Clinical Trial Protocol

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

Short Title:	A trial to assess efficacy and safety of octreotide subcutaneous depot in patients with acromegaly
Trial Code:	HS-18-633
EudraCT Number:	2019-001191-11
NCT Number:	NCT04076462
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Development Phase:	Phase 3
Investigational Medicinal Product:	Octreotide subcutaneous depot (CAM2029)
Indication:	Acromegaly
Sponsor:	Camurus AB

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Protocol Version and Date:	Final Version 5, 31-Jan-2023
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Sponsor:	Camurus AB Ideon Science Park SE-223 70 Lund, Sweden
Coordinating Investigator:	Pamela Freda, MD

This trial will be conducted in compliance with the Clinical Trial Protocol, applicable regulations and with the principles of Good Clinical Practice.

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ABBREVIATIONS

AcroQoL	Acromegaly Quality of Life Questionnaire
AE	Adverse event
AIS	Acromegaly Index of Severity
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Autogel
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRO	Contract research organization
$C_{ss,trough}$	Trough concentration at steady state
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EQ-5D-5L	EuroQoL 5-dimension 5-level
FAS	Full analysis set
GCP	Good Clinical Practice
GDO	Glycerol dioleate
GH	Growth hormone
GI	Gastrointestinal
HbA1c	Hemoglobin A1c
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
IM	Intramuscular
IMP	Investigational medicinal product

INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
LAR	Long-acting release
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per protocol
PQC	Product Quality Complaint
PRO	Patient-reported outcome
QTcF	QTc interval corrected by Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SIAQ	Self-Injection Assessment Questionnaire
SSA	Somatostatin analogue
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale

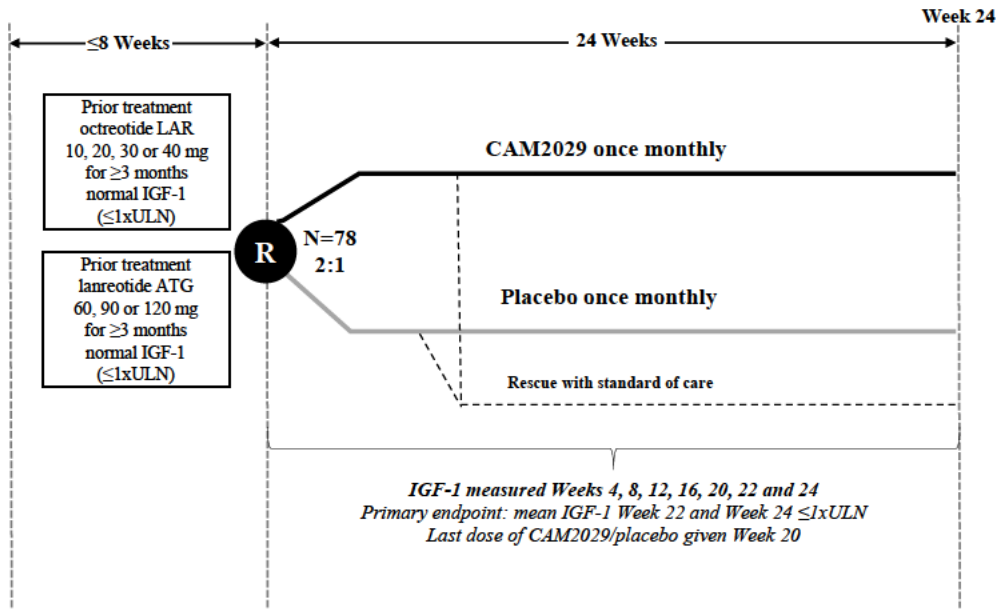
1 PROTOCOL SYNOPSIS

Name of Sponsor Camurus AB	
Trial 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	
Short Title A trial to assess efficacy and safety of octreotide subcutaneous depot in patients with acromegaly	
Sponsor Protocol No HS-18-633	
Phase Phase 3	
Coordinating Investigator Pamela Freda, MD	
Trial Sites The trial will be conducted in Europe and the United States.	
Objectives and Endpoints	
Primary Objective	*Primary Endpoint*
• To assess the superiority of CAM2029 compared to placebo in biochemical response for insulin-like growth factor-1 (IGF-1)	• Proportion of patients with mean IGF-1 levels ≤1x upper limit of normal (ULN) at Week 22 and Week 24 (average of the 2 measurements)
Secondary Objectives	*Secondary Endpoints*
• 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 ≤1xULN 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 growth hormone (GH)	• Proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24 and mean GH cycle levels <2.5 µg/L at Week 24
• To assess time to loss of response of CAM2029 compared to placebo	• Time to IGF-1 levels >1xULN • Time to IGF-1 levels ≥1.3xULN
• 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 standard of care
• 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	• Treatment Satisfaction Questionnaire for Medication (TSQM) scores over time using all 4 domains of TSQM (effectiveness, side effects, convenience and satisfaction) • Patient satisfaction scale scores at Week 24
• To measure the effects of CAM2029 and placebo on quality of life	• Change from baseline in Acromegaly Quality of Life Questionnaire (AcroQoL) and EuroQoL 5-dimension 5-level (EQ-5D-5L) scores
• To measure patients' satisfaction with self-administration of CAM2029 and placebo	• Change from PRE module to the POST module in Self-Injection Assessment Questionnaire (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 adverse events (AEs) and laboratory and electrocardiogram (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
Exploratory Objectives	*Exploratory Endpoints*
• To assess the treatment effects of CAM2029 and placebo on prolactin	• Prolactin levels
• To assess the immunogenicity of octreotide from CAM2029 in patients with acromegaly	• Qualification and quantification of anti-octreotide antibodies

Trial Design and Schedule

This is a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial that assesses the efficacy and safety of CAM2029 versus placebo in patients with acromegaly. Eligible patients who are biochemically controlled on treatment with long-acting somatostatin analogues (octreotide or lanreotide) and who have prior evidence of active acromegaly disease will be randomized to treatment with either CAM2029 or placebo in a 24-week Double-blind Treatment Phase. An overview of the trial design is shown in the following figure:



ATG: autogel; IGF-1: insulin-like growth factor-1; LAR: long-acting release; R: randomization; ULN: upper limit of normal

Screening Phase

The following patients will be eligible for inclusion in the trial:

- Patients with confirmed acromegaly on treatment with a stable dose of octreotide long-acting release (LAR; 10 mg, 20 mg, 30 mg or 40 mg once monthly) for at least 3 months and with IGF-1 levels ≤1xULN and mean GH cycle levels <2.5 µg/L at screening
- Patients with confirmed acromegaly on treatment with a stable dose of lanreotide autogel (ATG; 60 mg, 90 mg or 120 mg once monthly) for at least 3 months and with IGF-1 levels ≤1xULN and mean GH cycle levels <2.5 µg/L at screening

The Screening Phase will have a duration of ≤8 weeks. During this period, the patients will visit the site at least 2 times to perform the screening procedures. The first dose of CAM2029 or placebo on Day 1 in the Double-blind Treatment Phase will be given 4 weeks (±3 days) after the last dose of octreotide LAR or lanreotide ATG.

Double-blind Treatment Phase

Patients who are eligible for the Double-blind Treatment Phase will be 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

Randomization will be stratified based on previous treatment (octreotide LAR versus lanreotide ATG). Approximately 78 randomized patients are estimated to be needed for the double-blind phase in total, with 52 patients in the CAM2029 treatment arm and 26 patients in the placebo treatment arm.

The starting dose of CAM2029 is 20 mg once monthly, regardless of the patient's prior treatment and the previous octreotide LAR dose (10 mg, 20 mg, 30 mg or 40 mg) or lanreotide ATG dose (60 mg, 90 mg or 120 mg). Doses may be down-titrated to 10 mg CAM2029 (or corresponding placebo volume) based on safety and tolerability. After down-titration, the patient can return to the previous dose if the safety issue is resolved and the benefit-risk evaluation allows it.

During the 24-week Double-blind Treatment Phase, IGF-1 will be measured on Day 1 (before the first dose of CAM2029/placebo) and at Weeks 4, 8, 12, 16, 20, 22 and 24. The primary endpoint (IGF-1

levels ≤1xULN) will be evaluated as an average value of the measurements at Week 22 and Week 24. GH will be measured as random samples or cycles during the trial.

To maintain the integrity of the blind, patients, Investigators and the trial team will remain blinded to all individual IGF-1 and GH results until the trial is completed and a decision is made to unblind. IGF-1 results will be monitored by an independent reader during the trial. Patients should be discontinued from treatment with CAM2029/placebo and be switched to rescue with standard of care in case they experience worsening of signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3xULN at 2 consecutive visits. Patients who are switched to standard of care should continue participation in the trial and should follow all planned visits and assessments. The treatment allocation (CAM2029/placebo) of patients who are switched to standard of care will remain blinded until the trial is completed and a decision is made to unblind.

Safety will be evaluated continuously and plasma samples for assessment of octreotide concentration will be taken. Patient-reported treatment satisfaction will be assessed using a general questionnaire and will be compared between CAM2029 and placebo and with previous treatment. Health-related quality of life parameters will also be assessed.

Patients may self-administer CAM2029/placebo or have the investigational medicinal product (IMP) administered by their partner. The feasibility of self- or partner-administration of the IMP under the supervision of a trained trial personnel will be assessed. If the patients or their partners are considered competent by the trial personnel to administer the IMP, they may continue to administer the IMP monthly. If the IMP is not self- or partner-administered, the trial personnel will perform the administrations.

At Week 24, or 4 weeks after the last dose in case of premature withdrawal from the trial, the patients will come to the trial site for an End of Trial visit. Patients who complete the trial will be offered to continue with treatment with CAM2029 as roll-over patients in a long-term safety trial. Alternatively, patients will be switched back to their previous treatment for acromegaly.

Trial Treatments

Test Product

CAM2029 20 mg (1.0 mL, pre-filled syringes) will be administered through subcutaneous (SC) injections in the abdomen or thigh once monthly (28 days ±7 days). The dose may be decreased to 10 mg (0.5 mL administered in pre-filled syringes) based on safety and tolerability. After down-titration, the patient can return to the previous dose if the safety issue is resolved and the benefit-risk evaluation allows it. From the first dose on Day 1, CAM2029 may be self- or partner-administered. If CAM2029 is not self- or partner-administered, the trial personnel will administer CAM2029.

Comparator

Placebo (1.0 mL, pre-filled syringes) will be administered through SC injections in the abdomen or thigh once monthly (28 days ±7 days). The dose (volume) may be decreased to 0.5 mL (administered in pre-filled syringes) based on safety and tolerability. After down-titration, the patient can return to the previous dose volume if the safety issue is resolved and the benefit-risk evaluation allows it. From the first dose on Day 1, placebo may be self- or partner-administered. If placebo is not self- or partner-administered, the trial personnel will administer placebo.

Rescue Medication

Patients should be discontinued from treatment with CAM2029/placebo and be switched to rescue medication with standard of care in case they experience worsening of signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3xULN at 2 consecutive visits. Patients who are switched to standard of care should continue participation in the trial and should follow all planned visits and assessments

Trial Population

Adult male or female patients with acromegaly ≥18 years of age.

Number of Patients (Planned)

Approximately 78 patients will be randomized, with 52 patients in the CAM2029 treatment arm and 26 patients in the placebo treatment arm.

Planned Trial Period:

Estimated first patient first visit: Q2 2019

Estimated last patient first visit: Q4 2022

Expected total duration of the trial: Up to 32 weeks for the individual patients (including the Screening and Double-blind Treatment Phases).

Main Inclusion Criteria

- Diagnosis of acromegaly by historical evidence of (persistent or recurrent) acromegaly as documented by:
  - Pituitary adenoma on magnetic resonance imaging (MRI) or pathology report. Computerized tomography is accepted if MRI could not be performed
  - 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 >1xULN (for patients who have undergone pituitary surgery, the measurement should be performed at least 3 months after the surgery)
- Treatment with a stable dose of octreotide LAR (10 mg, 20 mg, 30 mg or 40 mg) or lanreotide ATG (60 mg, 90 mg or 120 mg) for at least 3 months as monotherapy prior to screening
- IGF-1 levels ≤1xULN (adjusted for age and sex; mean value of the first measurement at screening and the second measurement at 2 weeks before Day 1)
- Adequate liver, pancreatic, renal and bone marrow functions
- Normal ECG

Main Exclusion Criteria

- GH ≥2.5 µg/L at screening (cycle)
- Have 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])
- Patients who usually take octreotide LAR or lanreotide ATG less frequently than every 4 weeks (e.g. every 6 weeks or 8 weeks)
- Patients with compression of the optic chiasm causing any visual field defect for whom surgical intervention is indicated
- Patients who have undergone major surgery/surgical therapy for any cause within 1 month prior to screening
- Patients who have undergone pituitary surgery within 6 months prior to screening
- Patients who have received prior pituitary irradiation
- Patients with poorly controlled diabetes mellitus (hemoglobin A1c >8.0%)

Assessments of Efficacy and Safety Variables and Drug Concentration

Assessments of Efficacy Variables

IGF-1

IGF-1 will be assessed throughout the trial. Pre-dose blood samplings for evaluation of IGF-1 efficacy endpoints will be done immediately before the IMP administration. In addition, post-dose samples will be taken at Week 20 for a separate evaluation of the pharmacokinetic (PK)/pharmacodynamic (PD) relationship. The IGF-1 samples will be analyzed by a central laboratory.

GH

GH samples for evaluation of GH efficacy endpoints will be taken as pre-dose cycles (5 samples taken over a period of 2 hours, i.e. every 30 minutes) and as random pre-dose samples at different time points during the trial. The GH samples will be analyzed by a central laboratory.

MRI

Pituitary MRI (or computerized tomography if MRI is contraindicated or not available) will be performed at screening and at Week 24.

Patient-reported Outcomes

Patient-reported outcomes (PROs) for the assessment of convenience and treatment satisfaction include the TSQM v1.4, the SIAQ v2.0, a patient satisfaction scale and the health-related quality of life questionnaires AcroQoL and EQ-5D-5L. The PROs will be completed at various time points during the trial.

Clinical Signs and Symptoms of Acromegaly

Ring size and severity of symptoms of acromegaly (headache, sweating, fatigue, joint pain, paresthesia and soft tissue swelling) will be assessed throughout the trial.

Drug Concentration Assessments

Blood samples for assessment of plasma concentrations of octreotide will be taken during the trial.

Assessments of Safety Variables

Safety will be evaluated throughout the trial by recording of AEs, vital signs, ECGs and gallbladder ultrasounds and collection of safety laboratory samples (biochemistry, hematology, urinalysis, coagulation, thyroid stimulating hormone, vitamin B_{12} and hemoglobin A1c). Local tolerability at the injection sites will also be evaluated and blood samples for assessment of prolactin levels and presence of anti-drug antibodies will be taken.

Other Assessments

Patients and their partners will have the possibility to administer the IMP (CAM2029 or placebo) by themselves (after appropriate training). Qualified trial personnel will supervise the administration and assess the patient's/partner's ability to successfully administer the IMP.

Statistical Methods (Data Analysis)

Primary Efficacy Analysis

The *primary efficacy endpoint* is the proportion of patients with biochemical response, defined as the proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24 (average of the 2 measurements).

The *primary estimand* is 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 being ≤1xULN) between CAM2029 and placebo for patients with acromegaly.

The primary analysis of the primary endpoint will be performed by a common risk 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 will be rejected if the associated one-sided p-value is <0.025. In addition, the proportion of patients with IGF-1 ≤1xULN (adjusted for age and sex) will be provided descriptively by treatment arm.

For the primary efficacy endpoint, a patient will be considered as non-responder if he/she discontinues treatment with CAM2029/placebo prior to Week 22 (regardless of IGF-1 values) or if the mean of the IGF-1 values measured at Week 22 and Week 24 is >1xULN (adjusted for age and sex). If one of the IGF-1 values at Week 22 or Week 24 is missing, the other value will be used to define a responder/non-responder in the analysis. The variable (or endpoint) of interest will be missing only if no IGF-1 value can be obtained from both the Week 22 and Week 24 samples. Patients who have had their dose decreased (due to safety or tolerability reasons) will be regarded as non-responders.

Secondary Efficacy Analyses

The proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24, including patients who have their dose decreased to 10 mg CAM2029 (or 0.5 mL placebo), and the proportion of

patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24 and mean GH cycle levels <2.5 µg/L at Week 24 will be analyzed in a similar way as the primary efficacy endpoint.

Time to loss of response (i.e. time to IGF-1 levels >1xULN and time to IGF-1 levels ≥1.3xULN), data for IGF-1 and GH levels over time, proportions of patients with mean GH cycle levels <2.5 µg/L and <1.0 µg/L at Week 24 and proportion of patients who received rescue medication with standard of care will be presented for each treatment arm and stratum.

Tumor size volume data and acromegaly signs and symptoms will be summarized and presented by treatment arm and stratum for each time point.

Descriptive statistics will be used to summarize the PRO scores over time. Additionally, change from baseline in the scores will be summarized by treatment arm and stratum.

Results from the SIAQ will be summarized and changes in domain scores will be presented.

Adjustments for Multiplicity

Three evaluations of biochemical control are planned. To control the overall significance level of 5%, a stepwise closed testing procedure is planned.

Pharmacokinetic Analyses

The plasma concentrations of octreotide will be summarized using descriptive statistics over time by dose, if applicable. A population PK model will be developed using data generated from the current trial together with data from other clinical trials for population PK assessment. The population PK model will be reported separately.

Safety Analyses

Safety data will be analyzed descriptively. Analyses of time to first serious adverse event and time to first AE of special interest will be performed.

Exposure-response Analyses

PK, PD (IGF-1 and GH) and safety (ECG) data generated from this trial may be used together with PK, PD and safety data from other clinical trials for population PK and PK/PD assessments. These data will be reported separately.

Exploratory and Other Analyses

Prolactin levels and anti-octreotide antibody data will be presented descriptively.

Proportion of patients/partners declared competent by the healthcare professional to self- or partner-administer the IMP out of those trying will be presented by treatment arm.

Determination of 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 ≤1xULN, by treatment arm are made. It should be noted that the treatment difference in biochemical response is 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 is, thus, assumed that the proportion with biochemical response with this endpoint is very similar to response based on 1 measurement.

The proportion of responders at Week 22 and Week 24 in the CAM2029 treatment arm is assumed to be 0.80. For the group of patients receiving placebo it is assumed that the proportion of responders is 0.40 at Week 22 and Week 24. It is also assumed that the missing data frequency will 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 is 90% to show a difference between CAM2029 and placebo, if the percentages of responders, as defined by the primary endpoint, are 80% for CAM2029 and 40% for placebo. This power calculation is based on the Chi-squared test (with a continuity correction).

2 INTRODUCTION

2.1 Background

2.1.1 Acromegaly

Acromegaly is a rare, slowly progressing and debilitating disease caused by chronic hypersecretion of growth hormone (GH) by pituitary adenoma that in more than 90% of the cases are benign (1). The levels of insulin-like growth factor-1 (IGF-1), which mediates most of the growth-promoting actions of GH, are also elevated (2, 3).

The clinical manifestations of acromegaly are due to the peripheral actions of GH and IGF-1 and local tumor mass effect. The chronic excess of GH and IGF-1 leads to progressive somatic disfigurement due to excessive skeletal growth and soft tissue enlargement, resulting in widening of hands and feet and a characteristic facial aspect, bone deformation and thickening of the skin (1). Metabolic complications include increased blood glucose levels, hyperinsulinemia, diabetes and dyslipidemia. Respiratory complications can appear as consequences of anatomical changes affecting craniofacial bone and soft tissues (macroglossia and narrowing of upper airways) and alterations in the activity of respiratory muscles. Sleep apnea has been reported in over 60% of patients. Arterial hypertension, arrhythmias and valvular heart disease are also frequently observed in association with acromegaly. Moreover, concentric biventricular hypertrophy is the key feature of cardiomyopathy in patients with acromegaly (1). Local tumor effects may lead to visual field defects and to hydrocephalus or focal epilepsy in case of large extensive tumors. Acromegaly can cause a variety of other symptoms, such as headache, excessive sweating, arthralgia and paresthesia (1). It is well known that patients with acromegaly report impaired health-related quality of life, especially during the active phase of the disease (4). Patients with acromegaly have a shortened life expectancy, with a mortality rate that is approximately twice that of the general population. The excess mortality is primarily a result of cardiovascular diseases, respiratory complications, diabetes mellitus and malignancies (1, 5). The prevalence of acromegaly in Europe and the United States (US) is estimated to be around 8 cases per 100,000 people (6-8), meeting the orphan disease prevalence criteria. The annual incidence rates in these regions range between 0.2 and 1.1 cases per 100,000 people.

Goals of treatment of acromegaly are biochemical normalization, reduction of mortality risk, attenuation of symptoms, control of tumor mass and maintenance of pituitary function (3, 9). Treatment modalities for acromegaly include surgery, radiotherapy and medical treatment. Currently, the medical treatment options for acromegaly include somatostatin analogues (SSAs), GH antagonists, and dopamine agonists. The currently available medical treatments in acromegaly have been approved based on efficacy assessed as a biochemical response in terms of IGF-1 normalization and/or GH decrease below a pre-defined threshold. Biochemical control is also the primary efficacy parameter in Phase 3 trials with oral octreotide (ClinicalTrials.gov identifier: NCT03252353; NCT02685709).

2.1.2 Somatostatin Analogues and CAM2029

Octreotide was the first SSA approved for the treatment of acromegaly and is considered the gold standard with well-characterized profiles of efficacy and safety over 30 years of clinical use. Octreotide is available as a short-acting subcutaneous (SC) formulation, Sandostatin® (approved in the US in 1987), for 2 or 3 times daily administration and as a long-acting release (LAR) formulation, Sandostatin® LAR® (micro-encapsulated octreotide acetate; approved in the US in 1995), administered by intramuscular (IM) injection every 4 weeks. A large body of evidence is available on the efficacy of long–acting octreotide therapy. In most patients, the

biochemical effects of octreotide on IGF-1 are seen as early as during the first 3 months of treatment. Treatment with octreotide is associated with a decrease in tumor volume and, in contrast to surgical intervention, the success of octreotide therapy does not seem to be influenced by tumor size (10). Treatment with octreotide is also associated with improvement in arthralgia, hyperhidrosis, soft tissue swelling and headache (9).

Lanreotide is another SSA approved for the treatment of acromegaly and is available in a saturated aqueous formulation (lanreotide autogel [ATG]; Somatuline® Autogel® [Somatuline® Depot in the US]). The recommended initial injection frequency is every 4 weeks.

Current first-line medical management after surgery for patients with significant disease generally employs the use of either octreotide LAR or lanreotide ATG (3, 9, 11). The efficacy of octreotide and lanreotide reported in clinical trials in acromegaly is relatively similar (2, 12). The adverse event (AE) profile is also similar between octreotide and lanreotide and include transient gastrointestinal (GI) disorders (e.g. diarrhea, nausea and abdominal pain), cholelithiasis and injection site pain (13-16). Bradycardia has been reported in some patients.

CAM2029 represents a novel long-acting pharmaceutical formulation of octreotide for SC administration. Compared to Sandostatin LAR, which is administered as an IM injection and which needs to be reconstituted before injection, CAM2029 is provided in a pre-filled syringe with no need for reconstitution. CAM2029 also offers the option of self- or partner-administration and may be easier to handle and administer while improving patient convenience and care. In addition, the bioavailability of octreotide has been shown to be higher for CAM2029 than for Sandostatin LAR (see below).

The non-clinical development program performed for CAM2029 includes bridging studies of toxicity, pharmacokinetics (PK) and local tolerability. In addition, both the FluidCrystal® vehicle and the individual novel excipient glycerol dioleate (GDO) have been evaluated. The main effects observed in these studies were reversible injection site reactions, which were noted with the FluidCrystal vehicle, CAM2029 formulations and GDO. In addition, as observed with octreotide in other formulations, body weight decreases were observed, which is consistent with the pharmacology of octreotide. The PK of CAM2029 in dogs showed a higher maximum plasma concentration (C_{max}) compared to an equivalent dose of Sandostatin LAR, without any apparent difference in toxicity. Safety of GDO is further supported by published literature on diacylglycerides (for the concentrations that will be used in the clinical setting), which demonstrates a lack of reproductive toxicity or carcinogenic potential. The safety of CAM2029 is also supported by the available extensive database (pharmacology, PK, safety and toxicity) of octreotide (see further details in the Investigator's Brochure [IB]) (17). The scope of the available safety data of octreotide, the non-clinical studies conducted with CAM2029 and the literature addressing the reproductive and carcinogenic potential for the excipients supports the current Phase 3 trial.

The clinical program for CAM2029 includes 3 completed Phase 1 trials and 1 completed Phase 2 trial. The CAM2029 formulations used during the drug product development contained the same excipients, with minor differences in composition between the formulations. The Phase 1 trials consist of a single-dose trial (HS-05-194) with 3 different doses of a CAM2029 octreotide acetate formulation and 2 repeated-dose trials (HS-07-291 and HS-11-411) with 3 doses of different CAM2029 octreotide hydrochloride formulations. The activity of octreotide in these trials was measured by suppression of IGF-1, which is an established pharmacodynamic (PD) marker of SSA activity and a marker of therapeutic effects in acromegaly.

In addition, a Phase 2 trial (HS-12-455) was conducted with 2 doses of the CAM2029 [redacted] formulation (octreotide hydrochloride) in patients with acromegaly or functioning neuroendocrine tumors previously treated with Sandostatin LAR. In the current Phase 3 trial, the

formulation CAM2029-[redacted] will be used, which is similar to the CAM2029-[redacted] formulation, with the addition of a small amount of stabilizer.

The results of the Phase 1 clinical trials showed that octreotide release from CAM2029 had a rapid onset of action, with a C_{max} observed within approximately[redacted] to[redacted] hours after dosing. Thereafter, the octreotide plasma concentration slowly declined over time with therapeutic drug levels maintained for approximately [redacted] weeks, resulting in observable suppression of IGF-1 over [redacted] month after dosing. Dose-proportional PK was observed in the dose range of[redacted] to[redacted] mg CAM2029. The bioavailability of octreotide was approximately [redacted] times higher for CAM2029 than for Sandostatin LAR (trial HS-11-411).

The Phase 2 trial showed that switching from Sandostatin LAR (10 mg, 20 mg or 30 mg) to CAM2029-[redacted] (20 mg once monthly or 10 mg biweekly) was associated with maintenance or decrease in IGF-1 levels as compared to pre-switch values and in maintenance of GH levels in patients with acromegaly. The PK data from the trial confirmed the results from the trials in healthy volunteers and showed a higher exposure of octreotide after treatment with CAM2029 than after treatment with Sandostatin LAR.

Safety, including local injection site tolerability, was investigated in all Phase 1 and Phase 2 trials. The AE profile seen with CAM2029 was consistent with what has been recorded for octreotide in clinical trials with octreotide LAR and octreotide SC, with transient and mild-to-moderate GI events as the most frequently reported AEs (17).

The available non-clinical and clinical data in healthy volunteers and patients with acromegaly and functioning GI neuroendocrine tumors, hence, indicate that CAM2029 provides extended octreotide release over a period of [redacted] days in most subjects, supporting once-monthly administration. The safety profile observed with CAM2029 in the Phase 1 and Phase 2 trials that have been performed so far is consistent with the known safety profile of Sandostatin LAR.

2.2 Rationale for Conducting the Trial

Octreotide is considered the gold standard medical treatment for acromegaly and functioning neuroendocrine tumors. Sandostatin LAR was the first long-acting SSA developed for therapeutic use. It has been extensively studied in clinical trials and has been marketed for over 20 years. However, the procedure for preparation of octreotide LAR suspension for injection encompasses a number of steps, including very gentle handling to ensure homogenous suspension of the product. The cumbersome preparation procedure for octreotide LAR may also lead to errors in dosing. Because of the IM injection and the complex preparatory handling procedure, administration of Sandostatin LAR needs to be performed by a trained healthcare professional. The provision of a convenient long-acting formulation offered by CAM2029 that could potentially be self-administered or administered by the patient's partner as a small-volume SC injection in a pre-filled syringe (i.e. eliminating the need for reconstitution) with a thin needle and with higher bioavailability of octreotide than with Sandostatin LAR, is expected to lead to improved treatment convenience.

The current Phase 3 trial is designed to assess the superiority of CAM2029 to placebo in biochemical control in terms of proportion of patients with IGF-1 levels ≤1x upper limit of normal (ULN) and to evaluate the safety and tolerability of CAM2029 in patients with acromegaly. The trial will also evaluate the plasma concentration profile of octreotide delivered by CAM2029, the CAM2029 treatment satisfaction and the feasibility of self- or partner-administration of CAM2029.

Note: wherever normal range or ULN for IGF-1 is mentioned in the document (e.g. IGF-1 ≤1xULN), it refers to values adjusted by age and sex.

2.3 Dose Rationale

The dose selection of CAM2029 is based on the completed Phase 1 and Phase 2 trials in healthy volunteers and patients. A dose of 20 mg CAM2029 once monthly has been identified as a suitable starting and maintenance dose and the dose may be down-titrated to 10 mg once monthly for safety or tolerability reasons. Dose adjustments are allowed at any time point during the trial.

The trough concentration at steady state ($C_{ss,trough}$) 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 (18). In the clinical trial HS-11-411 (n=122), 3 repeated monthly injections of different formulations and doses of CAM2029 (10 mg, 20 mg and 30 mg) or Sandostatin LAR (30 mg) were administered to healthy volunteers. The mean (± standard deviation [SD]) $C_{ss,trough}$ at 28 days after the third monthly injection of 30 mg CAM2029-[redacted] ([redacted] ± [redacted] ng/mL; n=[redacted]) was found to be similar to the $C_{ss,trough}$ after the third monthly injection of 30 mg Sandostatin LAR (1.02±0.33 ng/mL; n=13). In the clinical trial HS-12-455, patients with acromegaly or neuroendocrine tumors were administered repeated monthly doses of 10, 20 or 30 mg Sandostatin LAR for at least 2 months prior to administration of 3 repeated monthly doses of 20 mg CAM2029-[redacted] or 6 repeated biweekly doses of 10 mg CAM2029-[redacted] after randomization in the trial. The switch from Sandostatin LAR to CAM2029 resulted in maintenance or improvement of biochemical disease control in terms of IGF-1 levels and maintenance of GH levels in patients with acromegaly. The mean (± SD) $C_{ss,trough}$ was [redacted] ± [redacted] ng/mL (n=[redacted]) after administration of 20 mg CAM2029 compared to 1.20±0.65 ng/mL (n=4) after administration of 30 mg Sandostatin LAR.

The mean (±SD) maximum plasma concentration at steady state of octreotide was [redacted] ± [redacted] ng/mL (n=[redacted]) and area under the plasma concentration-time curve at steady state was [redacted] ± [redacted] ng*h/mL (n=[redacted]) after repeated administration of 20 mg CAM2029 once monthly to patients with acromegaly (trial HS-12-455), showing that octreotide exposures are expected to remain at or below the exposures established for approved and available SC doses of Sandostatin (19, 20).

The dose of 20 mg in the current trial was chosen as the starting dose based on similar octreotide $C_{ss,trough}$ values and maintained or decreased IGF-1 levels at steady state after injection of 20 mg CAM2029 and 30 mg Sandostatin LAR.

2.4 Overall Benefit/Risk Aspects

Octreotide remains the gold standard of treatment of patients with acromegaly, with over 30 years of clinical use. Octreotide was shown to reach therapeutic goals in acromegaly in terms of providing sustained biochemical control of the disease, symptoms control and control of the tumor mass growth (3, 9, 11). Sandostatin LAR injections have to be given as monthly IM injections by a healthcare provider. CAM2029 offers an alternative to patients that may be equally or more efficacious and may allow for self- or partner-administration.

Sandostatin and Sandostatin LAR have over a million years of exposure to date. These drug products are well-tolerated and have safety profiles that are well-characterized. CAM2029 has the same active ingredient as Sandostatin and Sandostatin LAR (octreotide) and has been shown to have a safety profile that is similar to Sandostatin LAR in previous Phase 1 and 2 clinical trials (17). The most common adverse drug reactions after administration of octreotide include GI reactions, cholelithiasis, injection site reactions, headache and nasopharyngitis.

In the current trial, patients will receive active therapy (CAM2029) or placebo for 24 weeks with a randomization ratio of 2:1. The double-blind period of 24 weeks allows comparison of efficacy and safety in patients randomized to treatment with CAM2029 versus placebo and the double-

blind design minimizes the risk of potential bias. In a slowly progressive disease like acromegaly, which usually is diagnosed 5-10 years after the first symptom onset (1, 21), a 24-week treatment period with placebo can be considered as a relatively short period with minimal or no negative impact on the overall disease history or patient disease outcome. Patients should be discontinued from treatment with the blinded investigational medicinal product (IMP) and be switched to rescue with standard of care in case they experience worsening of signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3xULN at 2 consecutive visits.

During the trial, self- or partner-administration of CAM2029 in the abdomen or thigh is allowed after appropriate training and under the supervision of trial personnel who has been adequately trained. The patients or their partners will, however, not be permitted to administer CAM2029/placebo on their own until they have been appropriately trained and judged capable to do so by the trial personnel.

Patients in the trial will be regularly and carefully monitored for AEs, including those that have been observed for Sandostatin/Sandostatin LAR. Parameters that will be monitored regularly include vital signs, hematology laboratory assessments, blood chemistry (including renal and liver function and thyroid hormones), urinalysis, electrocardiogram (ECG), gallbladder ultrasound, local tolerability and assessments for other potential AEs. In addition, the protocol provides specific guidance for dose adjustment/IMP discontinuation and safety follow-up for adverse drug reactions, liver toxicity (increased liver enzymes) and QT prolongation. Furthermore, sampling for measurement of octreotide plasma concentrations will be conducted in all patients. Blood samples will also be taken for qualification and quantification of anti-octreotide antibodies to assess for potential immunogenicity.

More detailed information about the known and expected benefits and risks and reported AEs after administration of CAM2029 may be found in the current edition of the IB (17).

3 TRIAL OBJECTIVES AND ENDPOINTS

The objectives of this trial and the corresponding endpoints are listed in Table 1.

Table 1: Trial objectives and endpoints

Objectives	Endpoints
Primary Objective	***Primary Endpoint***
• To assess the superiority of CAM2029 compared to placebo in biochemical response for IGF-1	• Proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24 (average of the 2 measurements)
Secondary Objectives	***Secondary Endpoints***
• 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 ≤1xULN 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 ≤1xULN at Week 22 and Week 24 and mean GH cycle levels <2.5 µg/L at Week 24
• To assess time to loss of response of CAM2029 compared to placebo	• Time to IGF-1 levels >1xULN • Time to IGF-1 levels ≥1.3xULN
• 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 standard of care
• 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) • 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
Exploratory Objectives	***Exploratory Endpoints***
• To assess the treatment effects of CAM2029 and placebo on prolactin	• Prolactin levels
• To assess the immunogenicity of octreotide from CAM2029 in patients with acromegaly	• Qualification and quantification of anti-octreotide antibodies

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; TSQM: Treatment Satisfaction Questionnaire for Medication; ULN: upper limit of normal

4 INVESTIGATIONAL PLAN

4.1 Overall Trial Design and Plan

This is a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial that assesses the efficacy and safety of CAM2029 versus placebo in patients with acromegaly. Eligible patients who are biochemically controlled on treatment with long-acting SSAs (octreotide or lanreotide) and who have prior evidence of active acromegaly disease will be randomized to treatment with either CAM2029 or placebo in a 24-week Double-blind Treatment Phase.

An overview of the trial design is shown in Figure 1.

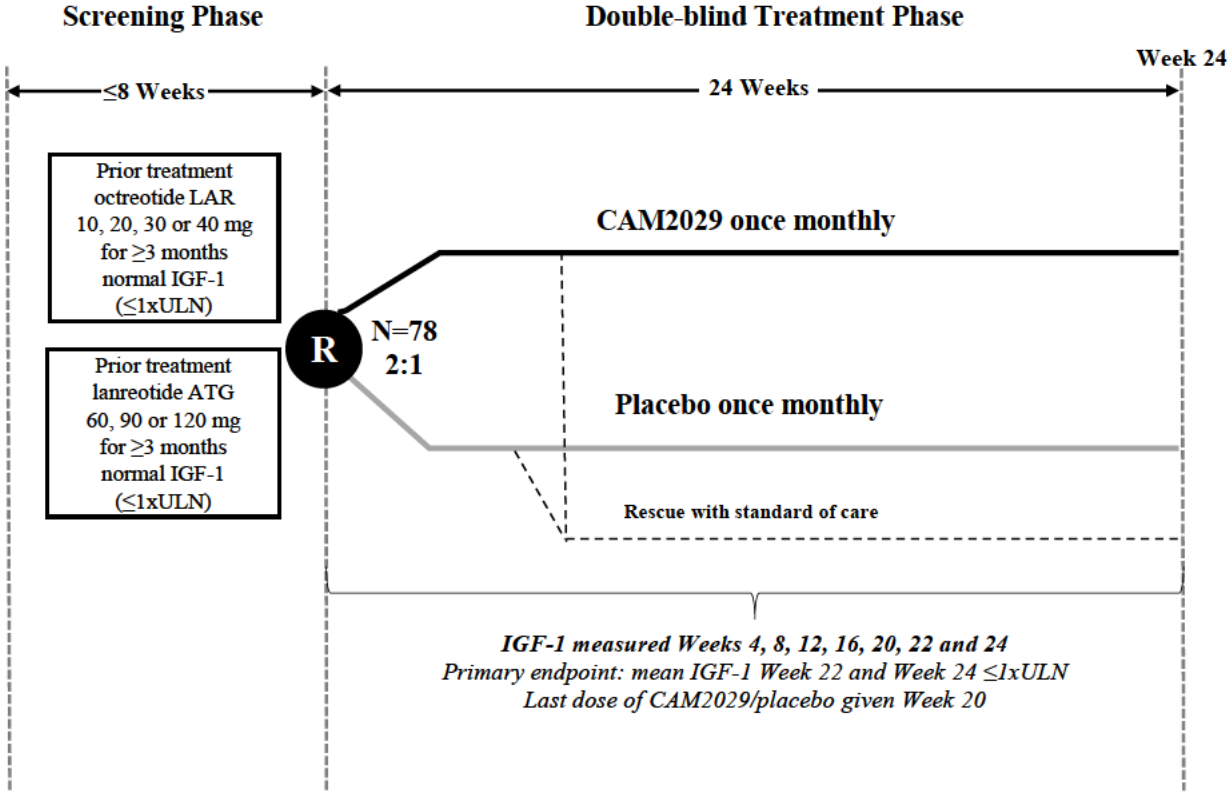


Figure 1: Trial design

ATG: autogel; IGF-1: insulin-like growth factor-1; LAR: long-acting release; R: randomization; ULN: upper limit of normal

4.1.1 Screening Phase

The following patients will be eligible for inclusion in the trial (see further details in Section 5):

- Patients with confirmed acromegaly on treatment with a stable dose of octreotide LAR (10 mg, 20 mg, 30 mg or 40 mg once monthly) for at least 3 months and with IGF-1 levels ≤1xULN and mean GH cycle levels <2.5 µg/L at screening
- Patients with confirmed acromegaly on treatment with a stable dose of lanreotide ATG (60 mg, 90 mg or 120 mg once monthly) for at least 3 months and with IGF-1 levels ≤1xULN and mean GH cycle levels <2.5 µg/L at screening

The Screening Phase will have a duration of ≤8 weeks. During this period, the patients will visit the site at least 2 times to perform the screening procedures. The first dose of CAM2029 or placebo on Day 1 in the Double-blind Treatment Phase will be given 4 weeks (±3 days) after the last dose of octreotide LAR or lanreotide ATG.

4.1.2 Double-blind Treatment Phase

Patients who are eligible for the Double-blind Treatment Phase will be 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

Randomization will be stratified based on previous treatment (octreotide LAR versus lanreotide ATG). Approximately 78 randomized patients are estimated to be needed for the double-blind phase in total, with 52 patients in the CAM2029 treatment arm and 26 patients in the placebo treatment arm.

The starting dose of CAM2029 is 20 mg once monthly, regardless of the patient's prior treatment and the previous octreotide LAR dose (10 mg, 20 mg, 30 mg or 40 mg) or lanreotide ATG dose (60 mg, 90 mg or 120 mg). Doses may be down-titrated to 10 mg CAM2029 (or corresponding placebo volume) based on safety and tolerability. After down-titration, the patient can return to the previous dose if the safety issue is resolved and the benefit-risk evaluation allows it. All dose adjustments must be discussed with the Medical Monitor prior to implementation. For further details regarding dose adjustments, please see Sections 6.2.1.2 and 6.2.2.2.

During the 24-week Double-blind Treatment Phase, IGF-1 will be measured on Day 1 (before the first dose of CAM2029/placebo) and at Weeks 4, 8, 12, 16, 20, 22 and 24. The primary endpoint (IGF-1 levels ≤1xULN) will be evaluated as an average value of the measurements at Week 22 and Week 24. GH will be measured as random samples or cycles during the trial.

To maintain the integrity of the blind, patients, Investigators and the trial team will remain blinded to all individual IGF-1 and GH results until the trial is completed and a decision is made to unblind. IGF-1 results will be monitored by an independent reader during the trial. Patients should be discontinued from treatment with CAM2029/placebo and be switched to rescue with standard of care in case they experience worsening of signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3xULN at 2 consecutive visits (see further details in Section 6.3). Patients who are switched to standard of care should continue participation in the trial and should follow all planned visits and assessments. The treatment allocation (CAM2029/placebo) of patients who are switched to standard of care will remain blinded until the trial is completed and a decision is made to unblind.

Safety will be evaluated continuously and plasma samples for assessment of octreotide concentration will be taken. Patient-reported treatment satisfaction will be assessed using a general questionnaire and will be compared between CAM2029 and placebo and with previous treatment. Health-related quality of life parameters will also be assessed.

Patients may self-administer CAM2029/placebo or have the IMP administered by their partner. The feasibility of self- or partner-administration of the IMP under the supervision of a trained trial personnel will be assessed. If the patients or their partners are considered competent by the trial personnel to administer the IMP, they may continue to administer the IMP monthly. If the IMP is not self- or partner-administered, the trial personnel will perform the administrations.

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

4.2 Rationale of Overall Trial Design and Choice of Control Groups

4.2.1 Trial Design

This Phase 3 trial is designed to assess the efficacy of CAM2029 versus placebo in patients with acromegaly. The primary efficacy objective will be assessed by the proportion of patients with biochemical control, defined as patients having a mean IGF-1 level ≤1xULN at Week 22 and Week 24 (assessed by a central laboratory; average of the 2 measurements).

Clinical guidelines for acromegaly management suggest evaluating the biochemical response to SSA treatment after at least 12 weeks of treatment (3, 9, 11). In addition, long-term response to SSAs has been demonstrated by normalization of GH/IGF-1 within the first 3 to 6 months of treatment (22-24). All patients who normalized their GH/IGF-1 levels after 3 months of treatment with IM octreotide LAR 20 mg once monthly (24 out of 56 enrolled patients) maintained biochemical control of the disease after 24 months of treatment (22).

The double-blind design minimizes the risk of potential bias. The double-blind period of 24 weeks in the current trial will allow comparison of efficacy and safety of CAM2029 versus placebo. IGF-1 levels are expected to be >1xULN at Week 22 and Week 24 (i.e. 26 and 28 weeks after the last dose of octreotide LAR or lanreotide ATG) for patients on placebo treatment. The double-blind period of 24 weeks will ensure that the effect size captured at the Week 24 is 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). In a slowly progressive disease like acromegaly, which is usually diagnosed 5 to 10 years after the first symptom onset (21), a 24-week treatment with placebo can be considered a relatively short time frame with minimal or no negative impact on the overall disease history or patient disease outcome. Patients should be discontinued from treatment with the blinded IMP and be switched to rescue with standard of care in case they experience worsening of signs and symptoms of acromegaly together with an increase in the levels of IGF-1 to ≥1.3xULN at 2 consecutive visits.

In line with recent recommendations, both patients with and without prior transsphenoidal surgery can be included in the trial, provided that at least 6 months have elapsed since the surgery (11).

4.2.2 Selection of Endpoints

The choice of the primary endpoint (proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24) and secondary endpoints in this trial is consistent with the endpoints used in recent interventional trials (ClinicalTrials.gov identifier: NCT03252353; NCT02685709). According to clinical guidelines, IGF-1 is considered to be the most reliable biomarker of disease activity and for monitoring the efficacy of treatment in patients with acromegaly (9, 25). In clinical practice, IGF-1 is the dominant driver for treatment decisions (9). IGF-1 is, hence, selected as the primary biomarker of efficacy in this Phase 3 trial. The primary objective of the current trial is to assess superiority of CAM2029 versus placebo in efficacy in terms of mean IGF-1 levels ≤1xULN at Week 22 and Week 24 (average of the 2 measurements).

The treatment effect on GH alone and combined with IGF-1 will also be assessed as secondary endpoints as both are considered biomarkers of disease control (3). GH circulating levels are subject to wide variation and GH levels are therefore usually calculated as mean levels (mean concentration of a 5-point profile within a 2-hour time period). In the current trial, both cycle and random values will be used for assessment of GH levels.

Because the CAM2029 product in a pre-filled syringe is planned to be provided for self- or partner-administration, the feasibility of self- or partner-administered injection of CAM2029 and

convenience/patient treatment satisfaction will be evaluated as part of the objectives. Patient-reported treatment convenience with CAM2029 will also be assessed through a general questionnaire and through a patient satisfaction scale and will be compared to the previous treatment.

Note: wherever normal range or ULN for IGF-1 is mentioned in the document (e.g. IGF-1 ≤1xULN), it refers to values adjusted by age and sex.

4.3 Trial Duration

Estimated first patient first visit: Q2 2019

Estimated last patient first visit: Q4 2022

Expected total duration of the trial: Up to 32 weeks for the individual patients (including the Screening and Double-blind Treatment Phases).

4.4 End of Trial Definition

The end of trial for patients continuing as roll-over patients in the long-term safety trial is defined as the visit at Week 24. The end of trial for all other patients is defined as the last protocol-specified contact with that patient (including follow-up of AEs as described in Section 7.5.1.7). The overall end of trial is defined as the last protocol-specified contact with the last patient ongoing in the trial.

4.5 Planned Number of Patients

Approximately 78 patients will be randomized, with 52 patients in the CAM2029 treatment arm and 26 patients in the placebo treatment arm.

5 SELECTION OF TRIAL POPULATION

5.1 Inclusion Criteria

Patients meeting the following criteria will be eligible to participate in the clinical trial:

1. Able to provide written informed consent to participate in the trial prior to any trial-related procedures are performed
2. Willingness and ability to comply with the requirements of the protocol
3. Male or female patients, ≥18 years at screening
4. 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 (CT) is 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 >1xULN (for patients who have undergone pituitary surgery, the measurement should be performed at least 3 months after the surgery)
5. Treatment with a stable dose of octreotide LAR (10 mg, 20 mg, 30 mg or 40 mg) or lanreotide ATG (60 mg, 90 mg or 120 mg) for at least 3 months as monotherapy prior to screening
6. IGF-1 levels ≤1xULN (adjusted for age and sex; mean value of the first measurement at screening and the second measurement at 2 weeks before Day 1)
7. Patients must have adequate liver, pancreatic, renal and bone marrow functions:
    a. Adequate liver function:
        i. Total serum bilirubin ≤1.5xULN*
        ii. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2xULN
        iii. International normalized ratio (INR) <1.3
    b. Adequate pancreatic function:
        i. Amylase and lipase ≤2xULN
    c. Adequate renal function:
        i. Estimated glomerular filtration rate ≥60 mL/min by the Modification of Diet in Renal Disease formula
    d. Adequate bone marrow function:
        i. Platelets ≥100x10^9/L
        ii. Hemoglobin >9 g/dL
        iii. White blood cells >3.0x10^9L

    *Patients with previous diagnose of Gilbert's syndrome may be included if the disease is not accompanied by other hepatobiliary disorders and if the total bilirubin is <3 mg/dL (<51.3 µmol/L) and the direct bilirubin is ≤ULN
8. Normal ECG defined as the following as determined by the mean value of a triplicate ECG:
    a. Resting heart rate 50-105 bpm
    b. QTc interval corrected by Fridericia's formula (QTcF) <450 msec
9. Female patients of childbearing potential must be willing to use an acceptable method of contraception during the entire trial (see Section 7.2.6)

10. Male patients must be willing to use condoms throughout the trial unless they have been sterilized by vasectomy (with an appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)

5.2 Exclusion Criteria

Patients meeting any of the following criteria will not be eligible to participate in the clinical trial:

1. GH ≥2.5 µg/L at screening (cycle)
2. Have 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])
3. Currently receiving other treatments known to affect GH or IGF-1 concentration (including oral estrogens for e.g. contraception or replacement treatment in hypogonadism or during menopause)
4. Patients who usually take octreotide LAR or lanreotide ATG less frequently than every 4 weeks (e.g. every 6 weeks or 8 weeks)
5. Compression of the optic chiasm causing any visual field defect for whom surgical intervention is indicated
6. Patients who have undergone major surgery/surgical therapy for any cause within 1 month prior to screening. Patients who have undergone surgery more than 1 month prior to screening must have recovered from the treatment and be in good clinical condition
7. Patients who have undergone pituitary surgery within 6 months prior to screening
8. Patients who have received prior pituitary irradiation
9. A history of another primary malignancy except the following:
    a. Stable and well-differentiated microcarcinoma of the thyroid
    b. Non-melanoma skin cancer, and carcinoma *in situ* of the cervix, uterus, or breast from which the patient has been disease-free for ≥3 years
    c. A primary malignancy that has been completely resected and in complete remission for ≥5 years
10. Participation in any other clinical trial to test an investigational drug or device within the last 30 days before screening
11. Patients with poorly controlled diabetes mellitus, defined as hemoglobin A1c (HbA1c) >8.0%
12. Patients with diabetes mellitus who have initiated treatment with insulin or who have changed the insulin treatment regimen within 6 weeks prior to screening
13. Hepatic/pancreatic-related exclusion criteria
    a. Presence of hepatitis B surface antigen
    b. Current hepatitis C virus infection
    c. History of alcohol/drug misuse within the past 12 months
    d. Patients with symptomatic cholelithiasis within 3 months prior to screening (patients with non-symptomatic cholelithiasis/sludge and patients who have undergone cholecystectomy more than 1 month prior to screening can be included in the trial)
14. Patients with presence of active or suspected acute or chronic uncontrolled infection or immunocompromised patients, including patients with positive human immunodeficiency virus (HIV) test result
15. Cardiac exclusion criteria: cardiac or cardiac repolarization abnormality, including any of the following:

a. History of myocardial infarction, angina pectoris or coronary artery bypass graft within 6 months prior to screening
b. Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block)
c. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
    i. Risk factors for Torsades de Pointes including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure or history of clinically significant/symptomatic bradycardia
    ii. Concomitant medication(s) with a "Known risk of Torsades de Pointes" (per www.crediblemeds.org) that cannot be discontinued or replaced by safe alternative medication/s. A wash-out of 5 half-lives or 7 days (whichever is longer) from previous treatment with drugs with a known risk of Torsades de Pointes is required prior to the first dose of IMP
    iii. Inability to determine the QTcF interval

16. Uncontrolled hypertension defined by a systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg. The patient needs to be on a stable dose of antihypertensive medication for at least 4 weeks before screening
17. Untreated or uncontrolled hypothyroidism, hypoadrenalism or diabetes insipidus. Patients must be adequately treated with stable doses of replacement therapy for a minimum of 3 months prior to screening
18. Any other current or prior medical condition that may interfere with the conduct of the trial or the evaluation of its results in the opinion of the Investigator or the Sponsor's Medical Monitor
19. Pregnant, lactating or planning to be pregnant during the trial
20. Clinically significant laboratory abnormalities, which in the opinion of the Investigator may prevent the patients from safely participating in the trial
21. Any known allergy, hypersensitivity or intolerance to octreotide or any related drug, or history of any drug hypersensitivity or intolerance which in the opinion of the Investigator, would compromise the safety of the patient or the trial
22. Any other contraindicated serious medical condition, which in the opinion of the Investigator may prevent the patients from safely participating in the trial
23. Unwilling or unable to comply with the requirements of the protocol or in a situation or condition that, in the opinion of the Investigator, may interfere with participation in the trial
24. On the staff, affiliated with, or a family member of the personnel directly involved with this trial

5.3 Lifestyle Considerations

No diet or physical restrictions are required during the trial. Patients should be fasting before safety laboratory sampling, except for the sampling at screening.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the trial but are not subsequently entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, possible other screen failure information and any serious adverse event (SAE).

Patients who do not meet eligibility criteria may be re-screened one more time and should receive a new screening number. However, if e.g. abnormal laboratory findings are considered by the Investigator to be temporary and not reflective of the usual state of the patient, the patient may be re-tested once within the screening period (keeping the original screening number). If the patient is re-screened, the informed consent form (ICF) must be re-signed prior to re-screening procedures being performed. The decision on re-screening or re-testing will be made on a case-by-case basis by the Investigator in consultation with the Medical Monitor. Applicable screening information and results obtained during the first screening may be used for eligibility assessments during re-screening.

Patients who are screened for the long-term safety trial (HS-19-647) and who are screening failures in that trial may be considered for screening in the current trial (HS-18-633). Such cases will be discussed with the Medical Monitor and when possible, screening information and results obtained during screening in the HS-19-647 trial may be used for eligibility determination for the current trial. Informed consent for the current trial (HS-18-633) must be obtained prior to initiating any new trial procedures.

6 TREATMENTS

6.1 Treatments Administered

The treatments to be administered in this trial are summarized in Table 2.

Table 2: Trial treatments

Treatment	CAM2029	Placebo
Treatment name	CAM2029 (octreotide subcutaneous depot)	Placebo
Manufacturer	[redacted]	[redacted]
Dosage formulation	Solution for injection in a ready-to-use pre-filled syringe	Solution for injection in a ready-to-use pre-filled syringe
Unit dose strengths	10 mg/0.5 mL for 10 mg 20 mg/1.0 mL for 20 mg	N/A
Dosage levels/volumes	10 mg 20 mg	0.5 mL 1.0 mL
Route of administration	SC injection	SC injection
Packaging and labelling	The IMP will be provided in pre-filled syringes. Each pre-filled syringe will be labelled in line with country requirements	The IMP will be provided in pre-filled syringes. Each pre-filled syringe will be labelled in line with country requirements

IMP: investigational medicinal product; N/A: not applicable; SC: subcutaneous

The placebo product is identical to the CAM2029 product regarding appearance, volume and viscosity of the solutions.

All administrations of the IMP (CAM2029 or placebo) should be performed in the morning and as close as possible to the time point of the first dose. The dose, date and exact time of each IMP administration should be recorded. This applies for all visits, regardless of the pre-administration assessments (e.g. IGF-1, GH random, GH cycle, pre-administration questionnaires).

6.2 Trial Treatment Administration

6.2.1 CAM2029

6.2.1.1 Administration

CAM2029 will be administered as an SC injection in the abdomen and/or thigh, regardless of who is giving the injection (trial personnel, patient or partner). CAM2029 will be administered once monthly (every 28 days ±7 days). If the date of a visit does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Day 1 visit. The injections should not be administered in a recently used injection site. The site of injection will be recorded. An injection site pictorial and specific instructions for use are included in the Manual of Procedures. The dose, date and exact time of dosing must be recorded on the electronic case report form (eCRF).

All administrations of CAM2029 will be performed at the trial site. Self- or partner-administration of CAM2029 in the abdomen or thigh is allowed after appropriate training and under the supervision of trial personnel who has been adequately trained. The first self- or

partner-administration should preferably be performed on Day 1. Trained trial personnel will document that the patient or partner understands the administration process, performs the injection correctly and administers a full dose (see the Manual of Procedures for a checklist of the feasibility of self- or partner-administration). If the patients or their partners are considered competent to administer CAM2029, they may continue with the self- or partner-administration. If CAM2029 is not self- or partner-administered, the trial personnel will administer CAM2029.

6.2.1.2 Doses and Dose Adjustments

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

Doses of CAM2029 may be down-titrated from 20 mg to 10 mg once monthly for safety/tolerability reasons. After down-titration, the patient can return to the previous dose if the safety issue is resolved and the benefit-risk evaluation allows it. If the patient is on the lowest permitted dose (10 mg) and a further dose reduction for safety reasons is required, the patient will be discontinued from treatment and continue to be followed in the trial. All dose adjustments must be discussed with the Medical Monitor prior to implementation. For instructions regarding dose modifications and dose delays in case of adverse drug reactions or QTcF prolongations, please refer to Section 17.1, Appendix 1.

6.2.2 Comparator Treatment (Placebo)

6.2.2.1 Administration

Placebo will be administered as an SC injection in the abdomen and/or thigh, regardless of who is giving the injection (trial personnel, patient or partner). Placebo will be administered once monthly (every 28 days±7 days). If the date of a visit does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Day 1 visit. The injections should not be administered in a recently used injection site. The site of injection will be recorded. An injection site pictorial and specific instructions for use are included in the Manual of Procedures. The dose, date and exact time of dosing must be recorded on the eCRF.

All administrations of placebo will be performed at the trial site. Self- or partner-administration of placebo in the abdomen or thigh is allowed after appropriate training and under the supervision of trial personnel who has been adequately trained. The first self- or partner-administration should preferably be performed on Day 1. Trained trial personnel will document that the patient or partner understands the administration process, performs the injection correctly and administers a full dose (see the Manual of Procedures for a checklist of the feasibility of self- or partner-administration). If the patients or their partners are considered competent to administer placebo, they may continue with the self- or partner-administration. If placebo is not self- or partner-administered, the trial personnel will administer placebo.

6.2.2.2 Doses and Dose Adjustments

If the patients are randomized to placebo, they will be treated with 1.0 mL placebo (corresponding to 20 mg CAM2029) on Day 1, regardless of their previous octreotide LAR dose (10 mg, 20 mg, 30 mg or 40 mg) or lanreotide ATG dose (60 mg, 90 mg or 120 mg). The first dose of 1.0 mL placebo will be administered 4 weeks (±3 days) after the last dose of octreotide LAR or lanreotide ATG.

Dose volumes may be down-titrated from 1.0 mL to 0.5 mL once monthly (corresponding to 10 mg CAM2029) for safety/tolerability reasons. After down-titration, the patient can return to the previous dose volume if the safety issue is resolved and the benefit-risk evaluation allows it. If the patient is on the lowest permitted dose volume (0.5 mL) and a further dose reduction for safety reasons is required, the patient will be discontinued from treatment and continue to be followed in the trial. All dose adjustments must be discussed with the Medical Monitor prior to implementation. For instructions regarding dose modifications and dose delays in case of adverse drug reactions or QTcF prolongations, please refer to Section 17.1, Appendix 1.

6.3 Rescue Medication

Patients should be discontinued from treatment with the blinded IMP and be switched to rescue medication with standard of care in case they experience worsening of signs and symptoms of acromegaly (as outlined in Section 7.3.5), together with an increase in the levels of IGF-1 to ≥1.3xULN at 2 consecutive visits (including unscheduled visits). If a patient experiences worsening of symptoms of acromegaly as judged by the Investigator, the Investigator should contact the Medical Monitor and obtain information regarding fulfilment of the IGF-1 criterion for switch to rescue medication with standard of care. Patients who are switched to standard of care should continue participation in the trial and should follow all planned visits and assessments.

6.4 Characteristics and Source of Supply, Packaging and Labelling

CAM2029 and placebo are provided by the Sponsor and will be handled according to the principles of Good Manufacturing Practice. The labelling will comply with applicable regulatory requirements.

6.5 Conditions for Storage

The IMP (CAM2029 and placebo) must be received by designated personnel at the trial site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated trial personnel have access. The IMP should be stored in a refrigerator (between 2 to 8°C [36 to 46˚F]) and should not be frozen. The IMP should be equilibrated to room temperature before use.

6.6 Method of Assigning Patients to Treatment Groups

6.6.1 Recruitment

Patients will be recruited by methods chosen at the discretion of the sites. Each site will maintain a screening log of all screened patients.

6.6.2 Randomization and Blinding

This is a double-blind trial. To minimize bias, patients fulfilling the eligibility criteria will be 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 is initiated, the log in information and directions for the interactive randomization system will be provided to each trial site.

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

The randomized treatment assignment to CAM2029 or placebo and all individual IGF-1 and GH results will remain concealed to patients, Investigators and the trial team until the trial is completed and a decision is made to unblind. IGF-1 results will be monitored by an independent reader during the trial.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure a patient's safety in managing a medical condition, the treatment may be unblinded at the trial site by using a code break module. The code break module will be provided by the Sponsor or designee. If possible, the Investigator should contact the Sponsor prior to unblinding. The Investigator must also contact the Sponsor after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the trial.

6.7 Treatment Compliance

6.7.1 Dispensing and Accountability

Only eligible patients participating in the trial will receive IMP. Only authorized site staff may dispense the IMP to the patients. Once dispensed, the IMP must not be relabeled or reassigned for use by other patients.

The Investigator (or his/her designated personnel) will maintain an Injection Log detailing the dates and quantities of IMP administered to each patient. The monitor will verify drug accountability during the trial.

Documentation of IMP administration and drug accountability will be done at all clinic visits (beginning with Day 1).

6.7.2 Assessment of Compliance

CAM2029 and placebo will be self- or partner-administered or administered by a designated healthcare professional during the trial. All administrations of IMP will be performed at the trial site.

Dosing compliance will be recorded by the Investigator or designee at the trial site. Treatment dates, including dates for treatment delays and/or dose reductions, will also be recorded in the eCRF.

6.8 Return and Destruction

All used IMP can be destroyed at the trial site (in accordance with local requirements) after the drug accountability has been finalized and signed off by the Investigator.

All unused IMP will be accounted for and must be destroyed in a certified way after approval by the Sponsor (either at the trial site or any other certified site, such as depot).

6.9 Product Quality Complaints and Device Malfunctions

A Product Quality Complaint (PQC) is any written, electronic or oral communication that alleges deficiencies related to device malfunctions or the identity, quality, stability, reliability or safety of a product, including its labeling, delivery system or packaging integrity.

Any PQC discovered during the initial inventory of the IMP should follow the instructions provided on the receipt letter; no PQC should be filed for issues identified when opening or unpacking a shipment. Any PQC discovered after allocation of an IMP to a patient should be reported as a PQC. Subsequently, any observation of a PQC requires immediate notification, within 24 hours after being made aware of the PQC, to the Sponsor via a completed and signed PQC form.

The following contact information is to be used for PQC reporting:

Email: Complaints@camurus.com

Any IMP associated with a PQC should be quarantined and withheld until further direction is received from the Sponsor. Photographs or physical samples may be requested to support an investigation. The IMP must not be disposed.

In addition, PQC information must be included on the Accountability Log or equivalent in the comments field. The monitor can assist in the event of questions relating to this process.

When enrolling patients into this trial it is the responsibility of the trial site to instruct patients not to use the IMP if they have a concern related to the IMP such as an issue with the labeling, IMP or package integrity and to immediately report it using contact information provided on the patient ID card or on the ICF.

If the PQC is associated with an AE or an SAE, this should be indicated in the PQC form and the event recorded on the AE page of the eCRF. In case of an SAE, the event must be reported as described in Section 7.5.1.3.

6.10 Prior and Concomitant Medication/Therapies

All non-trial medications, including prescription, over-the-counter or herbal therapies, used by the patient will be documented for the 3 months prior to screening and throughout the trial. The Investigator will determine if the prior/concomitant medication(s) affect the patient's eligibility to participate or continue to participate in the trial.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the trial. All medications (other than the IMP) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the trial must be listed in the eCRF.

For patients who are switched to standard of care, any use of standard of care must be recorded in the eCRF.

Permitted Concomitant Therapy Requiring Caution and/or Action

Dose adjustment of medicinal products such as beta blockers, calcium channel blockers or agents to control fluid and electrolyte balance may be necessary during octreotide administration. Dose adjustments of insulin and antidiabetic medicinal products may be required during concomitant administration of octreotide. Octreotide has been found to reduce the intestinal absorption of cyclosporin and to delay that of cimetidine (13).

Limited published data indicate that SSAs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 (CYP) enzymes, which may be due to the suppression of GH. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine and terfenadine) should, therefore, be used with caution (13, 15).

Drugs with a possible risk of causing Torsades de Pointes should be used with caution. Please see further information, including a list of drugs with a possible risk of causing Torsades de Pointes, on the Advisory Board of the Arizona CERT website: www.crediblemeds.org.

Prohibited Concomitant Therapy

The use of the following treatments is NOT allowed after the start of the trial:

- Other investigational drugs or therapies
- Medication known to affect GH or IGF-1 concentration (including oral estrogens for e.g. contraception or replacement treatment in hypogonadism or during menopause)
- Drugs with a known risk of causing Torsades de Pointes. Please see further information, including a list of drugs with a known risk of Torsades de Pointes, on the Advisory Board of the Arizona CERT website: www.crediblemeds.org. In case a patient needs to take any of these QT prolonging drugs, it will require prior trial drug discontinuation. Other appropriate treatment options should, therefore, be considered in order to avoid patient discontinuations as much as possible

6.11 Withdrawal Criteria

6.11.1 Discontinuation of Treatment

Patients may voluntarily discontinue the trial treatment for any reason at any time. If a patient decides to discontinue the trial treatment, the Investigator must make every effort to determine the primary reason for this decision. The reason for discontinuation should be recorded in the patient's chart and on the appropriate eCRF pages.

The Investigator should discontinue trial treatment for a patient if he/she believes that continuation would be detrimental to the patient's well-being. The Investigator must contact the Medical Monitor before a patient is discontinued from treatment.

Trial treatment must be discontinued under the following circumstances:

- Emergence of adverse drug reactions as per the guidance in Section 17.1.1, Appendix 1
- Pregnancy
- Use of prohibited treatment (see Section 6.10)
- Any other protocol deviation that results in a significant risk to the patient's safety or any protocol deviation that will interfere with the assessment of the efficacy endpoints of this trial, including significant non-compliance with the trial protocol and procedures

In addition to the general discontinuation criteria, the following toxicity-related criteria will also require premature trial treatment discontinuation:

Hepatic-related Discontinuation Criteria

The final decision to discontinue trial treatment is up to the judgment of the Investigator. Discontinuation of treatment should be considered if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

Re-challenge is not recommended when trial treatment was discontinued due to the above criteria.

For details on follow-up on potential drug-induced liver injury cases, refer to Section 17.1.2, Appendix 1.

QT-related Discontinuation Criteria

- QT/QTc ≥501 msec or >60 msec increase from baseline (average of triplicate ECG) after repeated measurement and as confirmed by central ECG reader
- Torsades de Pointes
- Polymorphic ventricular tachycardia
- Signs/symptoms of serious arrhythmia
- Use of QT prolonging medication with a known risk of Torsade de Pointes
- Hypokalemia (<3.5 mmol/L) or hypomagnesemia (<0.7 mmol/L), clinically significant hypocalcemia confirmed by repeat testing that is either a new finding or accompanied by vomiting or diarrhea and not corrected by treatment

For details on QT prolongation management, refer to Section 17.1.3, Appendix 1.

Hyperglycemia-related Discontinuation Criteria

- Patients with plasma glucose ≥250 mg/dL (13.9 mmol/L) and/or HbA1c ≥10% at 2 consecutive visits (including unscheduled visits) despite prior appropriate management and prior dose adjustment should be discontinued from trial treatment

Discontinuation of Treatment with IMP and Switch to Rescue Medication

IGF-1 results will be monitored by an independent reader during the trial. Patients should be discontinued from treatment with CAM2029/placebo and be switched to rescue medication with standard of care in case they experience worsening of signs and symptoms of acromegaly (as outlined in Section 7.3.5), together with an increase in the levels of IGF-1 to ≥1.3xULN at 2 consecutive visits (including unscheduled visits). If a patient experiences worsening of symptoms of acromegaly as judged by the Investigator, the Investigator should contact the Medical Monitor and obtain information regarding fulfilment of the IGF-1 criterion for switch to rescue medication with standard of care. Patients who are switched to standard of care should continue participation in the trial and should follow all planned visits and assessments.

6.11.2 Withdrawal from Trial

A patient is free to withdraw his/her consent and withdraw from participation in the trial at any time for any reason. A patient's participation must, therefore, be terminated immediately upon his/her request, and the reason(s) for withdrawal appropriately documented.

All efforts will be made to ensure that all patients are briefed on the importance of the clinical trial and collection of data they provide. The Sponsor will continue to retain and use all research results that have already been collected for the trial evaluation. Biological samples that have already been collected may be retained until the trial is completed and reported (or as required by local regulations).

The Investigator will be trained about the importance of patient retention and steps to prevent missing data. The Investigator must maintain a record of all patients who withdraw from the trial prior to completion; the reason(s) for withdrawal from trial will be documented. If a patient chooses to withdraw from the trial, the Investigator should make every effort to obtain and

record the reason(s) for withdrawal, if possible, although the patient is not obligated to provide such a reason.

Withdrawn patients will not be replaced.

Patients who are withdrawn from the trial should undergo an End of Trial visit. This visit should occur 4 weeks after the last treatment, according to the treatment schedule.

6.12 Lost to Follow-up

For patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the Investigator should contact the patient and document the steps taken to do so in the source documents, e.g. dates of telephone calls, registered letters, etc.
A patient should not be considered lost to follow-up until due diligence has been completed.
Patients who are lost to follow-up should be recorded as such in the eCRF.

7 TRIAL ASSESSMENTS AND PROCEDURES

7.1 Trial Procedures and Flow Charts

Trial procedures and their timing for patients during the trial are summarized in Table 3.

Table 3 Schedule of trial procedures and assessments

Procedure/Assessment	Screening Phase		Double-blind Treatment Phase							
	Week -8 to -4[a]	Week -2[b]	Day 1	Week 4[c]	Week 8[c]	Week 12[c]	Week 16[c]	Week 20[c]	Week 22[b]	Week 24[b]/ EOT[b,d]
Informed consent	X									
Inclusion/exclusion criteria	X		X							
Randomization			X							
Demographic and baseline characteristics	X									
Medical history	X									
Medication/treatment history	X									
Height, BMI	X									
Physical examination, weight	X		X							X
Pregnancy test[e]	X		X[f]			X[f]				X
Serology	X									
Clinical laboratory: hematology, biochemistry, coagulation and urinalysis	X		X[f]		X[f,g]	X[f]	X[f,g]			X
Clinical laboratory: thyroid function	X		X[f]							X
Clinical laboratory: HbA1c	X		X[f]		X[f]	X[f]	X[f]			X
Clinical laboratory: prolactin	X		X[f]							X
Clinical laboratory: immunogenicity	X									X
Clinical laboratory: vitamin B_{12}			X[f]							X
ECG	X		X[f]	X[f]		X[f]		X[h]		X
Vital signs	X		X[f]	X[f]		X[f]		X[h]		X
Administration of CAM2029/placebo[i]			X	X	X	X	X	X		
IGF-1 samples	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[j]	X	X
GH cycle	X		X[f]							X
GH random				X[f]	X[f]	X[f]	X[f]	X[f]	X	
Plasma samples for octreotide measurement			X[f]	X[f]	X[f]	X[f]	X[f]	X[j]	X	X
MRI[k]	X									X
TSQM			X[f]							X
SIAQ			X[l]					X[m]		
Competence to self- or partner-administer IMP			At the first 3 times (3 visits) of self- or partner-administration, then collected only if unsuccessful							
AcroQoL			X[f]							X
EQ-5D-5L			X[f]							X

Procedure/Assessment	Screening Phase		Double-blind Treatment Phase							
	Week -8 to -4[a]	Week -2[b]	Day 1	Week 4[c]	Week 8[c]	Week 12[c]	Week 16[c]	Week 20[c]	Week 22[b]	Week 24[b]/ EOT[b,d]
Patient satisfaction scale										X
Clinical signs and symptoms of acromegaly	X		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X
Gallbladder ultrasounds[n]	X									X
Local tolerability assessment			X	X	X	X	X	X		
AEs	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X

AcroQoL: Acromegaly Quality of Life Questionnaire; AE: adverse event; ATG: autogel; BMI: body mass index; C_{max}: maximum plasma concentration; CT: computerized tomography; ECG: electrocardiogram; EOT: End of Trial; EQ-5D-5L: EuroQoL 5-dimension 5-level; GH: growth hormone; HbA1c: hemoglobin A1c; IGF-1: insulin-like growth factor-1; IMP: investigational medicinal product; LAR: long-acting release; MRI: magnetic resonance imaging; SIAQ: Self-Injection Assessment Questionnaire; SC: subcutaneous; TSQM: Treatment Satisfaction Questionnaire for Medication

a. The last dose of octreotide LAR or lanreotide ATG should be given 4 weeks (± 3 days) before the first dose of CAM2029/placebo
b. Visit window: ±3 days. If the date of a visit after Day 1 does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Day 1 visit
c. Visit window: ±7 days. If the date of a visit does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Day 1 visit
d. The Week 24/EOT visit may be performed over more than 1 day, as long as all assessments are performed within the ±3-day visit window. The visit should take place at Week 24 or 4 weeks after the last dose in case of premature withdrawal from the trial. Patients who complete the trial will at Week 24 be offered to continue with treatment with CAM2029 as roll-over patients in a long-term safety trial. Alternatively, patients will be switched back to their previous treatment for acromegaly
e. Serum pregnancy test at screening, urine pregnancy tests at the other visits
f. Pre-dose
g. Only fasting glucose
h. Pre-dose, 8±1 hours and 24±4 hours after dose
i. CAM2029 or placebo may be self- or partner-administered or the administrations may be performed by trained trial personnel. The injections will be given SC in the abdomen or thigh
j. Blood samples will be collected for analysis of IGF-1 and octreotide at pre-dose and at 2±1 hours, 5±1 hours, 8±1 hours, 24±4 hours and 96±24 hours after dose
k. CT can be used when MRI is contraindicated or not available. Historical MRI/CT scanning performed within 3 months before screening may be used as baseline measurement
l. PRE and POST modules at first self-administration (which is preferably performed on Day 1)
m. Only POST module at Week 20
n. Gallbladder ultrasound is not requested for patients who have undergone cholecystectomy more than 1 month before screening or during the trial

7.2 Screening and Baseline Procedures and Assessments

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all screened participants and to confirm eligibility or record reasons for screening failure, as applicable.

7.2.1 Informed Consent

The nature of the trial and its risks and benefits will be explained to the patient by the Investigator or designated trial personnel. The patient must voluntarily provide written informed consent on an ethics-approved ICF, prior to performing any trial-related procedures. The patient's medical records must document that the consent process has been completed and that written informed consent has been obtained from the patient prior to the initiation of any trial-specific procedures. Documentation that the patient was given adequate time to ask the Investigator (or designee) questions about their participation in the trial and that a signed and dated copy of the ICF was provided to the patient should also be included in the medical records or clinical chart.

7.2.2 Demographics

The following demographics will be recorded: age, sex, race and ethnicity.

7.2.3 Medical History

Relevant medical history within 5 years prior to screening and any clinically significant medical history greater than 5 years prior to screening will be collected based on available medical records and patient interview. Data will include acromegaly history data; histories of acute, chronic, or infectious diseases; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

7.2.4 Medication/treatment History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the patients during the 3 months prior to screening will be recorded in the source documentation as medication history.

A complete medication/treatment history for acromegaly will be collected, including the date and time of the last dose of octreotide LAR or lanreotide ATG prior to the first dose of IMP.

7.2.5 Physical Examination

A physical examination including all major body systems (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system) will be performed at the time points indicated in Table 3. Significant findings that were present prior to signing of the ICF must be included in the Medical History page on the eCRF. Significant findings that begin or worsen after signing of the ICF must be recorded on the AE page of the eCRF.

Height, weight and body mass index will be measured/calculated at screening. Weight will also be measured at the time points indicated in Table 3.

7.2.6 Contraceptive Requirements

Women of childbearing potential must agree to use an acceptable method of birth control as defined in the ICF for the duration of participation in the trial and must agree to be tested for pregnancy. Acceptable method(s) of birth control include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal and post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks prior to screening. In the case of oophorectomy alone, the reproductive status of the woman must be confirmed by follow-up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient
- Barrier methods of contraception: female condom with or without spermicide; or cap, diaphragm or sponge with spermicide. Simultaneous use of male and female condoms with or without any other contraception method is not permitted
- Use of oral (progestin-only), injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), e.g. hormone vaginal ring or transdermal hormone contraception. Estrogen-containing oral contraceptives must not be used since oral estrogen influences IGF-1 and GH levels. Transdermal estrogen-containing contraceptive patches are allowed

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before starting trial treatment.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. appropriate age, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), or tubal ligation at least 6 weeks prior to screening. In the case of oophorectomy alone, the woman is considered not to be of childbearing potential only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

Male patients must agree to use condoms for the duration of the trial, unless they have been sterilized by vasectomy (with an appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

7.3 Efficacy Assessments

7.3.1 IGF-1

Serum levels of IGF-1 will be assessed at the time points depicted in Table 3. Pre-dose blood samplings for evaluation of IGF-1 efficacy endpoints will be done immediately before the IMP administration. In addition, post-dose samples will be taken at Week 20 for a separate evaluation of the PK/PD relationship. The date and exact time of IGF-1 sampling must be recorded in the eCRF. The IGF-1 samples will be analyzed by a central laboratory. Instructions for sampling and shipping of IGF-1 samples will be provided separately.

Note: wherever normal range or ULN for IGF-1 is mentioned in the document (e.g. IGF-1 ≤1xULN), it refers to age- and sex-adjusted values.

7.3.2 GH

GH samples for evaluation of GH efficacy endpoints will be taken as pre-dose cycles (5 samples taken over a period of 2 hours, i.e. every 30 minutes), and as random pre-dose samples at the time points defined in Table 3.

GH cycles will be assessed during 2 hours after 1 hour at rest in the morning before the IMP administration (120, 90, 60, 30 and 0 minutes before the administration). All GH cycles should be taken approximately at the same time as the first cycle.

GH random will be assessed after 1 hour at rest in the morning before the IMP administration.

The date and exact time of GH sampling must be recorded in the eCRF. The GH samples will be analyzed by a central laboratory. Sampling and shipping instructions will be provided separately.

Note: 0 minutes before administration should be understood as the planned time point for IGF-1 sampling, GH random sampling and other assessments to be performed immediately before IMP administration. Therefore, the 120-minute sampling should start 2 hours earlier (-120 minutes from time 0 minutes).

7.3.3 Magnetic Resonance Imaging

Pituitary MRI scanning with gadolinium enhancement will be performed at screening and at Week 24/End of Trial. The scans will be assessed centrally to screen for pituitary tumor volume change.

If MRI scan with intravenous contrast (gadolinium) is contraindicated for a patient, a non-contrast MRI scan should be performed. If the MRI cannot be performed at all, a CT of the pituitary (with intravenous contrast if not contraindicated) may be performed. Regardless of imaging type, all regularly scheduled pituitary imaging will be centrally reviewed for consistency in the measurement of dimensions. The modality should remain consistent unless there is a development of a contraindication.

Historical MRI/CT scanning performed within 3 months before screening may be used as baseline measurement. If such an MRI/CT scanning is available, the screening MRI/CT does not need to be performed.

7.3.4 Patient-reported Outcomes

Patient-reported outcomes (PROs) for the assessment of convenience and treatment satisfaction include:

- Treatment Satisfaction Questionnaire for Medication (TSQM) v1.4
- Self-Injection Assessment Questionnaire (SIAQ) v2.0
- Health-related quality of life questionnaires (Acromegaly Quality of Life Questionnaire [AcroQoL] and EuroQoL 5-dimension 5-level [EQ-5D-5L])
- Patient satisfaction scale

PROs will be completed in the patient's local language. The patient must be given enough space and time to complete the questionnaires.

The questionnaires should be completed per respective assessment schedule for each instrument (see Table 3) and in the following order, as applicable: TSQM, SIAQ, AcroQoL, EQ-5D-5L and patient satisfaction scale.

The trial personnel will check the questionnaires for completeness and should ask the patient to complete any missing responses. Patient's refusal to complete all or any part of a questionnaire must be documented in the eCRF and should not be captured as a protocol deviation. The reason for non-completion of the questionnaire should be recorded in the eCRF. Original responses to the questionnaire are regarded as source data.

Completed questionnaires and any unsolicited comments written by the patient must be reviewed and assessed by the Investigator for responses that may indicate potential AEs or SAEs. This assessment must be documented in trial source records. If AEs or SAEs are confirmed, the Investigator must follow the reporting instructions outlined in Section 7.5.1.

Investigators/trial personnel must not influence the completing of questionnaires by a patient through verbal or other non-verbal actions.

7.3.4.1 Treatment Satisfaction with Medication Questionnaire

The TSQM is a general PRO instrument designed to measure patient satisfaction with their medication (26). It has been previously used in patients with acromegaly to measure satisfaction with their medical treatment (27).

The TSQM Version 1.4 will be used to compare the patients' satisfaction with CAM2029 as compared to their previous treatment (octreotide LAR or lanreotide ATG) and assess satisfaction with CAM2029/placebo during the trial. The questionnaire has 4 domains (effectiveness, side effects, convenience and global satisfaction), each comprising 3 to 4 items. Responses are evaluated on a 5 to 7-point scale for each item. The calculation of domain scores will be done according to the instrument manual. All domain scores range from 0 to 100. Higher scores indicate a better outcome from the patient's perspective. The TSQM questionnaire and instrument manual will be included in the Manual of Procedures.

The TSQM questionnaire will be completed at the beginning of the scheduled trial visits according to Table 3, before the Investigator conducts any clinical assessment.

7.3.4.2 Self-Injection Assessment Questionnaire

The SIAQ is an instrument designed to measure overall patient experience with SC self-administration (28). It comprises a PRE self-injection module containing 7 items and a POST self-injection module containing 21 items and will be completed by patients who choose to self-administer CAM2029 (or placebo).

The SIAQ PRE module will be completed by the patient before the first self-administration of CAM2029 (or placebo) and contains the following domains:

- General feelings about injections
- Self-confidence about giving self-injections
- Satisfaction with the current way of taking medication

The SIAQ POST module will be completed 20 to 40 minutes after the first self-administration and after the self-administration at Week 20 according to Table 3. The POST module contains the PRE domains plus the following domains:

- Self-image
- Injection site reactions
- Ease of use of the self-injection device

Responses are evaluated on a 5- to 6-point scale for each item.

The calculation of domain scores will be done according to the instrument manual. All domain scores range from 0 to 10. Higher scores indicate a better patient experience. The SIAQ will be included in the Manual of Procedures.

7.3.4.3 Health-related Quality of Life

Health-related quality of life will be assessed by the AcroQoL questionnaire and utilities will be assessed using the EQ-5D-5L at the time points shown in Table 3.

The AcroQoL is a disease-specific scale for assessment of quality of life in patients with acromegaly (29). The AcroQoL is uni-dimensional and contains 22 items divided into 2 scales; physical (8 items) and psychological (14 items). The psychological scale is further divided into 2 sub-scales: physical appearance and impact of the disease on personal relationships of the patient (7 items each). The calculation of domain scores will be done according to the instrument manual. Higher scores indicate better quality of life.

The EQ-5D-5L is a measure of health status from which utilities can be calculated for use in economic modeling. It has 2 components, the EQ-5D-5L descriptive system and the EQ-5D-5L visual analog scale (VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and unable to do an activity or extreme problems. A utility index can be computed from the EQ-5D-5L descriptive system with utility scores ranging from -0.281 (worst imaginable health state) to 1 (best imaginable health state), with -0.281 representing an “unconscious” health state. The EQ-5D-5L VAS records the patient’s self-rated health state on a 100-point vertical VAS (0=worst imaginable health state; 100=best imaginable health state). Scorings will be derived as previously described (30, 31).

7.3.4.4 Patient Satisfaction Scale

At Week 24/End of Trial, the patients will complete a satisfaction questionnaire, in which they will rate their overall experience with CAM2029/placebo compared to their previous treatment with octreotide LAR or lanreotide ATG. The patients will evaluate the treatment on a 5-unit scale from “much worse” to “much better”. The patient satisfaction scale will be included in the Manual of Procedures.

7.3.5 Clinical Signs and Symptoms of Acromegaly

The Investigator will measure the patient’s ring size using the provided gauge at the time points outlined in Table 3. Ring size (circumference) will be measured at the fourth digit of the non-dominant hand. If a patient has a fourth digit size exceeding the highest size, the fifth digit of that hand will be used for initial and follow-up investigation.

At the same time points, the Investigator will also assess (together with the patient) the following symptoms of acromegaly on a 4-point score scale (none, mild, moderate and severe):

- Headache
- Sweating
- Fatigue
- Joint pain
- Paresthesia
- Soft tissue swelling

Worsening of signs and symptoms of acromegaly will be recorded as AEs at the discretion of the Investigator.

7.4 Drug Concentration Assessments

7.4.1 Blood Collection and Handling

Blood samples for evaluation of plasma concentrations of octreotide will be collected from all patients who receive at least one dose of IMP. Blood sampling will be performed at the time points indicated in Table 3.

All blood samples for analyses of octreotide will be taken by either direct venipuncture or indwelling cannula inserted in a forearm vein. Blood samples (2.5 mL) will be collected to yield 1 mL plasma for analysis of octreotide plasma concentration.

The date and exact time of dosing, as well as the date and exact time of blood sampling, must be recorded on the eCRF. Detailed instructions for the collection, handling and shipment of blood samples will be provided separately.

7.4.2 Analytical Method

Plasma concentrations of octreotide will be measured using a validated liquid chromatography-tandem mass spectrometry assay with a lower limit of quantification (LLOQ) of approximately [redacted] ng/mL.

7.5 Safety Assessments

7.5.1 Adverse Events and Serious Adverse Events

7.5.1.1 Adverse Event Definitions

An **AE** (synonym: adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, in a patient or clinical trial subject administered a trial treatment and which does not necessarily have a causal relationship with this treatment (i.e. whether or not considered drug-related). An AE can, therefore, be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a trial treatment, whether or not considered related to the trial treatment. Patients will be instructed to contact the Investigator at any time after enrollment if any symptoms develop.

Adverse drug reaction: All untoward and unintended responses to a trial treatment assessed as related to any dose administered.

AEs or SAEs assigned a causality assessment by the Investigator of "probably related" or "possibly related" will be considered by the Sponsor to be related for the purpose of defining adverse drug reactions and thereby also expedited reporting.

An AE is considered "unexpected" if the nature, severity, or outcome is not consistent with the reference safety information section in the current edition of the IB (17).

An **SAE** is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is another medically important event
    - Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. This is based on the medical and scientific judgment of the Investigator

*Exemptions may be made when hospitalization is due to:

- Routine treatment or monitoring of the investigated indication, not associated with any deterioration in the condition
- Treatment that was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under investigation and did not worsen
- Admission to a hospital or other institution for general care, not associated with any deterioration in the condition

Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported and followed up as indicated for an SAE (see Section 7.5.1.3). This includes:

- Pregnancy during exposure to a trial treatment. If a pregnancy is confirmed, the use of the IMP must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male patient, the necessary information must be collected from the patient, while respecting the confidentiality of the partner
- Lactation exposure to an IMP with or without an AE
- Overdose of an IMP as specified in this protocol with or without an AE
- Inadvertent or accidental exposure to an IMP with or without an AE

Any new event, sign or symptom occurring in the period between screening (after signing the ICF) and the first IMP administration on Day 1 will be recorded in the same manner as an AE.

7.5.1.2 Eliciting, Documenting and Reporting of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded on the AE page of the eCRF and reported to the Sponsor. AEs will be assessed from the time of informed consent until completion of all trial procedures and discharge from the trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

At every clinic visit, patients will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any

accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

Information to be collected includes drug treatment, type of event, time of onset, dosage, Investigator-specified assessment of severity and relationship to trial treatment, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs should be followed until they have reached a final outcome (recovered, recovered with sequelae, recovering, not recovered, fatal or unknown) or the patient's participation in the trial ends, whichever comes first. SAEs and severe, non-serious AEs assessed as "possibly related" or "probably related" to IMP that are still ongoing after ended trial participation should be followed on a regular basis according to the Investigator's clinical judgment until a final outcome has been established (see Section 7.5.1.7).

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the trial, it should be recorded as an AE.

7.5.1.3 Reporting of Serious Adverse Events

Any AE which meets any of the SAE criteria (Section 7.5.1.1) must be reported to the Sponsor immediately (within 24 hours after the Investigator has become aware of the occurrence of the SAE) to the contact details listed below, using the trial-specific SAE report form. The Investigator will assess whether there is a reasonable possibility that the trial treatment caused the SAE. Other reportable information as defined in Section 7.5.1.1 should also be reported to the below contact immediately (within 24 hours after the Investigator has become aware of the occurrence of the event).

The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAEs according to applicable legislation. The Investigator is responsible for notifying the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) directly, as per IEC/IRB requirements.

The following contact information is to be used for SAE reporting:

Email: safety@camurus.com
or
International SAE fax number: [redacted]

7.5.1.4 Assessment of Severity

Severity is defined as a measure of the intensity of an AE or SAE and will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). If CTCAE grading does not exist for an AE, the severities of mild, moderate and severe, corresponding to Grades 1 through 3, will be used. The CTCAE Grade 4 (life-threatening) and CTCAE Grade 5 (death) will not be used in this trial. Instead, life-threatening events and deaths will be used as criteria for SAE reporting.

Abnormal laboratory values shall be recorded as AEs if assessed as clinically significant by the Investigator. In that case, the severity will be assessed according to the CTCAE. Laboratory abnormalities that are associated with an already reported medical condition will not be reported as separate AEs but will be used for the assessment of the associated medical condition (e.g.

increased neutrophils level in case of reported infection or increased glucose in a patient with diabetes).

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

7.5.1.5 Assessment of Outcome

The outcome of an AE or SAE will be classified using the following outcome ratings:

0 = Unknown

1 = Recovered/resolved

2 = Recovering/resolving

3 = Not recovered/not resolved/ongoing

4 = Recovered/resolved with sequelae

5 = Fatal

7.5.1.6 Assessment of Causality

The Investigator will assess relationship to the trial treatment for all AEs and SAEs. The relationship will be characterized using the following causality ratings:

- **Probably related**: An AE with a reasonable time sequence to the administration of the IMP, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition
- **Possibly related**: An AE with a reasonable time sequence to the administration of the IMP, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
- **Not related**: An AE with a temporal relationship to drug administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide plausible explanations. There is no reasonable possibility that the event was caused by the trial treatment
- **Not applicable**: This assessment can be used, for example, in cases where the patient did not receive any treatment with IMP

7.5.1.7 Follow-up of Adverse Events

All AEs should be followed until they have reached a final outcome (recovered, recovered with sequelae, recovering, not recovered, fatal or unknown) or the patient's participation in the trial ends, whichever comes first.

SAEs and severe, non-serious AEs assessed as "possibly related" or "probably related" to the IMP, still ongoing after ended trial participation, should be followed on a regular basis according to the Investigator's clinical judgment until a final outcome has been established.

The outcome "recovering" can be used as the final outcome for events that are stabilized (i.e. no further worsening is expected) and expected by the Investigator to resolve over time.

The outcome "not recovered" can be used as the final outcome for events that are not expected to resolve over time (e.g. cancer).

SAEs occurring after the patient has completed the clinical trial and for which a reasonable possibility (assessed as "possibly" or "probably" related) of a causal relationship to the IMP is assessed by the Investigator, should be reported to the Sponsor by the Investigator regardless of the time that has elapsed (post-trial events).

7.5.2 Anticipated Risks and Safety Concerns of the Trial Drug

The most frequent adverse drug reactions during octreotide therapy include those related to GI disorders, nervous system disorders, hepatobiliary disorders and metabolism and nutritional disorders.

The most commonly reported adverse drug reactions in clinical trials with octreotide were diarrhea, abdominal pain, constipation, nausea, flatulence, headache, cholelithiasis, hyperglycemia and injection site reactions. Other commonly reported adverse drug reactions were dizziness, biliary sludge, thyroid dysfunction (e.g. decreased thyroid stimulating hormone, decreased total T4 and decreased free T4), loose stools, impaired glucose tolerance, vomiting, asthenia and hypoglycemia (13).

Cardiovascular System

Bradycardia has been reported in patients treated with octreotide with frequency ranging between 1 and 10% (13). Therefore, dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary during octreotide administration.

Gallbladder and Related Disorders

Octreotide inhibits secretion of cholecystokinin, resulting in reduced contractility of the gallbladder and an increased risk of sludge and stone formation. Development of gallstones has been reported in 15 to 30% of long-term recipients of SC Sandostatin. The prevalence in the general population (aged 40 to 60 years) is about 5 to 20% (13). If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Glucose Metabolism

Because of its inhibitory action on GH glucagon, and insulin release, octreotide may affect glucose regulation. Post-prandial glucose tolerance may be impaired. In some instances, the state of persistent hyperglycemia may be induced as a result of chronic administration. Hypoglycemia has also been reported (13).

In patients with concomitant type 1 diabetes mellitus, octreotide can affect glucose regulation, and insulin requirements may be reduced. In non-diabetics and type 2 diabetics with partially intact insulin reserves, Sandostatin SC administration resulted in increases in post-prandial glycemia in some subjects.

7.5.3 Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments (including biochemistry, hematology, serological markers [HIV and hepatitis B and C] and urinalysis) will be performed at screening and during the trial according to the time points outlined in Table 3. Patients should fast overnight for 8 hours prior to all safety blood samples being taken, except for the samples taken at screening. Blood samples will be taken in the morning. Water is allowed during this time.

A central laboratory will be used for the analysis of all laboratory evaluations. Details on the collections, shipment of samples and reporting of results by the central laboratory will be

provided separately. The results of the clinical safety laboratory assessments must be reviewed prior to enrollment in order to assess the patient's eligibility for the trial.

Clinically significant abnormalities present when the patient signed the ICF should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Sponsor prior to enrolling the patient in the trial. New or worsened clinically significant findings occurring after signing of the ICF must be recorded on the AE eCRF page.

Blood samples will be taken after the assessment of vital signs and ECG.

Locally required tests, e.g. for SARS-CoV-2, may be performed by sites and analyzed at local laboratory. Such tests will not be part of clinical trial assessments.

The assessments in Table 4 will be performed:

Table 4: Clinical laboratory parameters

Test category	Test name
Hematology	Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red blood cells, RDW-CV, platelets, WBC, WBC with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Biochemistry	Albumin, ALP, ALT, AST, amylase, bicarbonate, calcium, chloride, creatinine, creatine kinase, GGT, lipase, fasting[a] plasma glucose, inorganic phosphorus, magnesium, potassium, sodium, total bilirubin (direct bilirubin and indirect bilirubin only in patients with total bilirubin >2xULN), total cholesterol, low density lipoprotein, high density lipoprotein, total protein, triglycerides, blood urea nitrogen or urea, uric acid
Urinalysis	Macroscopic panel (bilirubin, blood, glucose, ketones, WBC, pH, protein, specific gravity)
Coagulation	Prothrombin time or INR, activated partial thromboplastin time
Thyroid	T3 (free), T4 (free), TSH
Serology	HBsAg, HCV antibodies (PCR required for HCV antibody-positive patients), HIV antibodies
Additional tests	HbA1c, prolactin, anti-octreotide antibodies, vitamin B_{12}

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; HbA1C: hemoglobin A1c; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; INR: international normalized ratio; PCR: polymerase chain reaction; RDW-CV: red cell distribution width – coefficient of variation; TSH: thyroid stimulating hormone; ULN: upper limit of normal; WBC: white blood cells

a Except for the screening sample

Prolactin

Prolactin levels will be assessed according to Table 3. Time point for blood sampling is pre-dose with respect to administration of IMP. The samples for prolactin will be analyzed by a central laboratory. Instructions for sampling and shipping will be provided separately.

Immunogenicity Assessments

Blood samples for immunogenicity assessment of anti-drug antibodies will be taken according to Table 3 and sent to a central laboratory. Detailed method descriptions of the immunogenicity assays will be provided separately.

Pregnancy Tests

Women of childbearing potential will have a serum beta-hCG pregnancy test at screening. This will be performed by a central laboratory. The results of the pregnancy test at screening must be reviewed and confirmed to be negative prior to enrollment to assess the patient's eligibility for the trial. Moreover, urine pregnancy test will be performed at the other visits, as indicated in

Table 3. Urine pregnancy test will be performed by dipstick locally. A positive pregnancy test requires immediate interruption of trial treatment until the assessment is confirmed via serum beta-hCG pregnancy test performed by central laboratory. If positive, the patient must be withdrawn from the trial.

7.5.4 Vital Signs

Vital signs consist of body temperature, blood pressure (systolic and diastolic, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) and will be collected at the time points outlined in Table 3, following a resting period of at least 3 minutes. More frequent examinations may be performed at the Investigator's discretion, if medically indicated. Vital signs will be taken prior to taking ECG and blood samples.

Significant findings that were present prior to signing of the ICF must be included on the Medical History page in the eCRF. Significant findings that begin or worsen after signing of the ICF must be recorded on the AE page of the eCRF.

7.5.5 Electrocardiogram

ECGs will be recorded, and readings will be transmitted to a selected ECG central laboratory for analysis. Triplicate 12-lead ECG (3 ECG recordings at approximately 2-minute intervals) will be performed at each scheduled time point. ECGs will be recorded at screening and at the time points outlined in Table 3.

The ECG assessments pre-dose and at the 8- and 24-hour time points have been selected to coincide with trough concentrations and near C_{max} of octreotide for CAM2029, based on PK results from trial HS-11-411. If at any visit QTcF >480 msec is observed, the procedures for QT-prolongation management described in Section 17.1.3, Appendix 1 must be followed.

ECGs will be recorded after the patient has been resting in a supine position for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. ECGs will be recorded after vital signs and prior to blood samples for PK, efficacy/PD and clinical safety laboratory assessments.

All ECG assessments will initially be assessed by the Investigator/qualified physician for any findings that require immediate medical attention. All ECGs will also be read by an ECG central reader. The clinical significance of any ECG findings will be determined by the Investigator, including after the central reading result is available. However, only ECG results provided by the central reader will be recorded in the eCRF and clinical database.

Clinically significant abnormalities present when the patient signed the ICF should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Sponsor prior to enrolling the patient in the trial. New or worsened clinically significant findings occurring after signing of the ICF must be recorded on the AE page of the eCRF.

7.5.6 Gallbladder Imaging

A gallbladder ultrasound will be performed locally at the visits indicated in Table 3. Information on the presence of gallstones or gallbladder sludge will be recorded on the appropriate eCRF page. Patients with symptomatic cholelithiasis within 3 months before screening will be excluded from participation in the trial (see Section 5.2).

Historical gallbladder ultrasound performed within 3 months before screening may be used as baseline measurement. If such a gallbladder ultrasound is available, the screening gallbladder ultrasound does not need to be performed.

Gallbladder ultrasound is not requested for patients who have undergone cholecystectomy more than 1 month before screening or during the trial.

7.5.7 Local Tolerability

The Investigator will assess the degree of local tolerability in terms of erythema and swelling at the injection site at scheduled time points in Table 3. The patient will also self-assess the injection site pain using a numerical rating scale at the same time points. The degree of severity of all parameters will be collected. Assessments will be done immediately and 1 hour after the injections. Any event that occurs or persists beyond 1 hour after the injection will be collected as an AE at the discretion of the Investigator.

The details on the data collection and the severity grading for each parameter are provided in Section 17.2, Appendix 2.

7.6 Other Assessments - Feasibility of Self-administration of IMP

Patients and their partners will have the possibility to administer the IMP (CAM2029 or placebo) by themselves (after appropriate training and the option of simulated injection). The first self- or partner-administration should preferably be performed on Day 1. Qualified trial personnel will supervise the administration and assess the patient's/partner's ability to successfully administer the IMP using a checklist based on assessments used in previous studies on SSAs (32, 33), see the Manual of Procedures.

The qualified trial personnel will provide appropriate training, and if judged successfully perceived, a supervised self- or partner-administration according to the provided checklist can be performed. The attempt to provide appropriate training to the patient or partner for the IMP administration will be allowed for a maximum of 3 times (3 visits). If the patient/partner is deemed as not capable to administer the IMP, the trial personnel will continue the administration at the scheduled time points. The training attempts and outcomes will be collected as "successful" or "unsuccessful" on the appropriate eCRF page.

If a patient or a partner is declared competent by the qualified trial personnel to successfully self- or partner-administer the IMP, then he/she will have the possibility to continue to self-/partner-administer the IMP at the clinic.

Any problem during the IMP administration (technical or human-factor-related), and any reason for why a patient decides to withdraw from self- or partner-administration of the IMP will be recorded in the eCRF throughout the trial.

8 STATISTICAL CONSIDERATIONS

8.1 Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to database lock and before unblinding the trial. This document will include more details of the analysis populations, summary strategies, and any amendments to the below proposed analyses, if necessary. Any changes to the SAP will be outlined in the final clinical trial report.

8.2 Determination of 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 ≤1xULN by treatment arm are made. It should be noted that the treatment difference in biochemical response is 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 is, thus, assumed that the proportion with biochemical response with this endpoint is very similar to response based on 1 measurement.

The proportion of responders at Week 22 and Week 24 in the CAM2029 treatment arm is assumed to be 0.80 (34). For the group of patients receiving placebo it is assumed that the proportion of responders is 0.40 at Week 22 and Week 24. It is also assumed that the missing data frequency will 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 is 90% to show a difference between CAM2029 and placebo, if the percentages of responders, as defined by the primary endpoint, are 80% for CAM2029 and 40% for placebo. The power calculation is based on the Chi-squared test (with a continuity correction).

8.3 General Considerations

All efficacy analyses will be based on the intention-to-treat (ITT) analysis set. Efficacy analyses of the primary endpoint will be repeated for the full analysis set (FAS), modified intention-to-treat (mITT) analysis set and per protocol (PP) analysis set as supportive analyses if the analysis sets differ from the ITT analysis set.

For all efficacy endpoints, descriptive measures and 95% confidence interval (CI) for the difference between the 2 treatment arms (CAM2029 and placebo) will be presented, unless otherwise specified.

Safety analyses will be based on the safety analysis set. Safety parameters will be compared descriptively between the 2 treatment arms (CAM2029 and placebo).

The statistical analyses will be performed using SAS version 9.3 or later.

8.4 Patient Disposition

All patients who provide informed consent will be accounted for. Patients who are screened but not enrolled will be listed. The number and percentage of patients in each analysis set will be presented by treatment arm (percentage of the number of patients randomized) and overall. The number and percentage of patients completing treatment and trial will be presented by treatment arm and overall. The number and percentage of patients who discontinue treatment or withdraw from the trial will be presented by the main reason of discontinuation or withdrawal, by

treatment arm and overall. Patients who withdraw from the trial due to COVID-19 will be listed separately.

8.5 Protocol Deviations

Major protocol deviation criteria will be established prior to database lock. Handling of protocol deviations due to COVID-19 will also be addressed prior to database lock.

8.6 Analysis Sets

8.6.1 Intention-to-treat Analysis Set

The ITT analysis set comprises all patients who have been randomized to a treatment arm. Analyses based on this population will group patients according to the treatment they were randomized to receive, regardless of actual treatment received. The efficacy analyses will be based on the ITT analysis set.

8.6.2 Full Analysis Set

The FAS comprises all randomized patients in the ITT analysis set who were administered at least one dose of the randomized IMP.

8.6.3 Modified Intention-to-treat Analysis Set

The mITT analysis set comprises all patients in the ITT analysis set who do not have COVID-19-related missing IGF-1 measurements at Week 22 and Week 24 (i.e. they either have at least one available measurement, or the missingness is not due to COVID-19).

8.6.4 Per Protocol Analysis Set

The PP analysis set is defined as all patients in the ITT analysis set with no major protocol deviations that would have an impact on the efficacy assessment.

8.6.5 Safety Analysis Set

The safety analysis set comprises all patients who were administered at least one dose of IMP. Analyses based on this population will group patients according to the actual treatment the patients received. The safety analysis set will be used for analysis of safety data.

8.7 Trial Population

8.7.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented by treatment arm. Demography and background characteristics summaries will be prepared for all analysis sets that are different from each other.

8.7.2 Medical History

Medical history (recorded at screening) will be coded using the MedDRA and data will be listed and presented descriptively.

8.7.3 Prior and Concomitant Medications and Treatments

Prior and concomitant medications will be summarized separately by Anatomical Therapeutic Chemical (ATC) classification levels (in decreasing order of frequency) and treatment arm. Prior and concomitant non-pharmacological treatments will also be presented by treatment arm.

Prior medications and treatments for acromegaly will be presented separately.

8.8 Efficacy Endpoints and Analyses

8.8.1 Missing Values

Procedural attempts with the aim to avoid missing data and keep the frequency of missing data to a minimum will be implemented in the trial (as described in Section 6.11).

Handling of missing values in the primary efficacy analysis is described in Section 8.8.2. Sensitivity analyses evaluating the impact of missing data will be performed as described in Section 8.8.2. For the secondary efficacy endpoint analyses, data from retrieved dropouts (i.e. following intercurrent events) will be set to missing, unless otherwise stated.

Further details on the handling of missing data will be presented in the SAP.

8.8.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with biochemical response, defined as the proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24 (average of the 2 measurements). The primary analysis of the primary endpoint will be 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 will be used for the assessment of the individual patient's response.

Definition of the Primary Estimand

Given the nature of the expected intercurrent events, a composite variable strategy has been chosen. The items that define the primary estimand are:

a) *Population of interest:* patients with acromegaly as defined by the inclusion/exclusion criteria in the trial

b) *Variable (or endpoint) of interest:* biochemical response defined as the mean of the IGF-1 values measured at Week 22 and Week 24 being ≤1xULN (adjusted for age and sex). A patient will be considered as non-responder if the mean of the IGF-1 values measured at Week 22 and Week 24 is >1xULN (adjusted for age and sex).

c) *Specification of how intercurrent events are reflected in the scientific question of interest:*

- Discontinuation: Patients who discontinue treatment with CAM2029/placebo prior to Week 22 (regardless of IGF-1 values) will be regarded as non-responders
- Rescue medication: Patients who receive rescue medication will be regarded as non-responders (as it results in treatment discontinuation)
- Dose decrease: Patients who have had their dose decreased (due to safety or tolerability reasons) will be regarded as non-responders

d) ***Population level summary for the variable:*** difference in the proportion of patients with biochemical response between the CAM2029 and placebo treatment arms, stratified by prior treatment

The *primary estimand* is thus 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 being ≤1xULN) between CAM2029 and placebo for patients with acromegaly. This estimand assumes that occurrence of intercurrent events other than those affecting dose received are considered irrelevant in defining the treatment effect of interest.

Statistical Analysis Methods

The frequency of intercurrent events and the number of missing data will be summarized separately.

If one of the IGF-1 values at Week 22 or Week 24 is missing, the other value will be used to define a responder/non-responder for the analysis. The variable (or endpoint) of interest will be missing only if no IGF-1 value can be obtained from both the Week 22 and Week 24 samples.

The following statistical hypothesis with a one-sided alternative will be tested to address the primary efficacy objective:

$$H_0: \theta \leq 0 \text{ versus } H_1: \theta > 0$$

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 primary analysis of the primary endpoint will be 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, H_0, will be rejected if the associated one-sided p-value is <0.025.

In addition, the proportion of patients with IGF-1 ≤1xULN (adjusted for age and sex) will be provided descriptively by treatment arm.

Sensitivity and Supportive Analyses

Several sensitivity analyses will be performed:

- Multiple imputation using retrieved dropouts: Missing IGF-1 values at Week 22 and Week 24 will be based on patients who discontinued trial treatment and had a measurement at Week 22 or Week 24. The imputation will be done within groups defined by the randomized treatment and stratum if the number of retrieved dropout patients is sufficient

  The responder/non-responder status for each patient will be determined from the imputed continuous response, i.e. the average of the values at Week 22 and Week 24 being ≤1xULN or >1xULN
- A control-based "wash-out" analysis will be used to impute missing data in the treatment arm using relevant baseline information and data from the placebo treatment arm
- A sensitivity analysis will be performed by imputing missing values for the primary endpoint with a multiple imputation approach only for patients who discontinue treatment due to reasons other than AEs or lack of efficacy
- A tipping point analysis will be performed to evaluate the potential impact of missing data using a graphical method
- A sensitivity analysis will be performed for patients with missing data due to COVID-19. For these patients, IGF-1 values will be imputed by multiple imputation, assuming non-informative missingness (data missing at random)

As supportive analyses, the responder rates by treatment arm at Week 22 and Week 24 and the difference in responder rates between the 2 treatment arms will also be estimated together with their respective 2-sided 95% CI, based on:

- Patients who received their Week 20 dose of IMP
- The FAS
- The mITT analysis set
- The PP analysis set
- The ITT analysis set using ULN for IGF-1 values based on actual age category at the time of each assessment and which are not carried forward from screening
- Logistic regression, with treatment arm, prior treatment (octreotide LAR or lanreotide ATG), sex and race as fix factors, and time since diagnosis, age and baseline IGF-1 value as covariates

Subgroup Analyses

- Exploratory subgroup analyses will also be performed by sex, race, age and prior treatment with octreotide LAR or lanreotide ATG.

Details of the sensitivity, supportive and subgroup analyses will be included in the SAP.

8.8.3 Secondary Efficacy Endpoints

8.8.3.1 Proportion of Patients with Biochemical Response Based on IGF-1 Levels, Irrespective of IMP Dose

Proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24, including patients who have their dose decreased to 10 mg CAM2029 (or 0.5 mL placebo), will be analyzed in the same way as the primary efficacy endpoint (including sensitivity analyses).

For this endpoint, intercurrent events will be handled in the same way as for the primary endpoint, with the exception that patients who have had their dose decreased (due to safety or tolerability reasons) will be evaluated based on the mean of the IGF-1 values measured at Week 22 and Week 24 being ≤1xULN (adjusted for age and sex).

8.8.3.2 Proportion of Patients with Biochemical Response Based on IGF-1 and GH Levels

Proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24 and mean GH cycle levels <2.5 µg/L at Week 24, will be analyzed in a similar way as the primary efficacy endpoint (including sensitivity analyses).

For this endpoint, intercurrent events will be handled in the same way as for the primary endpoint.

8.8.3.3 Time to Loss of Response

Time to loss of response (i.e. time to IGF-1 levels >1xULN and time to IGF-1 levels ≥1.3xULN) will be presented for each treatment arm separately. Time to loss of efficacy is defined as the earliest time when the IGF-1 levels of 2 consecutive measurements are >1xULN or ≥1.3xULN. Patients who are still receiving CAM2029/placebo at Week 24 and are still responders will be censored at Week 24. For patients who discontinue treatment or withdraw from the trial, IGF-1 values from the visit following their last injection will be used in this analysis, but all subsequent IGF-1 values (if any) will be set to missing. Patients who discontinue the treatment or withdraw

from the trial without having loss of response confirmed will be censored at their last available IGF-1 measurement.

A Cox proportional hazards model will be used for time to loss of response with treatment as factor and baseline IGF-1 as covariate, stratified by stratum. Hazard ratios will be presented from the model along with the associated 2-sided 95% CIs and p-values. Further details of the analyses will be outlined in the SAP.

8.8.3.4 Change from Baseline to Week 24 in IGF-1 and GH Levels

Data for absolute IGF-1 levels, relative IGF-1 values (IGF-1/ULN adjusted for age and sex at screening) and GH levels over time will be presented for each treatment arm and stratum separately.

An attempt will be made to analyze the data using a pattern mixture model approach. The estimated levels, and the treatment differences at Week 24, will be displayed and presented with a 2-sided 95% CI and p-values. Details of the analyses will be included in the SAP.

8.8.3.5 Proportions of Patients with Biochemical Response Based on GH Levels <2.5 µg/L and <1.0 µg/L

The proportions of patients with mean GH cycle levels <2.5 µg/L and <1.0 µg/L at Week 24 will be analyzed in a similar way as the primary efficacy endpoint (excluding the sensitivity analyses). For this endpoint, intercurrent events will be handled in the same way as for the primary endpoint.

8.8.3.6 Proportion of Patients who Received Rescue Medication with Standard of Care

Proportion of patients who received rescue medication with standard of care due to loss of efficacy will be presented for each treatment arm and stratum.

8.8.3.7 Change in Tumor Size

Tumor size assessed by pituitary MRI (or CT) will be summarized at screening and Week 24/End of Trial by treatment arm and stratum. Further analyses on tumor size will be described in the SAP.

8.8.3.8 Clinical Signs and Symptoms of Acromegaly over Time

Frequencies of acromegaly signs and symptoms (headache, sweating, fatigue, joint pain, paresthesia and soft tissue swelling) will be summarized at each time point. The Acromegaly Index of Severity (AIS) Overall Score will be calculated as the sum of the scores for the symptoms. The AIS will be presented by treatment arm and stratum at each time point using descriptive statistics. Change from baseline in AIS will be evaluated by a control-based imputation within a pattern-mixture model framework, assuming a missing not at random (MNAR) mechanism. An analysis of covariance (ANCOVA) model accounting for the fixed effect of treatment, prior treatment (octreotide LAR or lanreotide ATG) and baseline AIS scores as a covariate will then be applied.

Change from baseline in ring size will be summarized over time. Results will be presented by treatment arm and stratum. Further details will be included in the SAP.

8.8.3.9 Treatment Satisfaction Scores over Time (TSQM)

Calculation of domain scores based on raw item scores (including the handling of missing items) will be done according to the TSQM user manual (35).

The number of patients completing the questionnaires and the number of missing or incomplete assessments will be summarized by treatment arm and stratum for each assessment time point.

Descriptive statistics will be used to summarize the item and domain scores by treatment arm and stratum at each assessment. Additionally, change from baseline in domain scores will be summarized. 95% CIs for the mean change will be provided by treatment arm and stratum. Change from baseline in domain scores will be evaluated by a control-based imputation within a pattern-mixture model framework, assuming an MNAR mechanism. An ANCOVA model accounting for the fixed effect of treatment, prior treatment (octreotide LAR or lanreotide ATG) and baseline domain scores as a covariate will then be applied. Further details will be included in the SAP.

8.8.3.10 Patient Satisfaction Scale

Patient satisfaction scale scores at Week 24/End of Trial will be summarized descriptively.

8.8.3.11 Change from Baseline in Health-related Quality of Life Scores

Calculation of disease-specific AcroQoL total score and sub-scale scores based on raw item scores (including the handling of missing items) will be done according to the scoring guidelines from the developer (29). Descriptive statistics will be used to summarize change from baseline in AcroQoL scores. Change from baseline in AcroQoL scores will be evaluated by a control-based imputation within a pattern-mixture model framework, assuming an MNAR mechanism. An ANCOVA model accounting for the fixed effect of treatment, prior treatment (octreotide LAR or lanreotide ATG) and baseline AcroQoL scores as a covariate will then be applied. Further details will be provided in the SAP.

Computation of EQ-5D-5L index scores will be performed. Descriptive statistics will be used to summarize changes from baseline in EQ-5D-5L scores.

8.8.3.12 Self-injection Scores over Time (SIAQ)

All analyses of SIAQ data will be based on data from patients who were treated with IMP, self-administered IMP at least once and have at least one evaluable assessment of the SIAQ instrument (PRE and POST module).

Calculation of domain scores based on raw item scores (including the handling of missing items) will be done according to the scoring algorithm given in the SAP.

Descriptive statistics will be used to summarize the domain scores for the first self-administration and the administration at Week 20. Change in domain scores from the PRE module (completed before the first self-administration) to the POST module (completed after the first and later self-administrations) will be summarized for the domains of feelings about injections, self-confidence and satisfaction with self-injection.

8.8.4 Adjustments for Multiplicity

Three evaluations of biochemical control are planned. To control the overall significance level of 5%, a stepwise closed testing procedure is planned. The following test order, from 1 to 3, will be used:

1. Proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24 (average of the 2 measurements; primary endpoint)
2. Proportion of patients with mean IGF-1 levels ≤1xULN at Week 22 and Week 24, including patients who have their dose reduced to 10 mg CAM2029 (or 0.5 mL placebo)

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

In this testing procedure, a comparison will be eligible for superiority testing only if all previous comparisons, if any, have established superiority at the one-sided significance level of $p<0.025$. For all variables as given in the test order, a common risk difference test using Mantel-Haenszel stratum weights as described in Section 8.8.2 will be used.

8.9 Pharmacokinetic Analyses

The plasma concentrations of octreotide will be summarized using descriptive statistics over time by dose, if applicable. All concentrations below the LLOQ or missing data will be reported as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics of arithmetic mean and as LLOQ/2 in the calculations of the geometric mean. Individual and summarized octreotide concentration-time profiles will be displayed graphically. The FAS will be used for these presentations.

A population PK model will be developed using data generated from the current trial together with data from other clinical trials for population PK assessment. The population PK model will be reported separately.

8.10 Safety Endpoints and Analyses

8.10.1 Adverse Events

Summary tables for AEs will include only AEs that started or worsened after the first administration of IMP, i.e. treatment-emergent AEs (TEAEs). An overview of all TEAEs including severity, relationship to the IMP, treatment-emergent serious adverse events (TESAEs), TEAEs leading to discontinuation of IMP, TEAEs leading to withdrawal from trial, TEAEs resulting in death, TEAEs leading to dose reduction, injection site TEAEs, TEAEs of special interest and TEAEs related to COVID-19 will be presented by treatment arm, stratum and overall.

TEAEs will be summarized by treatment arm, stratum, system organ class and preferred term (according to MedDRA) displaying number of patients in the treatment arm, number and percentage of patients having the TEAE as well as number of TEAEs. Furthermore, TEAEs will be summarized according to severity, relationship, and seriousness.

In addition, a table will be prepared for TEAEs occurring in at least 5% of patients in any treatment arm.

TESAEs and TEAEs leading to discontinuation of IMP or withdrawal from trial will be listed and tabulated, if appropriate.

All AEs, deaths and SAEs will be listed and those collected during the pre-treatment period will be flagged. AEs related to COVID-19 will be listed separately.

Descriptive Analysis of Serious Adverse Events

To quantify the uncertainty in the treatment comparison for SAEs, a Cox proportional hazards model will be used for time to the first TESAE. The median time to the first TESAE and its 95% CI will be estimated, if possible. Patients with no TESAEs will be censored at the last assessment of the AE status. Treatment will be a fixed factor and stratification will be employed with the same strata as used in the primary efficacy analysis. Hazard ratios, a measure of the relative risk at a particular time point, will be presented from the model along with the associated 2-sided CIs with a confidence level of 95%. If possible, the number of TESAEs will be analyzed

in a negative binomial model with treatment as a fixed factor and the logarithm of the exposure time up to Week 24 will be an offset. The rates and rate ratio will be presented from the estimated model. This is a descriptive approach; no specific safety hypothesis will be pre-specified and p-values will generally not be presented for safety data.

Further details will be included in the SAP.

Descriptive Analysis of Adverse Events of Special Interest

The time to first TEAE of special interest will be analyzed and presented in the same way as for TESAEs.

8.10.2 Clinical Safety Laboratory Assessments

Grading of laboratory values will be assigned programmatically as per NCI CTCAE. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For all laboratory tests, results will be categorized as low clinically significant/low not clinically significant/normal/high not clinically significant/high clinically significant based on laboratory normal ranges.

The following will be generated separately for clinical laboratory tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges
- For numerical laboratory measurements and the change from baseline, descriptive statistics will be presented by treatment arm and stratum at each assessment time point

For all laboratory parameters for which CTCAE grading is available, shift tables using CTCAE grading will be used. In addition, shift tables based on the categories low clinically significant/low not clinically significant/normal/high not clinically significant/high clinically significant will be produced for all parameters to compare baseline to Week 24/EOT and to the worst high/low post-baseline value.

All laboratory values will be presented in SI units.

In addition to the above tables and listings, other exploratory analyses, e.g. figures plotting time course of change in laboratory tests over time or box plots may be specified in the SAP.

8.10.3 Vital Signs

Data on vital signs will be tabulated and listed. Abnormal values will be flagged.

8.10.4 Electrocardiogram

Triplicate 12-lead ECGs including PR, QRS, QT, QTcF and RR intervals will be obtained for each patient during the trial. Data will be listed and summarized descriptively.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

8.10.5 Gallbladder Imaging

Gallbladder data will be tabulated and listed.

8.10.6 Local Tolerability

Local tolerability results for erythema, swelling and pain scores will be listed. Frequency counts (n and percentages) will be provided for erythema and swelling by treatment arm, stratum, severity and time point. Pain assessments will be summarized (N, mean, SD, minimum 25% percentile, median, 75% percentile and maximum) by treatment arm and stratum over time.

8.11 Exposure-response Analyses

PK, PD (IGF-1 and GH) and safety (ECG) data generated from this trial may be used together with PK, PD and safety data from other clinical trials for population PK and PK/PD assessments. These data will be reported separately.

8.12 Exploratory Endpoints and Analyses

8.12.1 Prolactin Levels

Serum prolactin levels will be presented descriptively. The treatment effects of CAM2029 versus placebo on prolactin levels at EOT/Week 24 will also be assessed using an ANCOVA model accounting for the fixed effect of treatment, prior treatment (octreotide LAR or lanreotide ATG) and baseline prolactin as a covariate.

8.12.2 Anti-octreotide Antibodies

The incidence and titer of drug-specific antibodies will be correlated with safety and efficacy parameters collected across the trial. In addition, the duration of previous octreotide treatment will be put in correlation with the presence and titer of the anti-drug antibodies at the trial entry.

8.13 Other Endpoints and Analyses - Feasibility of Self-administration of IMP

For patients opting for self- or partner-administration, the proportion of patients/partners declared competent by the healthcare professional out of those trying will be presented by treatment arm. The number and proportion of patients/partners requiring 1, 2 or 3 attempts until success or failure after maximum of 3 attempts will be provided.

For patients/partners who were declared competent after at most 3 attempts, any unsuccessful administration will be listed.

8.14 Extent of Exposure and Treatment Compliance

Exposure and compliance will be calculated per patient and summarized by treatment arm, stratum and overall.

The duration of exposure in weeks will be summarized by means of descriptive statistics using the safety analysis set. The number of injections received will also be summarized.

The number of patients with dose adjustments (reductions, interruption or permanent discontinuation of IMP) and the reasons will be summarized by treatment arm, stratum and overall and all dosing data will be listed.

8.15 Interim Analyses

No interim analyses are planned for this trial.

9 DATA HANDLING

9.1 Source Data and Source Documents

The Investigator must maintain patient records. The Investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g. via an audit trail).

What constitutes source data is described in a Source Data Agreement.

Items directly entered in the eCRF that have no prior written or electronic record will be considered as source data.

9.2 Case Report Form

An eCRF system will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Sponsor and vendor procedures, in accordance with regulatory and system requirements.

Trial data should be entered into the eCRF in a timely manner after the patient has attended a visit or after the data become available, as applicable.

The Investigator or a designee will approve/authorize the eCRF entries for each patient with an electronic signature, which is equivalent to a handwritten signature.

Entry errors occurring in the eCRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

9.3 Data Management

A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation.

The relevant data management documents will define e.g. the data entry, data validation, electronic data capture (EDC) system settings, EDC user permission, reconciliation requirement, coding dictionary and coding setup.

10 MONITORING PROCEDURES

10.1 Periodic Monitoring

A systematic, risk-based approach to monitoring has been established and considering the current situation with COVID-19, some monitoring visits are performed remotely. The monitor will contact or visit the Investigator periodically by e.g. phone and/or video calls to ensure adherence to the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP) (36), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions. The Sponsor and/or the contract research organization (CRO) will investigate if alternative measures for remote monitoring and source data verification, in accordance with local regulations, may be implemented.

The Investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. Key trial personnel must be available to assist the monitor during these visits.

The source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

10.2 Audit and Inspection

The Investigator will make all trial-related source data and records available at any time to auditor(s) mandated by the Sponsor, or to domestic/foreign regulatory inspectors or representatives from IECs/IRBs who may audit/inspect the trial.

The patients must be informed by the Investigator and in the ICF that authorized Sponsor representatives and representatives from regulatory authorities and IECs/IRBs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomization number will appear on these copies.

The Investigator should notify the Sponsor without any delay of any inspection by a regulatory authority or IEC/IRB.

10.3 Data Protection and Confidentiality of Patient Data

The Investigator will ensure that the confidentiality of the patients' data will be preserved. In the eCRF or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by their screening/randomization number. Documents that are not for submission to Sponsor, e.g. the confidential patient identification code and the signed ICF, will be maintained by the Investigator in strict confidence.

11 CHANGES IN THE CONDUCT OF THE TRIAL

11.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by the Sponsor, and agreed upon by the Investigator and Sponsor prior to its implementation. Amendments may be submitted for consideration to the approving IECs/IRBs and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial patients may be implemented prior to IEC/IRB approval/favorable opinion.

11.2 Deviations from the Protocol

If deviations from the protocol occur, the Investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented. A log of protocol deviations will be maintained by a CRO. The protocol deviation log and supporting documentation must be kept in the Investigator's File and the Trial Master File.

11.3 Premature Trial Termination

Both the Investigator (with regards to his/her participation) and the Sponsor reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the 2 parties. In terminating the trial, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the patients. Regulatory authorities and IECs/IRBs will be informed.

In addition, the Sponsor reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter patients at an acceptable rate.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Independent Ethics Committee/Institutional Review Board

Before implementing this trial, the protocol, the Patient Information and ICF and other documents as required, will be reviewed by properly constituted IECs/IRBs and by the national regulatory authorities.

A signed and dated statement that the protocol, Patient Information and ICF and other documents as required have been approved by the IECs/IRBs will be obtained before trial initiation.

IECs/IRBs will receive updates on trial progress according to local regulations.

12.2 Regulatory Authority Authorization/Approval/Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a patient is exposed to any trial-related procedure, including screening tests for eligibility.

12.3 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in compliance with the approved protocol, ICH GCP and applicable regulatory requirements (36, 37).

12.4 Patient Information and Consent

The Investigator (or authorized designee) will obtain a freely given written consent from each patient after an appropriate explanation of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the trial and the discomfort it may entail, post-trial provisions and any other aspects of the trial which are relevant to the patient's decision to participate. The patient must be given ample time to consider participation in the trial before the consent is obtained. The ICF must be signed and dated by the patient and the Investigator who has provided information to the patient regarding the trial before the patient is exposed to any trial-related procedure, including screening tests for eligibility. Patients must be given the option of being informed about the general outcome and the results of the trial.

The Investigator (or authorized designee) will explain that the patient is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for his/her further care and without the need to justify his/her decision.

The patient will receive a copy of the Patient Information and his/her signed ICF.

If new information becomes available that may be relevant to the trial patient's willingness to continue participation in the trial, a new Patient Information and ICF will be forwarded to the IECs/IRBs (and Regulatory Authorities, if required). The patients will be informed about this new information and written re-consent will be obtained.

Each patient will be informed that the monitor(s), quality assurance auditor(s) mandated by the Sponsor, IEC/IRB representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with national/local regulations.

12.5 Patient Card

Patients will receive a patient card, which they always need to carry. The patient card will state that the patient is participating in a clinical research trial, type of treatment and contact details for the Investigator and the Sponsor. The card should be presented to healthcare providers in the event of an emergency or if medications are required. Sample patient cards will be provided for the IEC/IRB submission.

13 LIABILITIES AND INSURANCE

13.1 ICH GCP Responsibilities

The responsibilities of the Sponsor, the monitor and the Investigator are defined in the ICH E6 GCP (Note for Guidance on Good Clinical Practice) consolidated guideline (36), and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH GCP responsibilities of Investigators, for dispensing the trial treatment in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

13.2 Liabilities and Insurance

The Sponsor has obtained an insurance covering, in its terms and provision, its legal liability for injuries caused to participating patients and arising out of trial procedures performed in accordance with this protocol, in accordance with applicable law and with ICH GCP.

14 ARCHIVING

14.1 Investigator File

The Investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH GCP. The trial documentation including all the relevant correspondence should be kept by the Investigator for at least 15 years, unless local regulations or institutional policies require a longer retention period, after the completion or discontinuation of the trial, if no further instructions are given by Sponsor.

No trial site document may be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the trial documents to another party, or move them to another location, the Sponsor must be notified. If the Investigator retires and the documents can no longer be archived by the site, the Sponsor can arrange to have the Investigator File archived at an external archive.

14.2 Trial Master File

The Sponsor will archive the Trial Master File in accordance with ICH GCP and applicable regulatory requirements.

15 REPORTING AND PUBLICATION

15.1 Clinical Trial Report

Upon completion of the trial, a clinical trial report will be prepared by the Sponsor and/or a CRO.

15.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the trial treatment or the trial, including any data and results from the trial will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the trial must protect the confidentiality of this proprietary information belonging to the Sponsor.

15.3 Publications and Public Disclosure

15.3.1 Publication Policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts in due time to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center trials only in their entirety and not as individual site data

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors' authorship requirements.

15.3.2 Public Disclosure Policy

The Sponsor will register the trial in an appropriate public registry according to applicable regulations. The trial results may be made publicly available in accordance with applicable regulatory requirements.

16 REFERENCES

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17 APPENDICES

17.1 Appendix 1 Dose Modifications and Dose Delays

17.1.1 General Management Guidelines for Adverse Drug Reactions

Table 5: IMP dose adjustment and management guidelines for suspected drug-related events

Toxicity severity	Dose adjustment and management recommendations
CTCAE grade ≤2 (mild or moderate)	No trial drug adjustment required
CTCAE grade ≥3 (severe) and assessed as trial drug related	Delay treatment until AE resolves or improves to CTCAE grade ≤2 (mild or moderate). If AE resolves or improves within 14 days, restart at the same dose level. If AE resolves or improves between 14 and 28 days to CTCAE grade ≤2 (mild or moderate) or AE recurs a second time at the same dose level, restart at reduced dose. If AE does not resolve or improve to CTCAE grade ≤2 (mild or moderate) within 28 days, treatment must be discontinued.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events
The above guidance generally applies to AEs except for changes in liver function tests (see Section 6.11.1) and for changes in QT intervals, which should be handled as described in Table 6. Note that these are only recommendations. Dose reductions must be discussed with the Medical Monitor prior to implementation. The nature of the AEs must be taken into consideration.

17.1.2 Follow-up on Potential Drug-induced Liver Injury Cases

Patients who were discontinued due to hepatic-related discontinuation criteria in Section 6.11.1 must be followed up. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time/INR and alkaline phosphatase
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted
- Obtain PK sample, as close as possible to last dose of IMP
- Additional testing for other hepatotropic viral infection (cytomegalovirus, Epstein-Barr virus, herpes simplex virus), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for liver function test abnormalities identified should be considered as “medically significant”, thus, meeting the definition of SAE (Section 7.5.1.1) and reported as an SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

17.1.3 Specific Management Guidelines for Cases of QTcF Prolongation

Table 6: Dose adjustments for QTcF prolongation

Severity	Dose adjustment and management recommendation
For all grades	Check the quality of the ECG and the QT value and repeat if needed. Perform analysis of serum electrolytes (potassium, calcium, phosphorus, magnesium). If electrolytes are significantly outside of normal range, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. Review concomitant medication usage for the potential to prolong the QT interval. Check compliance with correct dose and administration of IMP. Consider collecting a time matched PK sample; record date and time of last IMP intake.
Grade 1 Average QTcF 450 to 480 msec	No dose adjustment required.
Grade 2 Average QTcF 481 to 500 msec	Hold IMP. Perform repeat triplicate ECGs approximately 1 hour after the first QTcF of ≥481 msec. If QTcF <481 msec, restart IMP at the same dose. No dose adjustment required for the first occurrence. If QTcF remains ≥481 msec, repeat ECG as clinically indicated until the QTcF returns to <481 msec. Restart IMP at the same dose. No dose adjustment required for the first occurrence. If QTcF ≥481 msec recurs, IMP should be reduced (i.e. from 20 mg to 10 mg) or discontinued if the patient is already on reduced IMP dose (i.e. 10 mg). Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who had therapy interrupted due to QTcF ≥481 msec.
Grade 3 QTcF ≥501 msec or >60 msec change from baseline or Grade 4 Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Perform repeat triplicate ECGs within 1 hour of the first QTcF of ≥501 msec or >60 msec change from baseline. If QTcF remains ≥501 msec or if the change from baseline remains >60 msec, discontinue IMP. Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 msec.

ECG: electrocardiogram; IMP: investigational medicinal product; PK: pharmacokinetic; QTcF: QT interval corrected by Fridericia's formula

17.2 Appendix 2 Local Tolerability Assessments

The Investigator will assess the degree of erythema and swelling at the injection site immediately after injection and 1 hour after injection. Any event that occurs or persists beyond 1 hour after the injection will be recorded as an AE at the discretion of the Investigator.

Each injection site reaction will be scored and registered in the eCRF.

Erythema

- None (no erythema observed)
- Mild (erythema barely perceptible)
- Moderate (well-defined erythema)
- Severe (from beet redness to slight eschar formation)

Swelling

- None (less than depot size; <2 cm)
- Mild (more than depot size; longest diameter ≥2 to 5 cm)
- Moderate (well-defined swelling; longest diameter >5 to 10 cm)
- Severe (well-defined swelling; longest diameter >10 cm)

Pain will be assessed by the patient immediately after injection and 1 hour after injection using a numeric pain rating scale with scoring from 0 to 10, where 0= no pain and 10 = worst possible pain.