinical signs and symptoms of acromegaly in combination with increased IGF-1 levels and was switched to rescue medication with SoC.

All 6 patients who discontinued treatment remained in the trial on SoC and performed all planned visits.

- **Trial HS-19-647**

Up to 21-Jan-2024, 2 patients (1.5%; both new patients), discontinued treatment with CAM2029 in HS-19-647 due to an AE. The AEs leading to IMP discontinuation were both non-serious and included a CAM2029-related Grade 1 AE of injection site haemorrhage and a CAM2029-related Grade 1 AE of depression. Both patients continued participation in the main part of the trial and the AEs resolved.

Additionally, a third patient (a new patient) experienced an SAE of recurrent cervix carcinoma, which was assessed as not related to CAM2029 by the Investigator. This patient was going to be treated for this SAE and considered further participation in the trial to be impossible. The patient therefore withdrew consent [HS-19-647].

Adverse Events Leading to Dose Reduction: Trials HS-18-633 and HS-19-647

The dose could be reduced due to tolerability/safety in trials HS-18-633 and HS-19-647. No AEs resulted in a dose reduction in HS-18-633.

One AE (CAM2029-related Grade 1 diarrhoea; resolved after 4 days) in a placebo roll-over patient in HS-19-647 resulted in dose reduction after the first administration of CAM2029.

Overall, the treatment was discontinued in 7 patients in the phase 3 trials due to IMP-related AEs, including injection site induration, injection site erythema, migraine, injection site haemorrhage, and depression. Injection site reactions are very common ADRs, depression is not a known ADR of octreotide and warrants further discussion by the applicant.

Regarding dose reduction, in the phase 3 trials, one patient required a dose reduction due to diarrhoea. The event was subsequently resolved following the dose adjustment, indicating that dose management can be an effective strategy in mitigating some of the adverse events.

2.4.6.10. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.7. Discussion on clinical safety

The safety profile of CAM2029 was assessed across seven clinical trials, including four phase 1 trials, one phase 2 trial, and two phase 3 trials. In addition, safety information on the reference medicinal product SC Sandostatin IR is available.

Regarding treatment duration in the pivotal study, 42 out of 47 patients (almost 90%) were treated for ≥24 weeks, which aligns with the CHMP scientific advice recommending a core phase of 6 months.

In the open label phase 3 study, the overall mean duration of exposure to CAM2029 is about one year (55.0 weeks). By the end of the extension phase, new patients and CAM2029 roll-overs will have been exposed to CAM2029 for 104 weeks, and placebo roll-over patients for 80 weeks.

Absence of treatment-naive patients in the clinical development program

No treatment-naïve patients were included in the clinical development program of CAM2029. In the pivotal phase 3 trial, included patients were biochemically controlled acromegaly who had been treated with octreotide LAR or lanreotide autogel (ATG) for at least 3 months at screening. In the phase 3 Trial HS-19-647, 18 patients who received placebo for 6 months in HS-18-633 rolled over to HS-19-647. One of the 18 placebo roll-overs switched to rescue medication in HS-18-633 before being enrolled into HS-19-647. Thus, the applicant considers that 17 patients were not pharmacologically treated at start of HS-19-647 (had not been treated with octreotide or any other acromegaly treatment for 6 months during participation in HS-18-633).

Considering the adaptation period of the gastrointestinal and pancreatic effects of octreotide, GI-related events are more expected in subjects exposed to octreotide for the first time. This explains the findings in healthy volunteer trials as compared with the ones in the trials in patients with acromegaly. Gastrointestinal-related adverse events were notably more common in subjects exposed to octreotide for the first time compared to patients on stable SRL doses (for example, 70% subjects experienced diarrhoea in phase 1 trials, versus 8.9% in phase 3 open label trial). During the procedure, it was assessed whether safety data in treatment-naïve patients with acromegaly could be extrapolated from data in controlled patients included in phase 3 clinical trials, taking into account that GI adverse reactions would be more frequent in naive patients given the adaptation period of the GI and pancreatic effects of octreotide. It was concluded that it is not possible to extrapolate safety data from healthy volunteers and pharmacologically washed-out patients to drug-naïve patients and the safety of CAM2029 was not characterized in these patients.

Overall, the applicant response failed to adequately justify the extrapolation of safety data from healthy volunteers and pharmacologically washed-out placebo roll-over patients to drug-naïve acromegaly patients. Indeed, these patients cannot be considered as drug-naïve patients. Furthermore, the provided data indicates a higher risk of GI and pancreatic AEs in these groups the initial broad indication was restricted accordingly to maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues.

Medical devices used in the clinical development program

Two different devices were used during the clinical development: a pre-filled syringe and a pre-filled pen. Given the substantial difference with the reference medicinal product as regards to the device, as well as the fact that

most other octreotide-containing products use syringe devices, the applicant was asked to provide a comprehensive analysis of potential risks in association with self-administration by patients using a pre-filled pen with a particular attention on the potential risk of inappropriate dosing (underdosing and overdosing) due to incorrect self-administration.
The clinical trials did not report any adverse events related to device malfunctions, such as overdosing or underdosing. Still, the risk of underdosing was acknowledged, if the pen is removed prematurely. The product information leaflet includes detailed instructions and illustrations for proper use (IFU), this is endorsed.

Medication errors (including underdosing cases) will be reviewed in each PSUR, accompanied by a discussion on the appropriateness of the established risk minimisation measures to prevent medication errors. This is endorsed.

Adverse events (AEs) and adverse drug events (ADRs)

Regarding AEs, in the pivotal phase 3 trial, the proportion of patients reporting AEs was almost similar Regarding AEs, in the pivotal phase 3 trial, the proportion of patients reporting AEs was almost similar between CAM2029 group and placebo group. However, the proportion of IMP-related AEs was lower in the CAM2029 group compared to the placebo group (51.1% vs. 62.5%). The most common ADRs were injection site reactions (40.4%) (erythema, swelling, and pruritus), followed by gastrointestinal ADRs (10.6%) (upper abdominal pain, diarrhoea, and nausea), musculoskeletal and connective tissue ADRs (4.3%) (arthralgia, joint swelling), nervous system ADRs (6.4 %) (headache), hepatobiliary ADRs (4.3%) (chronic cholecystitis and hepatic cyst), and skin and subcutaneous tissue ADRs (4.3%) (pruritus and erythema).

In the open-label phase 3 trial, IMP-related AEs were comparable between the roll-over groups (CAM2029 and placebo) and lower in the new patient group. The nature and distribution of reported ADRs were generally similar to the pivotal study, with slight frequency differences between the groups. Cholelithiasis was reported in six cases (4.4%) during the open label phase 3 trial, whereas it was not reported in the pivotal study. Cholelithiasis is a known ADR of octreotide and listed as a very common ADR in the product information. Octreotide can induce cholelithiasis by inhibiting gallbladder motility and reducing bile secretion, leading to bile stasis and stone formation.

The applicant addressed with the response to the D-120 LoQ the following reported adverse drug reactions associated with CAM2029 in phase 3 trials: *hepatic cysts, increased glycosylated haemoglobin, decreased HDL, decreased weight, vitamin B12 deficiency, and vertigo*. All of them were reported in 0.7% of patients, occurring as single, non-serious cases.

For hepatic cysts, the applicant highlighted a pre-existing condition in some patients and the absence of evidence linking octreotide treatment to hepatic cyst formation, this is consistent with the reference product SmPC and other octreotide-based products.

Regarding increased glycosylated haemoglobin, the response aligns with known effects of octreotide on glucose regulation and is already addressed in the SmPC. In addition, the absence of literature evidence linking octreotide to decreased HDL or vertigo supports the conclusion to not update the SmPC.

Decreased weight and vitamin B12 deficiency are acknowledged as potential effects of octreotide, but these are already addressed in the SmPC under related categories (anorexia in section 4.8 and vitamin B12 deficiency in section 4.4 of the SmPC). This is in line with the reference product and other octreotide-based products.

In addition, the following CAM2029-related AEs not known to be related to somatostatin analogues were reported and were also discussed: *joint swelling, electrocardiogram T wave inversion, depression, insomnia,*

abnormal uterine bleeding, and breast mass, postmenopausal haemorrhage. The Applicant provided a thorough analysis for each reported ADR, emphasizing their limited occurrence (single cases) and lack of established association with octreotide or somatostatin analogues in the literature. They also provided plausible alternative explanations, such as underlying medical histories or pre-existing conditions for most events.

Adverse Events of Special Interest (AESIs)

Regarding AESIs, in the pivotal study, the proportion of reported AESIs was lower the treatment group compared to the placebo group (48.9 % vs. 62.5 %), with most AESIs related to the IMP.

In the phase 3 open label trial, more than half of patients experienced an AESI (56.3%), with injection site reactions being the most commonly reported AESI and all of them were assessed as treatment-related. The other treatment-related AESIs were cholelithiasis, hyperglycaemia, neoplasm, vitamin B12 deficiency, tachycardia, liver transaminase increased, thyroid function abnormality, and acute pancreatitis. In total, 7 cases of AEs neoplasms have been reported, the narratives were provided as requested.

Three cases of haemangioma of liver were reported, of which one was assessed as related to the treatment. Liver haemangioma was included as an ADR in the SmPC (section 4.8) with the frequency uncommon and neoplasms will be monitored in the future PSURs.

Serious adverse events (SAEs) and serious adverse reactions (SARs)

Regarding serious adverse events, in the phase 3 pivotal study, no IMP-related serious adverse events (SAEs) occurred in the CAM2029 treatment arm, while one SAE of cholecystitis in the placebo arm was assessed as IMP-related. In the open label phase 3 study, two SAEs were assessed as CAM2029 related: 1 patient with a Grade 2 SAE of cholelithiasis and another patient with a Grade 1 SAE of acute cholecystitis. Grade 3 SAEs occurred in 9 patients (6.7%) including 3 Grade 3 SAEs that occurred in CAM2029 roll-overs already in HS-18-633. The only Grade 3 SAE reported in >1 patient was COVID 19 (2 patients).

Long-term safety

Regarding long-term safety, the applicant provided long-term safety data for CAM2029, focusing on results from study HS-19-647. They report data for 109 patients treated for at least one year, which demonstrate that the safety profile of CAM2029 is consistent with other injectable octreotide products. In addition, the final clinical trial report of the 52-week extension study will be provided in the post- marketing setting. The applicant explained that interim trial report will not be provided as the last patient last visit is planned on May 2025. This is endorsed.

One fatal SAE had occurred in the extension part, but the event of death was assessed as not related to CAM2029.

Treatment discontinuation due to adverse events

Among patients with acromegaly, a total of 7 patients discontinued treatment due to IMP-related AEs. During the pivotal phase, treatment discontinuation was higher in the treatment group compared to placebo group (4 vs.1 respectively). The adverse events leading to discontinuation in this phase were related to the IMP and included injection site induration, erythema, and migraine.

In addition, in the ongoing open label phase trial, 3 patients discontinued treatment due to AEs, specifically injection site haemorrhage, depression, and recurrent cervix carcinoma (case not related to IMP). All these AEs were mild or moderate, and non-serious, except of the case of carcinoma which was classified as serious.

In another hand, one patient required a dose reduction due to diarrhoea. The event was subsequently resolved following the dose adjustment, indicating that dose management can be an effective strategy in mitigating some of the adverse events.

However, it was unclear if a pre-filled pen or a pre-filled syringe was used.

The applicant clarified that two separate pre-filled pens for dose adjustments were used: a 10 mg pen and a 20 mg pen. Since, the marketed product is a fixed-dose pre-filled pen of 20 mg clear guidance on managing ADRs, including practical recommendations for patients unable to tolerate the fixed 20 mg dose, were included in the SmPC to address this limitation and ensure safe and effective treatment.

2.4.8. Conclusions on clinical aspects

CAM2029 (Oczyesa) 20 mg pre-filled pen presents some advantages (ready to use pre-filled pen, low injection volume formulation administered through shorter and thinner needles compared to the existing long-acting products, self-administration by the patient himself, storage at ambient conditions), while combining a more rapid onset and long-acting release of octreotide for the patients with acromegaly compared to the other SRL treatments.

The applicant claimed the initial indication "treatment of acromegaly in adult patients in whom surgery is inappropriate or ineffective" but considering that no drug-naïve patients were included in the 2 phase 3 studies and only well-controlled patients were included in the pivotal study, this was restricted to "maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues".

The choice of the dose of CAM2029 20 mg every 4 weeks for the phase 3 studies was mainly based on the results of the phase 1 study [HS-11-411] and the limited clinical data of the phase 2 study [HS-12-455]. The CHMP has concluded that the 20mg dose is more adapted for the well-controlled patients with other SRLs who does not need a dose titration, rather than for the treatment initiation in the case of drug-naïve patients.

In the phase 3 studies, CAM2029 was not compared directly to other SRL treatments. Therefore, although CAM2029 was superior to placebo as regards to the proportion of well-controlled patients in the pivotal study, it is not known whether the efficacy of CAM2029 is superior or equivalent to the other SRL treatments. The comparisons with the other SRL treatments were only performed from baseline to W24 or W52.

In the 2 phase 3 studies, a fixed dose of CAM2029 20 mg every 4 weeks was administered to the patients with acromegaly whatever the type of patients (well-controlled or uncontrolled) and whatever the previous dose of the other SLRs treatments with only the possibility to reduce the dose to 10 mg CAM2029 every 4 weeks in case of adverse events.

The applicant only recommends in the SmPC a fixed dose of CAM2029 20 mg every 4 weeks for all the patients with acromegaly without any possibility of dose titration after start of treatment especially for the drug-naïve patients or any possibility of dose adjustment according to the patient's response.

The applicant did not keep the dose of 10 mg of Oczyesa because only 1 patient used this dose in the 2 phase 3 studies due to a mild diarrhoea. Indeed, there are no clinical data with this dose in the phase 3 studies.

In the pivotal phase 3 study, an overtime 20.5% decrease of the proportion of responders (IGF-1 ≤ ULN) among the well-controlled patients (previously treated with octreotide LAR or lanreotide ATG at baseline) was also observed in the treatment arm.

According to the subgroup analysis of study HS-19-647, only 1/3 of uncontrolled patients with other SRLs at baseline are well-controlled after 12 months of treatment with 20 mg CAM2029 every 4 weeks.

This decrease was justified by the applicant by the withdrawal of some patients and the fluctuation of the IGF-1 levels. Some results of the extension study were also provided, but , no conclusion as regards to the potential overtime reduced effectiveness of Oczyesa and the long-term safety could be drawn.

This was accepted by the CHMP, but the efficacy of Oczyesa will be closely monitored in the extension part of the study [HS-19-647] and complete results of this extension study are expected no later than Q1 2026.

As there is no possibility of dose adjustment of Oczyesa based on patient's response or safety, in line with the other somatostatin analogues, the applicant accepted to reflect in the SmPC (section 4.2) that monitoring of IGF-1 levels and assessment of symptoms should be made periodically per clinician discretion. Discontinuation of Oczyesa and switching patients to another somatostatin analogue should be considered if IGF-1 levels are not maintained after treatment with dose of 20 mg monthly or the patient cannot tolerate treatment with Oczyesa.

In conclusion, the safety profile of CAM2029 was assessed through seven clinical trials, including pivotal and long-term phase 3 studies. CAM2029, shows a safety profile comparable to other octreotide treatments, with common adverse effects including injection site reactions (erythema, swelling, and pruritus), followed by gastrointestinal ADRs (upper abdominal pain, diarrhoea, and nausea), musculoskeletal and connective tissue ADRs (arthralgia, joint swelling), nervous system ADRs (headache), hepatobiliary ADRs (chronic cholecystitis and hepatic cyst), and skin and subcutaneous tissue ADRs (pruritus and erythema). However, three cases of liver haemangioma were reported during the phase 3 studies, including one case assessed as probably related to the treatment and two cases assessed as not related. The available data do not allow for the exclusion of a causal relationship between CAM2029 and the occurrence of liver haemangioma. The clustering of cases in a relatively small trial population, the probable relationship in one case, coupled with the mechanistic plausibility described above, indicated the need to include this ADR in section 4.8 of the SmPC with a frequency uncommon.

The CHMP considers the following measures necessary to address the clinical issues:

The applicant accepted to submit the complete results of the OLE phase of stud HS-19-647 in the frame of a MEA planned in the RMP in relation to the safety concern "long-term safety" which is considered as a missing information at this stage. The RMP has been amended as requested.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 47 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

2.5.2. Pharmacovigilance plan

Table 48 Summary table of additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
A trial to assess the long-term safety of octreotide subcutaneous depot in patients with acromegaly (HS-19-647) Ongoing	To assess the overall long-term safety and tolerability of CAM2029	Long-term safety	Final report	31/03/2026

2.5.3. Risk minimisation measures

None

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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.

2.7. Product information

2.7.1. 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

This application concerns a hybrid version of octreotide prolonged-release solution for injection in pre-filled pen. The reference product Sandostatin is indicated for treatment of acromegaly. Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application does contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information was considered sufficient.

No bioequivalence study was provided, since the final market formulation and device configuration were assessed in the Phase 3 trials. This was acceptable.

3.1. Therapeutic context

3.1.1. Disease or condition

Acromegaly 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 Acromegaly (ACM) is based on a set of biochemical and clinical criteria. Acromegaly is diagnosed clinically by symptoms and confirmed biochemically via elevated GH and IGF-1 serum levels.

Clinical symptoms include signs and symptoms attributed to tumour mass effects compressing the surrounding structures (e.g., headaches and vision loss), and by the chronic overproduction of both GH and IGF-1 leading to disordered growth (progressive skeletal and soft tissue overgrowth, mainly at the extremities and head) and metabolic complications including insulin resistance, increased blood glucose levels, hyperinsulinemia, diabetes, and dyslipidaemia.

ACM mortality determinants include elevated GH and IGF-1 levels above the normal values, hypertension, cardiovascular and cerebrovascular disease, requirement for glucocorticoid replacement, and prior pituitary radiation.

3.1.2. Available therapies and unmet medical need

According to clinical practice guidelines and expert consensus, medical therapy is recommended for the treatment of acromegaly in patients who have persistent or recurrent disease despite surgery, or who are waiting for radiotherapy, or who are not candidates for surgery or radiotherapy because of poor health (Melmed et al 2018, Gisutina et al 2024).

For patients not cured by surgery, SRLs are considered the first-line medical therapy based on the established efficacy in acromegaly and a favourable safety profile.

Currently, there are 2 drug classes approved for the treatment of acromegaly in Europe: 3 injectable SRLs or somatostatin analogues (SSAs; octreotide, lanreotide, and pasireotide), and a GH receptor antagonist (pegvisomant). At present, SRLs are the most widely used drugs to control acromegaly.

Currently approved octreotide-based therapies have significant limitations related to their administration, including complex handling, inconvenient dosing, and a low, or very low, bioavailability, resulting in low or variable plasma exposure. Octreotide IR is administered by SC injections up to t.i.d. Octreotide LAR is administered IM every 4 weeks by a trained healthcare professional and must be reconstituted in multiple steps before injection. Furthermore, the bioavailability of octreotide LAR is low and is associated with a 7- to 10-day lag-phase before reaching therapeutic levels after the first dose.

Complex handling and/or inconvenient dosing of currently approved SRL therapies with large needles for IM or deep SC administration constitute significant limitations.

3.1.3. Main clinical studies

HS-18-633 was a phase 3, randomized, double-blind, placebo-controlled, multi-centre trial that assessed the efficacy and safety of CAM2029 versus placebo in patients with acromegaly.

Eligible patients, who were biochemically controlled on stable doses of monotherapy treatment with long-acting SRLs (octreotide LAR 10, 20, 30, 40 mg or lanreotide Autogel 60, 90 or 120 mg) and who had prior evidence of active acromegaly disease, were randomized to treatment with either CAM2029 or placebo in a 24-week Double-blind Treatment Phase. Both patients with and without prior transsphenoidal surgery could be included in the trial, provided that at least 6 months had elapsed since surgery. Patients who had received prior pituitary irradiation were excluded. The diagnosis of acromegaly by historical evidence of (persistent or recurrent) acromegaly should have been performed. Patients should be well-controlled with IGF-1 levels $\leq 1 \times$ ULN (adjusted for age and sex).

HS-19-647 was a phase 3, open-label, single - arm, multi-centre trial that assessed the long-term safety (primary objective) and efficacy (secondary objective) of CAM2029 in patients with acromegaly.

Main phase

[HS-19-647] enrolled both patients who were directly recruited into the trial ('new patients') and patients who completed participation in the preceding trial [HS-18-633] ("roll-over patients").
"Roll over patients" included patients who were randomised to CAM2029 ('CAM2029 roll-over patients') or to placebo ('placebo roll-over patients') in study [HS-18-633]. The treatment allocation in [HS-18-633] was kept blinded also after patients had rolled over to [HS-19-647], until the blind in [HS-18-633] was broken at the time of the primary analysis.
Of note, "placebo-roll-over" patients were considered by the applicant as "pharmacologically washed-out patients". These patients are regarded as "non-pharmacologically treated" for acromegaly as they remained untreated for 6 months during the previous trial.
The "new patients" had been treated with a stable dose of monotherapy of octreotide LAR (10, 20, 30 or 40 mg) or lanreotide ATG (60, 90 or 120 mg) for at least 3 months before screening.
Patients can be "well-controlled" with IGF-1 ≤ ULN or "uncontrolled" with IGF-1 >1×ULN and ≤2×ULN at screening. Patients can also have been treated with or without previous pituitary irradiation more than 3 years before screening or/and been treated with pituitary surgery performed more than 6 months before screening.

Extension phase

The 52-week extension part of the trial was added in protocol amendment 4 to enable further collection of long-term safety, efficacy, and PRO data on CAM2029, and to provide an opportunity for patients who completed treatment with CAM2029 in the main part of the trial to continue treatment with CAM2029.

3.2. Favourable effects

1) Pivotal phase 3 study [HS-18-633]

Primary endpoint

The primary objective was to assess the superiority of CAM2029 compared to placebo in biochemical response for IGF-1 at 24 weeks. The primary endpoint was "Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24 (average of the 2 measurements)".

This objective and primary endpoint are in line with the guidelines on treatment of acromegaly (Giustina et al 2010, Giustina et al 2024) and on the FDA guidance on acromegaly for industry of January 2023.

The primary endpoint "Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24 (average of the 2 measurements)" was significantly different compared to placebo (p = 0.0018] with one-sided p-values below the pre-defined significance level of 0.025.

The proportion of patients with mean IGF-1 levels ≤1×ULN at W24 was 72.2% in the CAM2029 group compared to 37.5% in the placebo group. The difference is 34.6% [95% CI (11.3, 57.9)].

Key secondary efficacy endpoints

The key secondary objectives were to assess the superiority of CAM2029 compared to placebo in biochemical response for IGF-1 at 24 weeks including patients with IMP dose reduction and for IGF-1 in association with mean GH cycle <2.5 µg/L at Week 24.

- The first key secondary efficacy endpoint "Proportion of patients with mean IGF 1 ≤1×ULN at Week 22 and Week 24, including patients with IMP dose reduction" was also met compared to placebo (p = 0.0018] with one-sided p-values below the pre-defined significance level of 0.025.

Of note, there is no dose reduction in any patient at W24.

- Second key secondary efficacy endpoint "Proportion of patients with mean IGF 1 ≤1×ULN at Week 22 and Week 24 and mean GH cycle <2.5 µg/L at Week 24" was also met compared to placebo (p = 0.0035] with one-sided p-values below the pre-defined significance level of 0.025.

The proportion of patients with mean IGF-1 levels ≤1×ULN and mean GH cycle <2.5 µg/L at Week 24 was 70 % in the CAM2029 group compared to 37.5% in the placebo. The difference of proportion was 32.3 [95%CI (8.8, 55.7)].

These results were expected as octreotide is a well-known substance with a relevant efficacy on IGF-1 levels in patients with acromegaly.

Of note, no patients reduce the dose due to adverse events. Only 1 placebo patients switched to rescue medication with SoC due to worsening of signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3×ULN at 2 consecutive visits.

4 patients treated with CAM2029 and one placebo patients were discontinued due to adverse events and were switched to SOC.

Other secondary efficacy endpoints were also assessed. The relevant secondary endpoints are the following:

- the time to loss of response defined as the earliest time when the IGF-1 levels of two consecutive measurements were >1×ULN, was statistically significantly longer in the CAM2029 treatment arm than in the placebo treatment arm, p<0.0001.

The median time to loss of response was not reached in the CAM2029 treatment arm, whereas it was 8.4 weeks in the placebo treatment arm. The hazard ratio (CAM2029/placebo) was 0.10 (95% CI: 0.04, 0.28; p<0.0001).

- change from Baseline to Week 24 in mean IGF-1 and GH

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

The analysis of change from baseline to Week 24 in IGF-1/ULN showed a significant increase in mean IGF-1/ULN in patients receiving placebo and stable values in patients receiving CAM2029, with a mean difference between the treatment arms of -0.47 in favour of CAM2029 (95% CI: -0.72, -0.21; two-sided p=0.0004).

. the mean GH levels remained around or below 1.0 µg/L throughout the 24-week treatment period in the CAM2029 treatment arm and increased to around 1.0 to 2.1 µg/L in the placebo treatment arm.

The analysis of change from baseline to Week 24 in mean GH levels showed a significant increase in the placebo treatment arm and stable values in the CAM2029 treatment arm, with a mean difference of

-0.5393 µg/L in favour of CAM2029 (95% CI: -0.9882 µg/L, -0.0905 µg/L; two-sided p=0.0185).

2) Long-term Phase 3 study [HS-19-647] is considered as a supportive study

Two baselines were defined in the trial.

The SoC baseline (or cumulative baseline) represented the baseline on SoC before receiving the first IMP dose in [HS-18-633] for roll-over patients and before receiving the first CAM2029 dose in [HS-19-647] for new patients (i.e., pre-dose Day 1 or the mean of Week -2 and pre dose Day 1, depending on the efficacy variable).

Additionally, another baseline was defined as the last measurement prior to the start of treatment with CAM2029. For "new patients" and "CAM2029 roll-over patient's, this baseline coincided with the SoC baseline.

For "placebo roll-over patients", the placebo baseline was the closest measurement before receiving the first CAM2029 dose in the HS-19-647 trial (i.e., pre-dose Week 24 or the mean of Week 22 and pre-dose Week 24, depending on the efficacy variable).

The main objective was the evaluation of the long-term safety throughout the trial. The secondary objectives included efficacy analyses at W52.

Two different definitions for biochemical response based on IGF-1 were applied:

- Proportion of Patients with Biochemical Response Based on IGF-1

• Proportion of patients with mean IGF-1 ≤1×ULN" at Week 50 and Week 52 (average of the two measurements, adjusted for age and sex at screening)

. There was an estimated increase in the proportions of responders at the end of main part of the trial compared to the SoC baseline of 12.7% (95% CI: 5.5%; 19.9%) in the overall population.

. For "new patients", the estimated increase was 22.8% (95% CI: 11.6%, 33.9%).

. For "CAM2029 roll-over patients", there was an estimated decrease in the proportion of responders among the patients at W50/52 from SOC Baseline of -2% (95% CI: -13.3%, 9.2%).

. For the "placebo roll-over patients",, there was an estimated increase from the placebo baseline for placebo roll-over patients (68.5% [95% CI:47.4%, 89.5%]).

The estimated differences in proportions of patients with mean IGF-1 <1.3×ULN was -2.5% (95% CI: -9.5%; 4.5%) in the overall population.

The estimated differences could not be determined using the model in "roll-over patients", since the proportions of responders in both patient groups were approximately 100% both at baseline and at the end of the main part of the trial.

3.3. Uncertainties and limitations about favourable effects

The pivotal phase 3 study [HS-18-633] has evaluated the effect of CAM2029 compared to placebo and not compared to SOC: octreotide LAR or lanreotide ATG.

The comparison of CAM2029 to SOC was only indirect. It is not known whether the efficacy of CAM2029 is superior or equivalent to the SOC. There are only comparisons of CAM2029 to SOC from baseline to W24.

The clinical data from study [HS-19-647] are considered as only supportive given the study design (open-label, single-arm.

The recommended fixed dose of CAM2029 20 mg 4qW has not been evaluated in treatment-naïve patients in the phase 3 studies.

No treatment- naïve patients were included in the 2 phase 3 studies and the dose of 20 mg 4qw CAM2029 has not been evaluated in these patients.
However, treatment-naïve patients with acromegaly need a dose titration with a starting dose which can be adjusted according to their response (IGF-1≤ ULN).
Therefore, the applicant accepted to restrict the indication of Oczyesa in "maintenance treatment in adult patients with acromegaly who have responded to and tolerated treatment with somatostatin analogues"in line with the target population of the 2 phase 3 studies. Indeed, the fixed dose of CAM2029 20 mg 4qW is more adapted for this population who does not need dose titration.

In study [HS-18-633], although the mean IGF-1 levels were maintained below ULN from baseline to W24, when looking at the secondary objective "proportion of responders" in terms of "proportion of patients with mean IGF 1 ≤1×ULN over time", the proportion of responders at baseline was 91.7% in both treatment arms. The proportion was 70.8% at the end of the trial (mean of the values at Week 22 and Week 24). The estimated difference in proportions (Week 22/Week 24-baseline) of -20.5% (95% CI: -33.7%, -7.3%). This highlights that there could be decrease of the proportion of responders over time compared to the baseline showing an overtime reduced effectiveness of the fixed dose of 20 mg 4qw CAM2029 in well-controlled patients with acromegaly already treated with SOC (octreotide LAR or lanreotide ATG). This could be due to the impossibility to adjust the dose according to the patient's response in line with the other SRL treatments.

Of note, at 3 months, 4/44 = 9% of patients were not "well-controlled" compared to baseline. This means that they did not respond to CAM2029 as the proportion of patients not well-controlled increased over time until W24.

However, this overtime reduced effectiveness of Oczyesa might be due to withdrawal of some patients and to the fluctuation of the IGF-1 levels. H The efficacy of Oczyesa will be closely monitored in the extension part of study HS-19-647. The results of this extension study will be provided no later than Q1 2026 in the frame of a MEA, as planned in the RMP. The RMP has been amended as requested.

The SmPC mentions that the treatment can be stopped or switched to another treatment, in the case IGF-1 levels are not maintained after treatment with dose of 20 mg monthly.

The proportion of patients treated with CAM2029 with GH< 1 µg/L was 83.3% at baseline and this proportion was 58.3% at W24.

Likewise, the proportion of patients treated with CAM2029 with GH < 2.5 µg/L was 95.8% at baseline and this proportion was 85.4% at week 24.

Of note, according to the guidelines on acromegaly, random GH < 1 µg/L was a therapeutic target, but it is no more considered in the last consensus of Giustina et al 2024.

Despite the biochemical and symptomatic control at baseline, a further decrease in signs and symptoms was observed when the patients were switched to treatment with CAM2029. However, the change from baseline to Week 24 of the AIS (Acromegaly Index Score) was not significant and there was no difference compared to placebo. This could highlight that at short-term, there is no improvement of the symptoms of acromegaly in well controlled patients treated with CAM2029.

Based on the applicant, it should be noted that trial [HS-18-633] was not powered to detect a difference between the treatment arms in AIS scores or ring size. Based on the data from study [HS-19-647], long-term exposure to CAM2029 appear to have a positive effect on signs and symptoms of acromegaly. However, this study was open-label, with a single arm and there was no comparison with placebo. Therefore, it is difficult to draw any conclusion.

Regarding the QoL, in study [HS-18-633], the Acro-QoL overall score have increased at Week 24 but the difference is not significant compared to placebo. Indeed, the AcroQoL Physical Domain Score and the Psychological Domain Total Score, as well as the Psychological Subdomain Scores, also showed significant improvements from baseline to Week 24 in the CAM2029 treatment arm, while no significant changes were seen in the placebo arm or between the treatment arms for any of the domains.

This highlights that the quality of life of the patients treated with CAM2029 is not significantly improved after 6 months of CAM2029 treatment compared to placebo.

It is also difficult to draw any conclusion as regards to patient's health QoL assessed with Acro-QoL and the satisfaction with treatment assessed through TSQM. Indeed, the trial [HS-18-633] was not powered to detect a difference between the treatment arms in AcroQoL scores and TSQM scores.

Based on the applicant, although there were minor differences in AcroQoL and TSQM scores between the CAM2029 and placebo treatment arms in HS-18-633, the data indicate that long-term use of CAM2029 can have a positive effect on patients' QoL and treatment satisfaction due to the convenience of administration of CAM2029. Indeed, in study [HS-19-647], increases were seen in the TSQM convenience, effectiveness, and global satisfaction domain scores from the SoC baseline to Week 52 in the overall population.

In study [HS-19-647], although there is an increase of the proportion of the responders (IGF-1 ≤ ULN) at week 52 in the overall population, in the "new patients" and in "placebo roll-over patients" following the treatment at a fixed dose of 20 mg 4qw CAM2029, there was a decrease of the proportion of well-controlled patients (IGF-1 ≤ ULN) in the "CAM2029 roll-over patients" (estimated difference –2.0%) (95% CI: -13.3, 9.2%).

Moreover, the mean IGF 1/ULN in the "new patients" remained stable around 1.2 to 1.3×ULN throughout the trial. Therefore, in these patients, the disease does not seem well-controlled according to the therapeutic target "IGF-1 levels ≤ULN" in the guidelines on diagnosis and treatment of acromegaly but were considered as well controlled by the applicant based on the other definition of the biochemical control in this study (IGF-1 < 1.3x ULN).

Of note, there was also a decrease of the proportion of "new patients" with mean IGF-1 <1.3×ULN from baseline to W52 (62.2% to 59.5%).

According to the subgroup analysis of study [HS-19-647] requested at D121, only 1/3 of uncontrolled patients with other SRLs at baseline are well-controlled after 12 months of treatment with 20 mg CAM2029 every 4 weeks.
In the phase 3 studies, there is no effect of CAM2029 on the size of the tumour. Therefore, the size of the tumour should be regularly evaluated during the treatment. This is in line with the other SRL treatments.

3.4. Unfavourable effects

Overall, the safety profile of CAM2029 is largely consistent with the safety profile of other injectable octreotide-based treatments, though certain potential safety concerns warranted particular attention.

Regarding AEs, in the pivotal phase 3 trial, 51.1% of patients experienced IMP-related AEs in CAM2020 group versus 62.5% in the placebo group. Common adverse drug reactions (ADRs) observed in phase 3 trials included injection site reactions such as erythema, swelling, and pruritus (40.4%), and GI disorders like upper abdominal pain, diarrhoea, and nausea (10.6%). Musculoskeletal ADRs like arthralgia (4.3%) and nervous system ADRs, such as headache (6.4 %), were also reported. Cholelithiasis, a well-known side effect of octreotide due to its impact on gallbladder motility, was reported in the open-label phase 3 trial (4.4%) but not in the pivotal trial. Given that cholelithiasis is a known and very common ADR of octreotide, its occurrence underlines the importance of monitoring hepatobiliary function during treatment with CAM2029.

In the main part of the trial, 102 of the 135 patients (75.6%) reported at least 1 AE since start of CAM2029 administration in trial HS-18-633 (for roll-over patients randomized to CAM2029) or in trial HS-19-647 (for placebo roll-over patients and new patients). The 3 most common AEs, regardless of relationship to CAM2029, were injection site erythema (27.4%), injection site swelling (15.6%), and COVID-19 (14.8%). AEs assessed as related to CAM2029 occurred in 76 patients (56.3%). The most commonly reported AEs related to CAM2029 were injection site AEs. The most common non-injection site AEs related to CAM2029 were diarrhoea (8.9%), headache (7.4%), and cholelithiasis (4.4%).

Serious adverse events (SAEs) were uncommon, with no IMP-related SAEs reported in the pivotal study for the CAM2029 group. However, in the open-label phase 3 trial, two CAM2029-related SAEs were observed, including cholelithiasis and acute cholecystitis, both consistent with the known hepatobiliary effects of octreotide.

Treatment discontinuation due to AEs occurred in a small proportion of patients (6 patients in total), with injection site reactions being the most common reason for discontinuation.

3.5. Uncertainties and limitations about unfavourable effects

Submission of the final report of the extension part HS-19-647 study no later than Q1 2026 as planned, will provide valuable insights and strengthen the overall assessment of CAM2029 long-term safety profile. The applicant accepted to submit the Complete results of this OLE phase will be submitted in the frame of a MEA planned in the RMP.

Regarding SAEs, one fatal SAE had occurred in the extension part of HS-19-647, but the event of death was assessed as not related to Oczeysa.

3.6. Effects table

Table 49 Effects table

Effect	Short description	Unit	Treatment	Control (placebo)	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint Proportion of patients with mean IGF-1 levels ≤1×ULN at W24	Difference of proportion	%	72.2	37.5	34.6 (11.3, 57.9) P = 0.0018 There is no direct comparison of CAM2029 with SOC (octreotide LAR or lanreotide ATG). It is not known if the efficacy of CAM2029 is superior to SOC	Trial 18-633
Key secondary endpoint Proportion of patients with mean IGF 1 ≤1×ULN at Week 22 and Week 24 and mean GH cycle <2.5 µg/L at Week 24	Difference of proportion	%	70	37.5	32.3 (8.8, 55.7) p = 0.0035	Trial 18-633
Time to loss of response	Number of weeks	N	Not reached	8.4	Hazard ratio: 0.10 (0.04, 0.28) <0.0001	Trial 18-633
Proportion of Patients with Mean GH <1.0 µg/L at Week 52	Estimated difference of proportion (W52-SoC baseline)	%	Overall (n= 124) 62.9 53.8, 71.4 (at baseline) 60.5 51.3, 69.1 (at W52) New patients (n= 74) 48.6 36.9, 60.6 (at baseline) 45.9 34.3, 57.9 (at W52) Prior CAM2029 (n = 33)		Overall - 3.9 -10.8, 2.9 New patients -2.6 -11, 5.7 Prior CAM2029 -8.8 -18.8, 1.2 Placebo roll-over patients -0.2 -27.1, 26.6	Trial 19-647

Effect	Short description	Unit	Treatment	Control (placebo)	Uncertainties / Strength of evidence	References
			87.9 71.8, 96.6 (at baseline) 81.8 64.5 93 (at W52) Placebo roll-over patients 76.5 50.1, 93.2 (at baseline) 82.4 56.6, 96.2 (at W52)			
Unfavourable Effects						
Injection site reactions	Patients experienced at least one 1 TEAE or ADR	N (%)	19 (40.4%)	15 (62.5)	most common, consistent with the known safety of octreotide	Trial 18-633
Abdominal pain upper		N (%)	3 (6.4%)	0	consistent with the known safety of octreotide	Trial 18-633
Cholelithiasis		N (%)	6 (4.4)	0	consistent with the known safety of octreotide	Trial 19-647
SARs		N	2	0	1 cholelithiasis and 1 acute cholecystitis	Trial 19-647
Neoplasm AEs		N	7	0	unknown	Trials 18-633 and 19-647

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the pivotal study [HS-18-633], the superiority of CAM2029 compared to placebo was demonstrated as regards to the primary endpoint was "Proportion of patients with mean IGF-1 levels ≤1×ULN at Week 22 and Week 24" and key secondary endpoint "Proportion of patients with mean IGF 1 ≤1×ULN at Week 22 and Week 24 ". This was expected as octreotide is a well-known substance with a relevant efficacy on IGF-1 levels in patients with acromegaly in line with the other SRL treatments. The patients were biochemically controlled with IGF-1 ≤ ULN at baseline remained well-controlled compared to placebo at W24. However, Oczyesa was not compared directly to other SRL treatments in the phase 3 studies. Therefore, it is not known whether the efficacy of Oczyesa is superior or equivalent to the other SRL treatments. The comparisons with the other SRL treatments were only performed from baseline to W24 or W52.

In phase 3 study [HS-18-633], although the mean IGF-1 levels were maintained below ULN from baseline to W24, when looking at the secondary objective "proportion of responders" in terms of "proportion of patients with mean IGF 1 ≤1×ULN over time", the proportion of responders at baseline was 91.7% in both treatment

arms. The proportion was 70.8% at the end of the trial (mean of the values at Week 22 and Week 24). The estimated difference in proportions (Week 22/Week 24-baseline) of -20.5% (95% CI: -33.7%, -7.3%).

There were no treatment-naïve patients included in the phase 3 studies and a fixed dose of 20 mg 4qW was evaluated in the phase 3 studies in patients already treated with octreotide LAR or lanreotide ATG. The approved indication reflects that.

The clinical data from the long-term phase 3 study [HS-19-647] can only be considered as supportive given the study design (open-label and single-arm).

The PROs showed no significant difference between treatment arm and placebo, but more data will be available after the results of the OLE part of study HS-19-647 will be available.

There is no effect of Oczyesa on the size of the tumour in both studies.

Regarding the safety profile of Oczyesa, it was overall consistent with the known safety profile of octreotide-based products. In the pivotal phase 3 trial, the proportion of patients reporting AEs was almost similar between CAM2029 group and placebo group. However, the proportion of IMP-related AEs was lower in the CAM2029 group compared to the placebo group (51.1% vs. 62.5%). The most common ADRs were injection site reactions (40.4%) (erythema, swelling, and pruritus), followed by gastrointestinal ADRs (10.6%) (upper abdominal pain, diarrhoea, and nausea), musculoskeletal and connective tissue ADRs (4.3%) (arthralgia, joint swelling), nervous system ADRs (6.4 %) (headache), hepatobiliary ADRs (4.3%) (chronic cholecystitis and hepatic cyst), and skin and subcutaneous tissue ADRs (4.3%) (pruritus and erythema).

3.7.2. Balance of benefits and risks

A positive benefit/risk ratio can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

3.8. Conclusions

The overall benefit/risk balance of Oczyesa is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Derogation from market exclusivity

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 the following derogation laid down in Article 8.3 of Regulation (EC) No. 141/2000 applies:

- the holder of the marketing authorisation for Mycapssa is unable to supply sufficient quantities of the medicinal product (see appendix)

Outcome

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

Oczyesa 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.

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

- **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.