Clinical Trial Protocol

A randomized, placebo-controlled, double-blind, multi-center trial to assess efficacy and safety of octreotide subcutaneous depot (CAM2029) in patients with symptomatic polycystic liver disease

Short Title:	A trial to assess the efficacy and safety of octreotide subcutaneous depot in patients with PLD
Acronym	POSITANO (POlycystic liver Safety and effIcacy TriAl with subcutaNeous Octreotide)
Trial Code:	HS-20-677
EudraCT Number:	2021-003764-27
EUCT Number:	2023-505313-24-00
Development Phase:	Phase 2/3 (Phase 2b in the US)
Indication:	Polycystic liver disease
Investigational Medicinal Product:	CAM2029 (octreotide subcutaneous depot)
Protocol Version:	Final version 9
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Sponsor:	Camurus AB Rydbergs torg 4 SE-224 84 Lund, S3weden
Coordinating Investigator:	Joost PH Drenth, MD, PhD Professor of Hepatology Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Amsterdam, The Netherlands

Lists of Principal Investigators responsible for conducting the trial, medically qualified physicians responsible for all trial site-related medical decisions (if other than the Investigators), Sponsor personnel, trial monitors, vendors, clinical laboratories and other medical and/or technical departments and/or institutions involved in the trial are available as separate documents.

This trial will be conducted in compliance with the Clinical Trial Protocol, regulation (EU) No 536/2014, other applicable regulations, and Good Clinical Practice.

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ABBREVIATIONS

ACLF	Acute-on-chronic liver failure
ADPKD	Autosomal dominant polycystic kidney disease
[redacted]	[redacted]
ADPLD	Autosomal dominant polycystic liver disease
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
[redacted]	[redacted]
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{ss}	Area under the plasma concentration-time curve at steady state
Ca^{2+}	Divalent calcium ion
cAMP	Cyclic adenosine monophosphate
$C_{av,ss}$	Average plasma concentration during a dosing interval at steady state
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	[redacted]
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
CLIF-C	Chronic Liver Failure-Consortium
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal

htTLV	Height-adjusted total liver volume
htTKV	Height-adjusted total kidney volume
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
IMP	Investigational medicinal product
IR	Immediate release
IRB	Institutional Review Board
ITT	Intention-to-treat
LAR	Long-acting release
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
PC1	Polycystin-1
PC2	Polycystin-2
PD	Pharmacodynamics
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PLD	Polycystic liver disease (also referred to as PCLD)
PLD-I	Polycystic Liver Disease Impact
PLD-S	Polycystic Liver Disease Symptoms
PLD-Q	Polycystic Liver Disease Questionnaire
PQC	Product quality complaint
PRO	Patient-reported outcome
[redacted]	[redacted]
QTcF	QTc interval corrected by Fridericia's formula
RSD	Residual standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
[redacted]	[redacted]

SF-36	Short Form-36
[redacted]	[redacted]
SRL	Somatostatin receptor ligand (previously referred to as SSAs)
SSA	Somatostatin analog (term used in the eligibility criteria in Section 5.2 and Section 5.3 instead of SRL, see above)
TEAE	Treatment-emergent adverse event
TLV	Total liver volume
[redacted]	[redacted]
US	United States

1 PROTOCOL SYNOPSIS

Name of Sponsor: Camurus AB	
Title: A randomized, placebo-controlled, double-blind, multi-center trial to assess efficacy and safety of octreotide subcutaneous depot (CAM2029) in patients with symptomatic polycystic liver disease	
Acronym: POSITANO (POlycystic liver Safety and effIcacy TriAl with subcutaNeous Octreotide)	
Short Title: A trial to assess the efficacy and safety of octreotide subcutaneous depot in patients with PLD	
Trial Code: HS-20-677	
Trial Registry Number: EudraCT 2021-003764-27; EUCT 2023-505313-24-00; NCT05281328	
Development Phase: Phase 2/3 (Phase 2b in US)	
Coordinating Investigator: Professor Joost PH Drenth, MD, PhD	
Trial Sites: The trial will be conducted in the United States and Europe.	
Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
• To evaluate the treatment effect of CAM2029 compared to placebo on liver volume in patients with polycystic liver disease (PLD)	• Change from baseline to Week 53 in height-adjusted total liver volume (htTLV) as determined by magnetic resonance imaging (MRI) volumetry
Key Secondary Objective	**Key Secondary Endpoint**
• To evaluate the treatment effect of CAM2029 compared to placebo on patient-reported PLD-related symptoms	• Change from baseline to Week 53 in the Polycystic Liver Disease Symptoms (PLD-S) measure score
Secondary Objectives	**Secondary Endpoints**
• To evaluate the treatment effect of CAM2029 on liver volume over time in patients with PLD	• Change from baseline in htTLV as determined by MRI volumetry
• To evaluate the treatment effect of CAM2029 on patient-reported PLD-related symptoms over time	• Change from baseline in the PLD-S measure score
• To evaluate the treatment effect of CAM2029 over time on kidney volume in patients with presence of kidney cysts	• Change from baseline in height-adjusted total kidney volume (htTKV) as measured by MRI volumetry
• To evaluate treatment effect of CAM2029 over time on total liver cyst volume	• Change from baseline in total liver cyst volume determined by MRI volumetry
• To evaluate the treatment effect of CAM2029 over time on renal function in patients with presence of kidney cysts	• Change from baseline in estimated glomerular filtration rate (eGFR), assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation using serum concentrations of creatinine and cystatin C
• To evaluate the treatment effect of CAM2029 over time on patient-reported PLD-related impact on functioning and well-being	• Change from baseline in the Polycystic Liver Disease Impact (PLD-I) measure score
• To evaluate the treatment effect of CAM2029 over time on PLD-related symptoms	• Change from baseline in the Clinical Global Impression of Severity (CGI-S) score • Change from baseline in the Patient Global Impression of Severity (PGI-S) score • Change from baseline in the Patient Global Impression of Change (PGI-C) score

• To evaluate the treatment effect of CAM2029 over time on functioning and well-being	• Change from baseline in the Short Form-36 (SF36) scores
• To evaluate the treatment effect of CAM2029 over time on PLD-related symptoms	• Change from baseline in the Polycystic Liver Disease Questionnaire (PLD-Q) score
• To evaluate the safety and tolerability of CAM2029	• Incidence of adverse events (AEs) • Changes from baseline in laboratory values, vital signs and electrocardiogram (ECG) readings
• To assess the pharmacokinetics (PK) of octreotide after administration of CAM2029	• Octreotide plasma concentrations over time

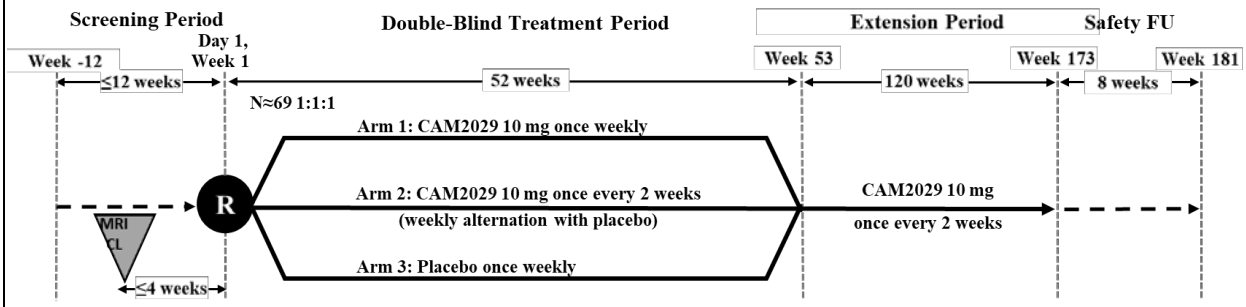
Trial Design: This is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-center trial designed to evaluate the efficacy and safety of 2 treatment regimens of CAM2029 versus placebo in patients with PLD.

The trial consists of an up to 12-week Screening Period followed by a 52-week (12-month) Double-Blind Treatment Period for which approximately 69 patients will be randomized in a 1:1:1 ratio to 1 of the 3 treatment arms:

- Arm 1: CAM2029 10 mg once weekly
- Arm 2: CAM2029 10 mg once every 2 weeks (weekly alternation with placebo)
- Arm 3: Placebo once weekly

Following completion of the Double-Blind Treatment Period, all patients will continue to a 120-week (30-month), open-label, single-arm, Extension Period with CAM2029 10 mg every 2 weeks, followed by an 8-week Safety Follow-Up Period.

An overview of the trial design is shown in the following figure:



CL: clinical laboratory sampling; FU: Follow-Up; MRI: magnetic resonance imaging; N: number of patients; R: randomization

Screening Period: Screening assessments will take place within 12 weeks before the Day 1 Visit for patients that have consented to participate in the trial. The screening MRI and clinical laboratory samples will take place within 4 weeks before the Day 1 Visit.

Randomized, Double-Blind Treatment Period: Eligible patients will receive their first dose of investigational medicinal product (IMP; CAM2029 or placebo) on Day 1. Patients will be treated with IMP as a subcutaneous (SC) injection every week for a total of 52 weeks. Patients will be encouraged to perform self- or partner-administration at home, which is allowed after appropriate training.

Following Day 1, there will be at least 6 visits during the 52-week Double-Blind Treatment Period (Weeks 5, 13, 21, 25, 39 and 53) for assessment of efficacy, PK, pharmacodynamics (PD) and safety. In addition, at Week 2, trial personnel will contact the patients by phone to assess any concomitant medication and AEs. Additional visits may be necessary for training of self- or partner-administration of IMP or for IMP administration by trial personnel if self- or partner-administration is not possible. Patients who discontinue IMP treatment during the randomized, Double-Blind Treatment Period will continue to be followed in the trial and complete all the assessments up to Week 53. A PK sample and an immunogenicity sample should be collected at least 5 weeks after the last dose of IMP.

Open-Label Extension Period: After completion of the 52-week Double-Blind Treatment Period, patients will continue to a 120-week Open-Label Extension Period, in which they will be treated with CAM2029 10 mg administered every 2 weeks. The Extension Period will be offered to patients with an expected

positive benefit risk ratio. The Extension Period will be available only to patients who did not discontinue IMP treatment during the Double-Blind Treatment Period and for whom self- or partner-administration at home is possible. The first dose in the Extension Period will be administered at Week 53, after the last assessments of the Double-Blind Treatment Period have been completed. The last dose will be administered at Week 172. Following the dose at Week 53, there will be at least 8 visits at the clinical site during the Extension Period (Weeks 57, 65, 77, 89, 101, 125, 149, and 173 [End-of-Treatment Visit]) for assessment of efficacy, PK, and safety. Patients who discontinue CAM2029 treatment during the Extension Period will be asked to complete an End-of-Treatment visit as soon as possible after the last dose of IMP, and a Safety Follow-Up visit at least 5 weeks after last dose of CAM2029. If MRI volumetry has been performed as part of the trial assessments within 1 month prior to the End-of-Treatment visit, a new MRI is not required.

Safety Follow-Up Period: A Safety Follow-Up Visit will be performed 8 weeks after the Week 173/End-of-Treatment Visit to assess PK and immunogenicity, and to collect information regarding any AEs ongoing at Week 173 and any new serious adverse events considered related to the IMP.

Trial Population: Adult patients (≥18 years) who are diagnosed with PLD associated with autosomal dominant polycystic kidney disease (ADPKD) or isolated as in autosomal dominant PLD (ADPLD).

Interventions:

CAM2029: During the Double-Blind Treatment Period, CAM2029 10 mg (0.5 mL) will be administered as an SC injection using a pre-filled pen once weekly in treatment arm 1 and every 2 weeks in treatment arm 2 (weekly alternation with placebo). During the Extension Period, CAM2029 10 mg (0.5 mL) will be administered as an SC injection using a pre-filled pen every 2 weeks.

Placebo: During the Double-Blind Treatment Period, placebo (0.5 mL) will be administered as an SC injection using a pre-filled pen every 2 weeks in treatment arm 2 (weekly alternation with CAM2029) and once weekly in treatment arm 3.

IMP injections will be administered in the abdomen, thigh or buttock. Self- or partner-administration of the IMP will be encouraged after appropriate training.

Ethical Considerations: Somatostatin receptor ligands (SRLs) such as octreotide, have shown promising effects in patients with PLD. CAM2029 has been found to be well-tolerated in clinical trials conducted to date and to have a favorable benefit-risk profile for further clinical development.

Throughout this trial patients will be regularly and carefully monitored for AEs and followed closely with several safety assessments, including the assessments to address potential immunogenicity. A Data Monitoring Committee (DMC) will be established and conduct periodic reviews of safety data up and until safety data from the last patient in the randomized, Double-Blind Treatment Period have been reviewed. Once the DMC has been decommissioned, the Sponsor will be responsible for the continued safety monitoring during the remainder of the Open-Label Extension Period. The protocol provides specific guidance for IMP discontinuation and safety follow-up for ADRs, potential liver toxicity and QT prolongation.

There is no currently available, approved pharmacological treatment for PLD. Supportive care agents and medications for treatment of symptoms associated with PLD will be allowed as per clinical practice and regardless of trial treatment given.

A randomized, double-blind, placebo-controlled trial design followed by the open-label, active treatment extension period, will ensure the most reliable and robust efficacy and safety assessment of CAM2029 without any significant impact of placebo on the patients' safety or their PLD course outcome.

2 INTRODUCTION

2.1 Background

2.1.1 Polycystic Liver Disease

PLD is a rare genetic disorder defined by the formation of multiple fluid-filled cysts in the liver. In adults, PLD can occur independently in the liver as in ADPLD (also commonly referred to as PCLD), but it is also a common accompanying condition to ADPKD (1).

Disease severity, including cyst numbers and sizes, vary considerably among patients with PLD and not all patients develop clear clinical symptoms (2, 3). The prevalence of clinically significant ADPLD has been estimated to <1/10 000 to <1/100 000 (4, 5), and of ADPKD to <5/10 000 (6, 7). Although hepatic cysts may be present in >80% of ADPKD patients (8), it has been estimated that only 16% of the patients suffer from moderate or severe PLD with associated clinical symptoms (9).

The genetic background of PLD in ADPLD and ADPKD is complex. To date, mutations in 9 genes have been linked to PLD, each harboring multiple pathogenic variants. Most of these mutations are assumed to act on a common pathway, ultimately leading to a lack of functional and active receptor-channel complex for transport of Ca^{2+} in the cilia membranes of epithelial cells (10). The complex is composed of the 2 integral membrane proteins PC1 and PC2 coded by the genes cyclin-dependent kinase 1 and 2 (11). A reduction in functional PC1 has been proposed as a major determinant of disease phenotype in both ADPLD and ADPKD and a central pathway involves the increase in cAMP (12). cAMP is a critical and well characterized regulator of pathways involved in cystogenesis and elevated cAMP is a major driving force behind cyst development by activating fluid secretion into the cystic lumen and cell proliferation (13).

The clinical heterogeneity in PLD may partially be explained by the effect of different mutations on PC1 expression or function (14). Studies have shown that patients with ADPLD have larger volume and greater number of hepatic cysts than patients with PLD associated with ADPKD, but the most serious hepatic conditions are more common in PLD associated with ADPKD (15). Age and gender are other reported factors contributing to disease severity; increasing age is positively associated with both cyst sizes and numbers, and women are highly overrepresented among symptomatic patients (2, 4, 15). Disease progression and liver expansion is particularly rapid in younger women (<48 years), which may be linked to estrogen levels (16).

The natural history of PLD is characterized in some patients by a continuous increase in the volume and number of cysts. In severe cases, polycystic livers can grow up to 10 times their normal size causing massive hepatomegaly with compression of the surrounding organs and symptoms such as dyspnea, early satiety and abdominal distention (3, 17). Other pressure-related, but rare, complications include obstructive jaundice, portal vein occlusion, portal hypertension, and compression of the inferior vena cava leading to peripheral edema and ascites (2). Increasing liver size in PLD has also been associated with lower quality of life (18). In addition, patients with PLD can suffer from acute intra-cystic complications including cyst hemorrhage, rupture and infections (2).

Most patients with PLD are diagnosed in their thirties after reporting a sudden and accelerated increase in abdominal girth, together with other PLD-related symptoms (2). The diagnosis is typically performed by detection of cysts by ultrasonography, MRI, or CT (1). There is currently no clear definition for PLD diagnosis based on imaging; >20 liver cysts have traditionally been used as a general cut-off value for diagnosis but recently the international PLD Registry steering committee came to a consensus to consider PLD in the context of >10 cysts (2).

Different systems have been established to differentiate between phenotypes and characterize disease severity in patients with PLD. In most cases, liver function tests are normal and there are currently no established molecular biomarkers for detection of PLD and monitoring of disease progression (3). Instead, the primary endpoint biomarker for PLD in clinical trials has typically been measurement of TLV or htTLV by CT or MRI, which has been associated with both symptom impact and quality of life (2). A htTLV of ≥1600 to <3200 mL/m is associated with increased risk of abdominal and pressure-related symptoms and has been classified as moderate PLD in the literature, whereas a htTLV ≥3200 mL/m is considered severe PLD with a further increase in complications (9). Also, for improved assessment of patient's disease-burden, questionnaires evaluating the degree of PLD-specific symptoms have been used, including the PLD complaint-specific assessment and the PLD-Q (19-21).

Liver transplantation is currently the only cure for PLD but only a minority of patients with the most severe symptoms qualify for this intervention. Other surgical treatments such as percutaneous sclerotherapy, transarterial embolization, cyst fenestration and hepatic resection are indicated to specific groups of patients with PLD. Although surgical therapies may be successful in reducing liver volume in selected patients, they can also cause significant morbidity and mortality. Most surgical interventions are also only partially effective and associated with a high rate of reoccurrence, and most importantly, are unable to change the natural course of the disease (17).

There is currently no approved pharmacological treatment for PLD, but different drugs have been tested. SRLs (previously referred to as SSAs), including lanreotide and octreotide, have been shown to inhibit the growth of hepatic cysts by reducing cAMP in experimental animal studies (22). High doses of octreotide LAR (40 mg monthly) and long-acting lanreotide (120 mg monthly) have been evaluated in Phase 2 trials in patients with PLD. In these trials, both octreotide and lanreotide were well-tolerated and showed promising effects. In treated patients, the average TLVs decreased with 2% to 8% over the treatment periods, whereas the liver sizes of placebo controls increased or remained unchanged (23-30). Meta-analysis of data from 5 of these trials (n=311) demonstrated that patients treated with lanreotide or octreotide had on average 0.15 L lower TLV than untreated controls (p=0.01). The most common adverse effects as demonstrated by meta-analysis were GI symptoms (31). SRLs are currently used off-label in highly specialized clinics for treatment of symptomatic PLD (2).

2.1.2 CAM2029

CAM2029 (octreotide subcutaneous depot) is a novel and long-acting SC injection depot based on the active substance octreotide and formulated with Camurus' proprietary FluidCrystal® injection depot technology. It is provided as a pre-filled pen with no need for reconstitution and offers the option of self- or partner-administration at home. Therefore, compared to the currently available long-acting octreotide product Sandostatin® LAR®, which is administered as an intramuscular injection with a syringe and which needs reconstitution before injection, CAM2029 may be easier to handle and to administer, thereby potentially improving patient convenience and care. In addition, the bioavailability of octreotide has been shown to be higher for CAM2029 than for Sandostatin LAR (32).

The non-clinical development program for CAM2029 includes bridging studies of toxicity, PK and local tolerability. In addition, the FluidCrystal vehicle and the excipient glycerol dioleate have been evaluated. The main effects observed in these studies were reversible injection-site reactions. For CAM2029, body weight decreases were observed, which is consistent with the pharmacology of octreotide. The PK of CAM2029 in dogs showed a higher C_{max} of octreotide after administration of CAM2029 than after administration of an equivalent dose of Sandostatin LAR, without any apparent difference in toxicity. The safety of CAM2029 is also supported by

the available extensive database (pharmacology, PK, safety, and toxicity) of octreotide (see further details in the IB) (33).

The clinical program for CAM2029 includes 3 completed Phase 1 trials in healthy volunteers (a single-dose trial [HS-05-194] and 2 repeated-dose trials [HS-07-291 and HS-11-411]), and 1 completed, repeated-dose, Phase 2 trial (HS-12-455) in patients with acromegaly or functioning neuroendocrine tumors previously treated with Sandostatin LAR. In addition, CAM2029 is currently being studied in 2 multinational Phase 3 trials in patients with acromegaly in the US and Europe. A Phase 1 trial is also ongoing, in which the PK of octreotide after administration of CAM2029 with a pre-filled pen is investigated.

The results of the completed Phase 1 clinical trials showed that octreotide release from CAM2029 had a rapid onset of action, with an octreotide C_{max} observed within approximately 4 to 24 hours after dosing. Thereafter, the plasma concentration slowly declined over time with therapeutic drug levels maintained for approximately 4 weeks, resulting in observable suppression of IGF-1, which is an established PD marker of SRL activity, over the same period. Dose-proportional PK was observed in the dose range of 10 to 30 mg CAM2029. The bioavailability of octreotide was approximately 5 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 once monthly) to CAM2029 (20 mg once monthly or 10 mg every 2 weeks) was associated with maintenance or beneficial effects of octreotide treatment including decrease in IGF-1 levels (as compared to pre-switch values) and in maintenance of growth hormone levels in patients with acromegaly. It was also associated with maintenance or improvement of symptom control, as measured by flushing episodes and bowel movements, in patients with neuroendocrine tumors. 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 trials. The AE profile seen with CAM2029 was consistent with what has been recorded for octreotide LAR and octreotide IR, with transient and mild to moderate GI events being the most frequently reported AEs.

Further details on CAM2029 are found in the current version of the IB (33).

The scope of the available safety data of octreotide, the non-clinical studies and clinical trials conducted with CAM2029, and the literature addressing the reproductive and carcinogenic potential for the excipients, support the current Phase 2/3 trial.

2.2 Rationale for Conducting the Trial

PLD is a rare condition that can lead to a progressive increase in liver cysts with considerable impact on health and quality of life. There is a high unmet need for pharmacological treatments that can alter the natural course of the disease and prevent cyst growth. Currently, patients must rely on high-risk surgical interventions such as liver transplantation, aspiration sclerotherapy and liver cyst fenestration, or off-label pharmaceutical treatment (17).

The SRLs lanreotide and octreotide in long-acting formulations have shown beneficial effects on both TLV and quality of life in patients with PLD while also being well tolerated (23-28). SRLs are therefore currently the most effective pharmacological treatment of PLD.

CAM2029 represents a novel and long-acting pharmaceutical formulation of octreotide for SC administration, which offers simplified administration and improved prospects for treatment

efficacy compared with currently available long-acting octreotide products (e.g., Sandostatin LAR).

This Phase 2/3 trial (Phase 2b in the US, as agreed with the US FDA) is the first trial in the drug development program for CAM2029 in PLD. The trial aims to explore efficacy and safety of 2 treatment regimens of CAM2029 compared to placebo in patients with symptomatic PLD.

A 120-week Open-Label Extension Period is added to the 52-week Double-Blind Treatment Period of the trial to provide an opportunity for the patients who completed the 52-week Double-Blind Treatment Period to continue treatment with CAM2029 and enable collection of long-term safety and efficacy data.

2.2.1 Benefit Assessment

SRLs have shown promising effects in patients with PLD and is the only known medical therapy that alters the natural course of PLD. Current off-label use of SRLs in PLD is restricted to the most severe cases and specialized clinics (2, 34). The bioavailability of octreotide has been shown to be approximately 5 times higher for CAM2029 than for Sandostatin LAR. Thus, even at similar doses, CAM2029 is expected to give a higher exposure of octreotide and the current trial will investigate the effects of CAM2029 on the liver volume and on symptoms in patients with PLD.

CAM2029 is a ready-to-use, long-acting formulation that is administered as a small-volume SC injection in a pre-filled pen with a thin-needle, without the need for reconstitution that is required for octreotide LAR. Therefore, CAM2029 is expected to lead to improved treatment convenience.

In the current trial, self- or partner-administration of the IMP (i.e., CAM2029 or placebo), with the pre-filled pen is allowed after appropriate training under the supervision of trained trial personnel and after the patient or their partner has been judged eligible to administer IMP. Eligibility of self- or partner-administration will allow administration of IMP at home, which is expected to greatly improve treatment convenience by reducing the number of required patient visits to the clinic.

2.2.2 Risk Assessment

CAM2029 is based on the FluidCrystal injection depot technology. CAM2029 and other products based on this technology have been extensively investigated in Phase 1 to Phase 3 clinical trials. The buprenorphine-containing product Buvidal®, also based on the FluidCrystal injection depot technology, was approved by the European and Australian authorities in November 2018 for treatment of opioid dependence. Buvidal has a favorable safety profile based on post-marketing experience with more than 90,000 patient-years of exposure as of 19-Feb-2024.

All clinical trials with CAM2029 performed to date have demonstrated good or very good local tolerability, with generally mild or moderate transient injection-site reactions, such as injection-site pain, pruritus, erythema, swelling and induration, at low incidence.

Octreotide, the active substance in CAM2029, is well documented, and has been in clinical use for more than 30 years. The most commonly reported ADRs in clinical trials with octreotide products have been GI disorders (such as nausea, diarrhea, abdominal pain, flatulence and constipation), headache, hyper- and hypoglycemia, hair loss and injection-site reactions, and cholelithiasis (35). More than 339 participants (healthy volunteers and patients) have been exposed to single or repeated doses of CAM2029 in the 6 clinical trials completed to date. In these trials, the AE profile of CAM2029 has been consistent with the AE profile of Sandostatin

IR and Sandostatin LAR. Injection-site reactions (e.g., injection-site pain, erythema, swelling, and pruritus) were also observed, and were generally of mild or moderate intensity. Only one SAE possibly related to CAM2029 has been recorded in the trials completed to date (an event of syncope due to diarrhea and vomiting, reported as circulatory collapse in a healthy volunteer). Further details on the safety profile of CAM2029 are given in the IB (33).

Even though the bioavailability of octreotide is approximately 5 times higher for CAM2029 than for Sandostatin LAR, no significant differences between these drugs in their safety profiles with regards to the nature and severity of AEs have been observed so far.

The patients will be followed closely with several safety assessments throughout the trial. Parameters that will be monitored regularly include vital signs, hematology laboratory assessments, blood chemistry (including renal and liver function, and thyroid hormones), urinalysis and ECG. Gallbladder imaging examination will be performed at screening, Week 77, Week 125 and End-of-Treatment (Week 173) and may be repeated as clinically indicated during the trial if a patient experiences symptoms of cholelithiasis. In addition, the MRI of the liver and kidneys may also be used for the safety assessment of the gallbladder if it includes images of satisfactory quality for the purpose. Patients will be regularly and carefully monitored for AEs. The protocol provides specific guidance for IMP discontinuation and safety follow-up for ADRs, liver toxicity (increased liver enzyme values) and QT prolongation (see Section 6.10.1). Furthermore, samples for measurement of octreotide plasma concentrations will be collected from all patients. Blood samples will also be taken for assessment of anti-octreotide antibodies to address potential immunogenicity.

A DMC will be established and will conduct periodic reviews of safety data up and until safety data from the last patient in the randomized, Double-Blind Treatment Period have been reviewed. Once the DMC has been decommissioned, the Sponsor will be responsible for the continued safety monitoring during the remainder of the Open-Label Extension Period.

Once the 52-week data from the randomized, Double-Blind Treatment Period of the trial are made available, the Sponsor will assess the benefit/risk ratio for the continuation of the Open-Label Extension Period. If the benefit/risk ratio is not positive, the trial will be terminated early.

The Sponsor will prepare a specific COVID-19-related risk assessment and mitigation plan to be followed during the trial.

2.2.3 Overall Benefit/Risk Conclusions

CAM2029 has been found to be well-tolerated in clinical trials conducted to date. The overall results from these clinical trials, together with the data from the non-clinical safety, toxicology, and PK studies, support a favorable benefit-risk profile of CAM2029 for further clinical development. Based on the available information, it is considered that the benefits outweigh the risks in the trial patient population.

More detailed information about the known and expected benefits and risks and reported AEs after administration of CAM2029 are found in the IB (33).

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 evaluate the treatment effect of CAM2029 compared to placebo on liver volume in patients with PLD	• Change from baseline to Week 53 in htTLV as determined by MRI volumetry
Key Secondary Objective	**Key Secondary Endpoint**
• To evaluate the treatment effect of CAM2029 compared to placebo on patient-reported PLD-related symptoms	• Change from baseline to Week 53 in the PLD-S measure score
Secondary Objectives	**Secondary Endpoints**
• To evaluate the treatment effect of CAM2029 on liver volume over time in patients with PLD	• Change from baseline in htTLV as determined by MRI volumetry
• To evaluate the treatment effect of CAM2029 on patient-reported PLD-related symptoms over time	• Change from baseline in the PLD-S measure score
• To evaluate the treatment effect of CAM2029 over time on kidney volume in patients with presence of kidney cysts	• Change from baseline in htTKV as measured by MRI volumetry
• To evaluate treatment effect of CAM2029 over time on total liver cyst volume	• Change from baseline in total liver cyst volume determined by MRI volumetry
• To evaluate the treatment effect of CAM2029 over time on renal function in patients with presence of kidney cysts	• Change from baseline in eGFR, assessed by the CKD-EPI cystatin C equation using serum concentrations of creatinine and cystatin C
• To evaluate the treatment effect of CAM2029 over time on patient-reported PLD-related impact on functioning and well-being	• Change from baseline in the PLD-I measure score
• To evaluate the treatment effect of CAM2029 over time on PLD-related symptoms	• Change from baseline in the CGI-S score • Change from baseline in the PGI-S score • Change from baseline in the PGI-C score
• To evaluate the treatment effect of CAM2029 over time on functioning and well-being	• Change from baseline in the SF-36 scores
• To evaluate the treatment effect of CAM2029 over time on PLD-related symptoms	• Change from baseline in the PLD-Q score
• To evaluate the safety and tolerability of CAM2029	• Incidence of AEs • Changes from baseline in laboratory values, vital signs and ECG readings
• To assess the PK of octreotide after administration of CAM2029	• Octreotide plasma concentrations over time
Exploratory Objectives	**Exploratory Endpoints**
[redacted]	

AE: adverse event; CGI-S: Clinical Global Impression of Severity; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; htTKV: height-adjusted total kidney volume; htTLV: height-adjusted total liver volume; [redacted]; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PK: pharmacokinetics; PLD: polycystic liver disease; PLD-I: Polycystic Liver Disease Impact; PLD-Q: Polycystic Liver Disease Questionnaire; PLD-S: Polycystic Liver Disease Symptoms; [redacted]; SF-36: Short Form-36; [redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Trial Design and Plan

This is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-center trial designed to evaluate the efficacy and safety of 2 treatment regimens of CAM2029 versus placebo in patients with PLD. Approximately 69 patients will be included in the trial.

The trial consists of an up to 12-week Screening Period followed by a 52-week (12-month) Double-Blind Treatment Period for which patients will be randomized in a 1:1:1 ratio to 1 of the 3 treatment arms:

- Arm 1: CAM2029 10 mg once weekly
- Arm 2: CAM2029 10 mg once every 2 weeks (weekly alternation with placebo)
- Arm 3: Placebo once weekly

Following completion of the Double-Blind Treatment Period, all patients will continue to a 120-week (30-month), open-label, single-arm, Extension Period with CAM2029 10 mg every 2 weeks, followed by an 8-week Safety Follow-Up Period. The estimated duration of the trial for each patient is approximately 47 months.

A primary endpoint analysis will be performed when the last patient has completed the Double-Blind Treatment Period (Week 53).

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

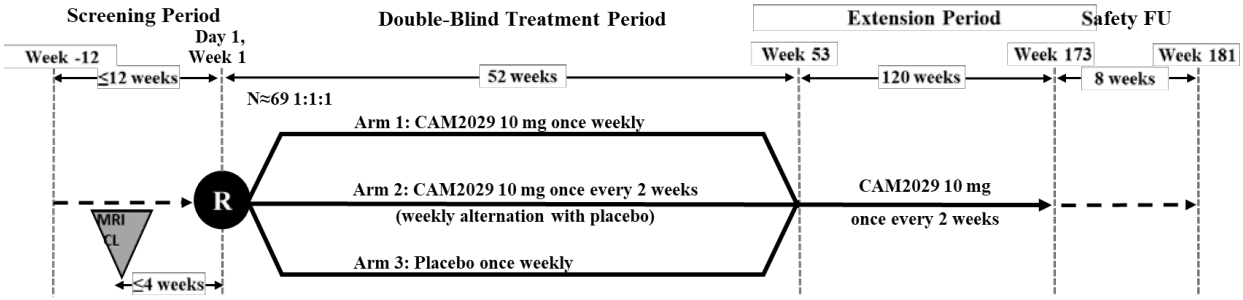


Figure 1: Trial design

CL: clinical laboratory sampling; FU: Follow-Up; MRI: magnetic resonance imaging; N: number of patients; R: randomization

4.1.1 Screening Period

Screening assessments will take place within 12 weeks before the Day 1 Visit for patients that have consented to participate in the trial. Screening assessments include, e.g., vital signs, physical examination, ECG, blood and urine sampling, and an MRI volumetric scan. The screening MRI and clinical laboratory sampling will take place within 4 weeks before the Day 1 Visit.

[redacted]

4.1.2 Double-Blind Treatment Period

Eligible patients will receive their first dose of IMP (CAM2029 or placebo) on Day 1. Patients will be treated with IMP as an SC injection every week for a total of 52 weeks. Patients will be

encouraged to perform self- or partner-administration at home, which is allowed after appropriate training (see Section 6.2.2).

Following Day 1, there will be at least 6 visits during the 52-week Double-Blind Treatment Period (Weeks 5, 13, 21, 25, 39 and 53) for assessment of efficacy, PK, PD and safety. At Week 2, trial personnel will contact the patients by phone to assess any concomitant medication and AEs. Additional visits may be necessary for training of self- or partner-administration of IMP or for IMP administration by trial personnel if self- or partner-administration is not possible. Where applicable, patients will be offered the possibility to complete trial visits at home. In such cases a nurse will come to the patient's home.

Patients who discontinue IMP treatment during the Double-Blind Treatment Period will continue to be followed in the trial and complete all the assessments up to Week 53 (see Section 6.10.1). A PK sample and an immunogenicity sample should be collected at least 5 weeks after the last dose of IMP.

4.1.3 Open-Label Extension Period

After completion of the 52-week Double-Blind Treatment Period, patients will continue to a 120-week Open-Label Extension Period, in which they will be treated with CAM2029 10 mg administered every 2 weeks. The Extension Period will be offered to patients with an expected positive benefit-risk ratio. The Extension Period will be available only to patients who do not discontinue IMP treatment during the Double-Blind Treatment Period and for whom self- or partner-administration at home is possible. The first dose in the Extension Period will be administered at Week 53, after the last assessments of the Double-Blind Treatment Period have been completed. The last dose will be administered at Week 172. Following the dose at Week 53, there will be at least 8 visits at the clinical site during the Extension Period (Weeks 57, 65, 77, 89, 101, 125, 149 and 173 [End-of-Treatment Visit]) for assessment of efficacy, PK, and safety.

Patients who discontinue IMP treatment during the Extension Period will be asked to complete an End-of-Treatment visit as soon as possible after the last dose of IMP, and a Safety Follow-Up visit at least 5 weeks after last dose of CAM2029 (see Section 6.10.1). If MRI volumetry has been performed as part of the trial assessments within 1 month prior to the End-of-Treatment Visit, a new MRI is not required.

4.1.4 Safety Follow-Up Period

A Safety Follow-Up Visit will be performed 8 weeks after the Week 173/End-of-Treatment Visit to assess PK and immunogenicity, and to collect information regarding any AEs ongoing at Week 173 and any new SAEs considered related to the IMP.

4.2 Rationale of Overall Trial Design, Endpoints, Trial Population, and Choice of Control Groups and Dose

4.2.1 Overall Trial Design

This is a Phase 2/3, randomized, placebo-controlled, double-blind, multi-center trial designed to evaluate the efficacy and safety of 2 treatment regimens of CAM2029 in patients ≥18 years old

with a diagnosis of symptomatic PLD, either in isolation as in ADPLD or in association with ADPKD.

The trial starts with a 52-week (12-month) placebo-controlled, Double-Blind Treatment Period with 2-dosing regimens of CAM2029. Results from trials with SRLs in patients with PLD have shown statistically significant effects on TLV and quality of life after 6 to 12 months of treatment (23, 24, 26, 27). Considering the high bioavailability of CAM2029, together with the inclusion of symptomatic patients with a minimum htTLV of 1800 mL/m (see Section 4.2.3), the probability of reaching significant treatment effects compared to placebo after the 52-week Double-Blind Treatment Period in this trial is considered high (see Section 8.2).

After the 52-week Double-Blind Treatment Period, all patients will be transferred to a 120-week, single-arm, Open-Label Extension Period, in which they will be treated with 10 mg CAM2029 every 2 weeks. Thereby, all patients will receive the active compound and have the opportunity to benefit from the treatment. The Extension Period will also allow monitoring of treatment efficacy and safety over a longer period and for a larger number of patients.

4.2.2 Selection of Endpoints

The primary endpoint in this trial is change in htTLV from baseline to Week 53 assessed by MRI volumetry. Assessment of TLV or htTLV has been used as primary outcome measure in PLD trials since established molecular biomarkers for detection and monitoring of PLD are lacking. Liver volume has been associated with both symptom severity, and quality of life (18).

To assess the PLD-related symptom burden and the impact of disease on functioning and well-being from the patient perspective, two PLD-specific PRO instruments, PLD-S and PLD-I, are currently under development (see Sections 7.3.3.1 and 7.3.3.2). These are included as secondary outcomes to assess treatment effect on patient reported PLD-related symptoms and impact on functioning and well-being, together with evaluation of the effect on liver volume, liver cyst volume and kidney volume (in patients with kidney cysts) over time, health-related quality of life, safety, tolerability and plasma concentrations of octreotide. Treatment effect on renal function in patients with presence of kidney cysts is also included as a secondary endpoint.

[redacted] In addition, the immunogenicity of CAM2029 will be assessed due to the immunogenic potential of octreotide (36).

4.2.3 Trial Population

The trial population is comprised of adult patients (≥18 years) who are diagnosed with PLD associated with ADPKD or isolated as in ADPLD. Liver size influences clinical severity in PLD and larger liver volume has been associated with both increasing symptom burden and lower quality of life in patients with PLD (18). The inclusion criterion of htTLV ≥1800 mL/m was chosen to provide a patient population that may benefit from the treatment and to show effects on the selected endpoints within the Double-Blind Treatment Period.

To ensure the inclusion of symptomatic patients, presence of at least 1 PLD-related symptom within 2 weeks before screening is required for participation in the trial. The list of PLD-related symptoms was generated from the literature (18) and has been agreed with clinical experts within the field (see Section 5.2). Patients who have been treated with an SRL within 3 months before screening, or who have been non-responsive to previous treatment of PLD with an SRL as per Investigator assessment, are excluded from entering the trial.

Enrolled kidney transplant patients will be monitored according to local clinical practice, including plasma levels of immunosuppressants, at the discretion of the Investigator. Before enrollment of a kidney transplant patient, the Investigator will contact the Medical Monitor who will evaluate each individual case and approve their inclusion in the trial.

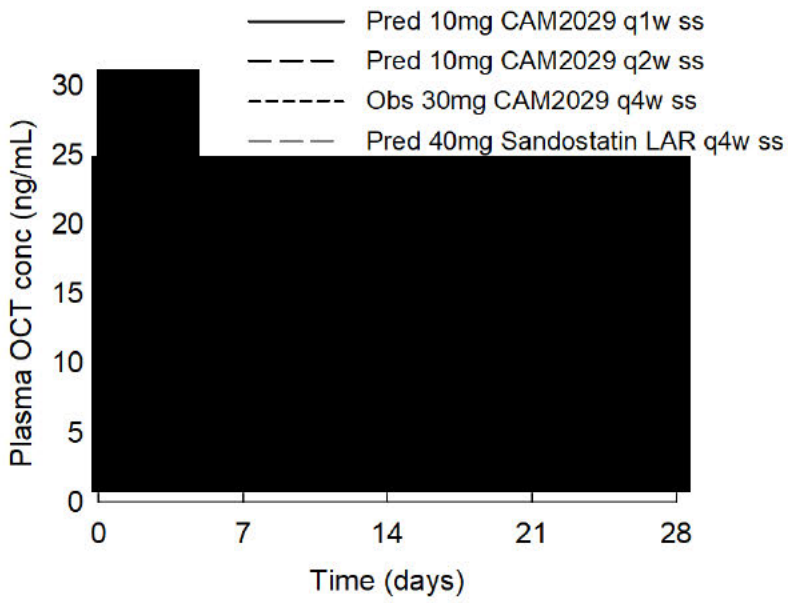
4.2.4 Dose Rationale

Treatment of patients with PLD with octreotide LAR doses of 40 mg/month has shown promising effects in previous Phase 2 clinical trials with significant impact on TLV (23-25). Due to the higher bioavailability of octreotide for CAM2029 compared with octreotide LAR (Sandostatin LAR), the octreotide exposure is expected to be higher for CAM2029, at the same administered dose of octreotide. In the current Phase 2/3 trial, a weekly dose of 10 mg CAM2029 was therefore selected.

Currently, 30 mg CAM2029 administered every 4 weeks is the highest dose that has been evaluated in Phase 1 clinical trials and this dose was well-tolerated among healthy volunteers (trial HS-11-411). In the current Phase 2/3 trial, 2 dosing regimens of CAM2029 (10 mg once weekly and 10 mg once every 2 weeks) will be evaluated for efficacy and safety in patients with PLD. For 10 mg CAM2029 once weekly, the predicted $C_{max,ss}$ is [redacted] ng/mL, which is lower than the observed $C_{max,ss}$ of [redacted] ng/mL for 30 mg CAM2029 every 4 weeks (trial HS-11-411) (Figure 2). The predicted overall exposure, calculated as $C_{av,ss}$=AUC_{ss}/dose interval, for 10 mg CAM2029 once weekly is just slightly higher ([redacted] ng/mL) than observed for 30 mg every 4 weeks ([redacted] ng/mL). Thus, based on predicted PK data, treatment with 10 mg once weekly is expected to be well-tolerated. Also, a retrospective literature analysis indicated promising results on tolerability when increasing the dose or the dosing frequency of SRLs (37), suggesting that shortening the dose interval of CAM2029 to 10 mg once weekly is not expected to expose the patients to higher risk. Instead, the fluctuation in octreotide plasma concentration will be lower (Figure 2) and a more even octreotide exposure is expected with dosing once weekly compared to monthly dosing of the same total monthly dose of CAM2029.

In addition to an acceptable degree of tolerability, the treatment effect of 10 mg CAM2029 once weekly and 10 mg CAM2029 once every 2 weeks on PLD-related endpoints is expected to be at least that observed in previous trials with Sandostatin LAR. This assumption is based on a higher predicted overall exposure of octreotide for 10 mg CAM2029 once weekly ($C_{av,ss}$ of [redacted] ng/mL) and 10 mg CAM2029 once every 2 weeks ($C_{av,ss}$ of [redacted] ng/mL) than what is predicted for 40 mg Sandostatin LAR every 4 weeks ($C_{av,ss}$ of [redacted] ng/mL).

To evaluate potential differences in efficacy and safety for CAM2029 at different octreotide exposures, a treatment arm with a dosing regimen of 10 mg CAM2029 once every 2 weeks has been included in the trial. As reported above, the predicted exposure (i.e., $C_{av,ss}$) for 10 mg CAM2029 once every 2 weeks is half of that of 10 mg CAM2029 once weekly.



LAR: long-acting release; Obs: observed; OCT: octreotide; Pred: predicted; q1w: once weekly; q2w: once every 2 weeks; q4w: once monthly; ss: steady state

Figure 2: Observed/predicted steady-state octreotide concentration-time profiles after administration of 10 mg CAM2029 q1w and q2w, 30 mg CAM2029 q4w and 40 mg Sandostatin LAR q4w

4.3 Trial Duration

Planned first patient first visit: Q2 2022.

Planned last patient first visit: Q4 2023.

Expected total duration of the trial: Up to 47 months for the individual patient (including screening, Double-Blind Treatment Period, Extension Period and Safety Follow-Up).

4.4 End of Trial Definition

The end of trial for each patient is defined as the last protocol-specified contact with the patient (including follow-up of AEs as described in Section 4.1.4).

The overall end of trial is defined as the last protocol-specified contact with the last patient ongoing in the trial.

5 SELECTION OF TRIAL POPULATION

5.1 Planned Number of Patients

Approximately 69 patients will be included in this trial.

5.2 Inclusion Criteria

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

1. Voluntary and valid written informed consent to participate in the trial provided by the patient before any trial related procedures are performed.
2. Male or female patient, ≥18 years at screening.
3. Diagnosis of PLD (associated with ADPKD or isolated as in ADPLD) with htTLV ≥1800 mL/m at screening.
4. Presence of at least 1 of the following PLD-related symptoms within 2 weeks before screening: bloating, fullness in abdomen, lack of appetite, feeling full quickly after beginning to eat, acid reflux, nausea, rib cage pain or pressure, pain in side, abdominal pain, back pain, shortness of breath after physical exertion, limited in mobility, concern about abdomen getting larger, dissatisfied by the size of abdomen.
5. Not a candidate for, or not willing to undergo, surgical intervention for hepatic cysts during the trial.
6. Female patients of childbearing potential must be willing to use an acceptable method of contraception from screening and during the entire trial (see Section 7.2.7).
7. Male patients must be willing to use condom as method of contraception from screening and throughout the trial unless they have been sterilized by vasectomy (with an appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

5.3 Exclusion Criteria

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

1. Surgical intervention for PLD within 3 months before screening. *For sclerotherapy patients, at least 6 months before screening.*
2. Treatment with an SSA within 3 months before screening.
3. Non-responsive to previous treatment of PLD with an SSA as per the Investigator's assessment.
4. Symptomatic cholelithiasis within 3 months before screening or previous medical history of cholelithiasis induced by SSAs unless treated with cholecystectomy.
5. Presence of extrahepatic cysts that, in the Investigator's opinion, may prevent the patient from safely participating in the trial.
6. Severe kidney disease, as defined by eGFR <30 mL/min/1.73 m^2.
7. Severe liver disease defined as liver cirrhosis of Child-Pugh class C.
8. Use of oral estrogen contraceptives or supplementation within 3 months before screening.
9. Poorly controlled diabetes (hemoglobin A1c ≥10%) at screening.
10. Patients with a known history of hypothyroidism, unless they have been on adequate and stable replacement thyroid hormone therapy for at least 3 months before the first dose of the IMP.
11. Uncontrolled hypertension defined by a systolic blood pressure of >160 mmHg and/or diastolic blood pressure of >100 mmHg at screening.

12. History of significant cardiac disease or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the trial, such as uncontrolled or significant cardiac disease, including any of the following:
    a. History of myocardial infarction, angina pectoris or coronary artery bypass graft within 6 months before screening.
    b. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block or high-grade atrioventricular block (e.g., bifascicular block, Mobitz type II and third-degree atrioventricular 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. Treatment with 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 at least 5 half-lives or 7 days (whichever is longer) before the first dose of IMP.
        iii. Patients with a baseline QTcF >450 msec for males and >470 msec for females at screening.
13. Patients with vascular compromise, including, but not limited to, mesenteric thrombosis, portal hypertension and thrombocytopenia (platelet counts less than 100×10^9/L).
14. Pregnant, lactating or planning to be pregnant during the trial.
15. Clinically significant laboratory abnormalities, which in the opinion of the Investigator may prevent the patient from safely participating in the trial.
16. History of solid organ transplantation. Exception for kidney transplant patients.
17. Any known allergy, hypersensitivity or intolerance to octreotide or any related drug, or other components of CAM2029, or history of any drug hypersensitivity or intolerance that, in the opinion of the Investigator, would compromise the safety of the patient.
18. Contraindications to, or interference with, MRI assessments, as dictated by local hospital regulations.
19. Previously treated/randomized in the current clinical trial.
20. Participation in any other clinical trial to test an investigational drug or device within the last 30 days before screening or during the trial.
21. Any other contraindicated serious medical condition that, in the Investigator's opinion, may prevent the patient from safely participating in the trial.
22. 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.
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.

5.4 Lifestyle Considerations

Patients will be advised to avoid fatty or fried foods, and to eat small meals and snacks well distributed over the day, during the first 3 days after the first IMP injection, to avoid loose, pale or fatty stools (26). These symptoms may start 24 hours after first injection of octreotide and last for 1 to 4 days but should subside with subsequent injections.

No other dietary or physical restrictions are required during the trial.

5.5 Screen Failures and Re-Screening

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 patients to meet the publishing requirements of the Consolidated Standards of Reporting Trials and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, possible other screen failure information and any SAE.

Patients who do not meet eligibility criteria may be 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). The eCRF should clearly indicate that the patient has been re-screened and the original screening number. The 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. If an MRI volumetry was performed within 1 month of re-screening as part of the first screening procedures, it does not need to be repeated during the re-screening.

6 TREATMENTS

6.1 Treatment Administered

The IMP products used in this trial, i.e., CAM2029 and placebo, are not authorized in any market. The treatments to be administered in this trial are described in Table 2.

Table 2: Trial treatments

	Double-Blind Treatment Period			Extension Period
Arm name	Arm 1	Arm 2	Arm 3	N/A
Treatment	CAM2029 once weekly	CAM2029 every 2 weeks (weekly alternation with placebo)	Placebo once weekly	CAM2029 every 2 weeks
Dosage formulation	Solution for injection in a pre-filled pen	Solution for injection in a pre-filled pen	Solution for injection in a pre-filled pen	Solution for injection in a pre-filled pen
Unit dose strengths	10 mg/0.5 mL	CAM2029: 10 mg/0.5 mL Placebo: N/A	N/A	10 mg/0.5 mL
Dosage level or volume	10 mg once weekly	CAM2029: 10 mg every 2 weeks Placebo: 0.5 mL every 2 weeks	0.5 mL once weekly	10 mg every 2 weeks

N/A: not applicable

6.2 Investigational Medicinal Product Administration

6.2.1 CAM2029 and Placebo

Patients will receive weekly (every 7 days ± 2 days) SC injections of the IMP (CAM2029 or placebo) administered in the abdomen, thigh or buttock. The placebo product is identical to the CAM2029 product regarding appearance, volume and viscosity of the solutions. 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. An injection-site pictorial and specific instructions for use are provided separately. The dose, date and exact time of dosing must be recorded in the eCRF.

6.2.2 Self-Administration

Self- or partner-administration of the IMP will be encouraged after appropriate training, including at least 1 self- or partner-administration under the supervision of trial personnel who has been adequately trained. A “partner” may be the patient’s spouse, parent, child, or sibling etc. or any other person that the patient trusts to administer the injection. 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 (a checklist of the feasibility of self- or partner-administration will be provided separately). If the patients or their partners are considered competent to administer IMP, they may continue with the self- or partner-administration at home, starting from Week 2. If the partner who is administering IMP is replaced, the new partner must undergo appropriate training, as described above.

The Investigator or designated personnel will dispense an appropriate number of IMP packages for home administrations. The patients will use a patient diary to record date(s), and exact

time(s) of administration, the injection site, and who performed the injection. The trial personnel will document the administration dates and confirm whether the full dose was administered. Detailed instructions will be provided separately.

Patients will be instructed not to make up missed doses. A missed dose is defined as an event when the planned IMP dose is not taken ±2 days from the scheduled day of the dosing. In case of missed dose(s), the patient will continue treatment with the next scheduled dose as planned regardless of how many doses they miss. The site personnel should follow up with the patient to find out the reason for missing dose(s).

Patients will be asked to return any used and unused pens and packaging for assessment of accountability (see Section 6.6.1). It is important that patients contact the Investigator/trial personnel if they experience any AE/SAE or have any concerns, or if there are any problems with the medication (e.g., if there is something wrong with the pre-filled pen), during the period of IMP administration at home.

If self- or partner-administration is not possible, administration will be performed by trial personnel during the Double-Blind Treatment Period. The Extension Period will be available only for patients for whom self- or partner-administration at home is possible.

6.2.3 Dose Delay and Dose Adjustments

Recommendations for dose delay/interruption of IMP in case of ADRs to IMP or QTcF prolongation are included in Section 6.10.1 and Section 17.1.2, Appendix 1. All dose delays should preferably be discussed with the Medical Monitor before implementation.

10 mg is the lowest permitted dose of CAM2029, and 0.5 mL the lowest permitted volume of placebo in this trial. If a dose or volume reduction for safety reasons is required during the Double-Blind Treatment Period, the patient will be discontinued from treatment with IMP but continue to be followed until the end of the Double-Blind Treatment Period (see Section 6.10.1).

During the Extension Period, dose reduction will not be allowed.

6.3 Characteristics and Source of Supply, Packaging and Labelling

IMP will be provided by the Sponsor and will be manufactured according to the principles of Good Manufacturing Practice. The labelling will comply with applicable regulatory requirements.

6.4 Conditions for Storage

The IMP 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 accordance with the storage conditions specified on the labels.

6.5 Method of Assigning Patients to Treatment Groups

6.5.1 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.

6.5.2 Randomization and Blinding

The current trial consists of a double-blind treatment period that is followed by an open-label extension period. To minimize bias, patients fulfilling the eligibility criteria will be randomized in a 1:1:1 ratio to 1 of the 3 treatment arms (CAM2029 10 mg once weekly, CAM2029 10 mg every 2 weeks, or placebo) in the double-blind period, 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.

The IMP will be labelled the same for all arms regardless of treatment to ensure blinding. In the treatment arm receiving weekly alternations between CAM2029 and placebo (Arm 2: CAM2029 every 2 weeks, see Section 4.1), all patients will receive CAM2029 as the initial dose.

The randomized assignment to a treatment arm during the Double-Blind Treatment Period will be revealed to the Sponsor and trial team once the last patient has completed all activities related to Week 53 Visit. At this time point the database is locked and a decision will be made to unblind applicable persons. Patients, Investigators and the trial site team (including site Pharmacy) will remain blinded until the trial is completed, then again, the database is locked and a decision is made to unblind.

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 Medical Monitor or 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.

6.6 Treatment Compliance

6.6.1 Dispensing and Accountability

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

Patients will be asked to return used and unused pre-filled pens on a regular basis or at the latest at the last site visit for the Double-Blind Treatment Period (Week 53) and the Extension Period (End-of-Treatment Visit, Week 173) to ensure proper drug accountability.

The Investigator (or designated personnel) will maintain an Injection Log detailing the dates and quantities of IMP administered to each patient, as well as an Accountability Log detailing dates and quantities of IMP dispensed to and returned (used and unused IMP) by each patient in case of administration at home. The trial personnel will ensure that the appropriate dose of IMP has been administered as part of the drug accountability assessment. The monitor will verify drug accountability during the trial.

6.6.2 Assessment of Compliance

IMP will be self- or partner-administered or administered by a designated healthcare professional during the trial. The patients will be given a diary for recording of the injections at home.

Dosing compliance will be recorded by the Investigator or designee. Treatment dates, including dates for treatment delays, will also be recorded in the eCRF.

6.7 Return and Destruction

If the patient is self- or partner-administering IMP at home, they will be instructed to return used and unused IMP (see Section 6.6.1).

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).

6.8 Product Quality Complaints and Device Malfunctions

A 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: imp-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 7.6.1.3.

6.9 Prior and Concomitant Medication/Treatments

The patients must notify the trial personnel about any new medication he/she takes after the start of the trial. All non-trial medications, including prescription, over-the-counter or herbal therapies, used by the patient for the 3 months prior to screening and throughout the trial must be listed on the concomitant medication page in the eCRF. The Investigator will determine if the prior/concomitant medication(s) affect the patient's eligibility to participate or continue to participate in the trial.

6.9.1 Permitted Concomitant Medications/Treatments

Supportive care agents and medications required to treat AEs or concurrent diseases, e.g., pain medications, pancreatic enzyme replacement, anti-emetics, and anti-diarrheals are allowed.

6.9.2 Permitted Concomitant Medications/Treatments Requiring Caution and/or Action

Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, insulin and antidiabetic medicinal products, or agents to control fluid and electrolyte balance may be necessary during SRL administration. In addition, octreotide has been found to reduce the intestinal absorption of cyclosporin and to delay that of cimetidine (35). SRLs also increase the bioavailability of bromocriptine (35, 38).

Limited published data indicate that SRLs might decrease the metabolic clearance of compounds known to be metabolized by CYP enzymes, which may be due to the suppression of growth hormone. 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 (35, 39).

Medications with a possible risk of causing Torsades de Pointes should be used with caution by patients until the Safety Follow-Up Visit (see further information, including a list of drugs with a possible risk of Torsades de Pointes, on the Advisory Board of the Arizona CERT website: www.crediblemeds.org). Interruption of IMP treatment may be considered if the concomitant medication is only needed for a short time.

6.9.3 Prohibited Concomitant Medications/Treatments

The following treatments are NOT allowed after the start of the trial:

- Oral estrogen contraception or supplementation
- Other investigational drugs or therapies
- Treatment with drugs with a known risk of Torsades de Pointes is prohibited from 5 half-lives or 7 days (whichever is longer) before first dose of IMP to the Safety Follow-Up Visit (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). If a patient needs to take any of these QT-prolonging drugs, prior IMP discontinuation will be required first. Therefore, other appropriate treatment options should be considered to avoid patient discontinuations as much as possible.

6.10 Discontinuation and Withdrawal Criteria

6.10.1 Discontinuation of Treatment

Patients may voluntarily discontinue from treatment for any reason at any time. If a patient decides to discontinue from 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.

Patients who discontinue IMP treatment during the Double-Blind Treatment Period should NOT be considered withdrawn from the trial. Every effort will be made to keep patients who discontinue IMP treatment in the trial. They should return for the assessments indicated in Table 3, up to Week 53. A PK sample and an immunogenicity sample should be collected at least 5 weeks after the last dose of IMP.

If the patients fail to return for these assessments for unknown reasons, every effort (e.g., telephone, email, letter) should be made to contact them. Patients who discontinue IMP treatment during the Extension Period should be asked to complete an End-of-Treatment Visit as soon as possible after the last dose of IMP, and a Safety Follow-Up Visit at least 5 weeks after last dose of IMP.

The Investigator should discontinue a patient's IMP treatment if he/she believes that continuation would be detrimental to the patient's well-being or if the patient experiences an intercurrent illness that compromises the patient's ability to fulfil protocol requirements. The Investigator should contact the Medical Monitor before a patient is discontinued from IMP treatment.

IMP treatment must be discontinued under the following circumstances:

- Development of decreased kidney function as defined by eGFR <25 mL/min/1.73 m^2.
- Pregnancy (see Section 7.6.1.1).
- Any protocol deviation (including prohibited concomitant therapy, see Section 6.9.3) that results in a significant risk to the patient's safety or 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 treatment discontinuation criteria, the toxicity-related criteria listed below will also require IMP treatment discontinuation. The final decision to discontinue IMP treatment is up to the judgment of the Investigator.

Hepatic-related Discontinuation Criteria

- ALT or AST levels >8×upper limit of normal.
- ALT or AST levels >5×upper limit of normal for more than 2 weeks.
- Clinically significant and prolonged symptoms of reduced hepatic function, e.g., appearance of chronic fatigue, nausea, vomiting, right upper quadrant pain or tenderness, itchy skin, or swelling of legs and ankles.
- The patient is diagnosed with liver cirrhosis of Child-Pugh class C.
- The patient is diagnosed with hepatic decompensation with European foundation for the study of CLIF-C ACLF score 2 or 3 (40).

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

For details on follow-up of potential drug-induced liver injury cases, refer to Section 17.1.1, Appendix 1.

Cyst-related Discontinuation Criteria

- Progression of extrahepatic cysts that, in the Investigator's opinion, may prevent the patient from safely participating in the trial.

Cardiac-related Discontinuation Criteria

- QT/QTcF ≥501 msec or >60 msec increase from baseline (average of triplicate ECG) after repeated triplicate 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), or clinically significant hypocalcemia confirmed by repeated 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 17.1.2 Appendix 1.

Hyperglycemia-related Discontinuation Criteria

- Patients with hemoglobin A1c ≥10% at 3 consecutive visits (including unscheduled visits) despite prior appropriate management.

General Toxicity Discontinuation Criteria

- For ADRs with CTCAE grade 3, treatment should be delayed until the ADR resolves or improves to CTCAE grade ≤2. If the ADR is expected to re-occur upon re-challenge, consider discontinuing IMP permanently. If ADR does not resolve or improve to CTCAE grade ≤2 (mild or moderate) within 28 days, IMP must be permanently discontinued.
- For AEs with CTCAE grade ≥4 regardless of relatedness to the IMP, treatment will be discontinued until further review.

The events listed above will be reviewed by the DMC while active. Once the DMC is decommissioned, the Sponsor will be responsible for the continued safety monitoring of patients according to the general toxicity discontinuation criteria listed above during the remainder of the Open-Label Extension Period (see Section 7.7 for further details).

6.10.2 Withdrawal from Trial

A patient is free to withdraw his/her consent and discontinue participation in the trial at any time and for any reason. Patients who withdraw consent during a scheduled visit will be asked to complete that visit as the End-of-Treatment Visit. If they withdraw outside of a scheduled visit, they may be asked if they are willing to attend an End-of-Treatment Visit. The reason(s) for discontinuation will be appropriately documented.

All efforts will be made to ensure that all patients are informed of the importance of the clinical trial and collection of data they provide. The Sponsor will continue to retain and use all research results already 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 discontinue from the trial before completion; the reason(s) for trial discontinuation 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.

6.11 Stopping Rules

Based on the extensive safety data available for octreotide over 30 years, the use of CAM2029 in this trial is not expected to be a major concern. However, to ensure the safety of the patients the following stopping criteria will apply for the Double-Blind Treatment Period of the trial:

- More than 2 patients develop an ADR with CTCAE grade 3 or higher in the same preferred term (according to MedDRA).
- Two patients develop any ADR with CTCAE grade 4.
- One patient develops a grade 5 CTCAE.
- Two or more individual patients meet the IMP discontinuation criteria (see Section 6.10.1).

If all of the above stopping criteria are met or if new data become available that raise concern about the safety of the trial, no more patients will be dosed until the independent DMC has convened, evaluated all safety data from all patients and provided its recommendation as to whether the trial can continue, should remain on hold, or if other actions are warranted.

The DMC will provide their recommendation to the Sponsor, who will make a final decision on how to proceed. When the trial is on hold, no further dosing of any patient will be performed although patients will continue to follow the trial-specific visit schedule. More details about stopping rules and the DMC will be provided in the DMC Charter. See Section 7.7 regarding the function of the DMC and Section 11.3 regarding termination of the trial.

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 (3 documented telephone contacts and a registered letter) 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. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue trial intervention.

If applicable and if agreed with the Sponsor, visits or specific assessments may be conducted at a patient's home or at a suitable alternative location by mobile qualified and delegated trial personnel. In such cases, the Investigator remains responsible for oversight and protocol procedure adherence. For this purpose, the terms "clinic visit" and "visit to the clinic" in this protocol may also refer to a remote visit.

Table 3: Schedule of trial procedures and assessments

	Screening	Double-Blind Treatment Period[a]							
		D1	D8	D29	D85	D141	D169	D267	D365
Procedure/Assessment	**W-12 to -1**	**W1**	**W2[b]**	**W5**	**W13**	**W21**	**W25**	**W39**	**W53[c]**
Informed consent	X								
Inclusion/exclusion criteria	X	X[d]							
Demographic data	X								
Medical history including historical liver and kidney[e] volume	X								
Medication/treatment history	X								
Height, BMI	X								
Weight	X	X		X	X		X	X	X
Physical examination	X						X		X
Pregnancy test[f]	X	X[g]			X[g]		X[g]	X[g]	X[g]
Clinical laboratory: hematology, biochemistry, urinalysis, coagulation, thyroid and HbA1c	X[h]	X[d,g]		X[g]	X[g]		X[g]	X[g]	X[g]
Serology	X								
Vital signs	X	X[g]			X[i]		X[j]	X[g]	X[g]
ECG[k]	X	X[g]			X[i]		X[j]	X[g]	X[g]

a Visit window: ±1 day for visits with plasma sampling for octreotide measurement and ±2 days for other visits during the Double-Blind Treatment Period and Extension Period. 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.
b Visit may be performed as a phone call.
c The last dose of IMP in the Double-Blind Treatment Period will be administered in Week 52. The first does of IMP in the Extension Period will be administered at Week 53 after the last assessments of the Double-Blind Treatment Period have been completed.
d The Investigator will confirm the patient's eligibility prior randomization on Day 1 based on the data available at the same visit.
e Historical kidney volume will be collected, if available in medical records, in patients with confirmed ADPKD.
f Serum pregnancy test at screening; urine pregnancy test at other visits.
g Pre-dose.
h Performed within 4 weeks prior to the Day 1 Visit.
i Pre-dose and 24±4 hours after dose.
j Pre-dose and 24±14 hours after dose.
k Triplicate 12-lead ECG will be performed.

	Screening	Double-Blind Treatment Period[a]							
		D1	D8	D29	D85	D141	D169	D267	D365
Procedure/Assessment	**W-12 to -1**	**W1**	**W2[b]**	**W5**	**W13**	**W21**	**W25**	**W39**	**W53[c]**
Gallbladder examination[l]	X[m,n]								
MRI of liver and kidney volume and total liver cyst volume	X[h,o]				X[p]		X[p]		X[p]
Administration of IMP[q]		X	X	X	X	X	X	X	X
eGFR sampling (creatinine, cystatin C)	X	X[g]			X[g]		X[g]		X[g]
[redacted]	[redacted]								
Plasma samples for octreotide measurement		X[g]			X[r]		X[j]	X[g]	X[g]
Immunogenicity		X[g]			X[g]		X[g]		X[g]
PLD-S	X	X[g]			X[g]	X[g]	X[g]	X[g]	X[g]
PLD-I	X	X[g]			X[g]	X[g]	X[g]	X[g]	X[g]
PGI-S	X	X[g]			X[g]	X[g]	X[g]	X[g]	X[g]
PGI-C					X[g]	X[g]	X[g]	X[g]	X[g]
SF-36		X[g]					X[g]		X[g]
PLD-Q		X[g]					X[g]		X[g]
[redacted]	[redacted]								

l Gallbladder imaging may be repeated during the trial if symptoms of cholelithiasis appear (ultrasound is first choice).

m Historical gallbladder imaging assessments performed within 4 months before Day 1 Visit, may be used as baseline measurement. If such a gallbladder ultrasound or MRI is available and includes satisfactory information on presence of gallstones, gallbladder sludge or other findings, the screening gallbladder ultrasound does not need to be performed.

n If the MRI of the liver and kidneys performed at screening, Week 77, Week 125 and Week 173/End-of-Treatment include satisfactory images of the gallbladder, these scans may also be used for the safety assessment by the Investigator.

o The eligibility htTLV value will be calculated according to local clinical practice either using the MRI at screening or based on available historical imaging, as long as that the latter fulfils the imaging and schedule requirements of the trial (see footnote h and Section 7.3.1).

p Visit window ±3 days.

q The IMP will be administered every week during the Double-Blind Treatment Period (and every 2 weeks during the Extension Period) aligned from Day 1 (± 2 days) by self- or partner-administration or by the trial personnel. For home administrations the Investigator or designated personnel will dispense an appropriate number of IMP packages. Home administration of the IMP may be performed at Weeks 2-4, 6-12, 14-20, 22-24, 26-38, 40-52, 54-56, 58-64, 66-76, 78-88, 90-100, 102-124, 126-148, 150-160 and 162-172. For patients who are not self- or partner-injecting at home, visits for IMP administration will be performed during the Double-Blind Treatment Period. At visit days, assessments should be performed before dosing.

r Pre-dose and 2±1, 5±1, 24±4, 96±24 and 168±24 hours after dose.

s [redacted]

t [redacted]

	Screening	Double-Blind Treatment Period[a]							
		D1	D8	D29	D85	D141	D169	D267	D365
Procedure/Assessment	**W-12 to -1**	**W1**	**W2[b]**	**W5**	**W13**	**W21**	**W25**	**W39**	**W53[c]**
[redacted]									
CGI-S		X[g]			X[g]	X[g,v]	X[g]		X[g]
Concomitant medication	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X

u [redacted]

v In those cases where the at-home visit is needed, a video-call will be set up to allow CGI-S assessment by the Investigator.

	Extension Period[a]											Safety FU Period[p]
	D393	D449	D533	D617	D701	D785	D869	D953	D1037	D1121	D1205	D1265
Procedure/Assessment	**W57**	**W65**	**W77**	**W89**	**W101**	**W113[b]**	**W125**	**W137[b]**	**W149**	**W161[b]**	**W173 EOT**	**W181 Safety FU**
Informed consent												
Inclusion/exclusion criteria												
Demographic data												
Medical history including historical liver and kidney[e] volume												
Medication/treatment history												
Height, BMI												
Weight	X	X	X	X	X		X		X		X	
Physical examination			X		X		X		X		X	
Pregnancy test[f]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]		X[g]		X	
Clinical laboratory: hematology, biochemistry, urinalysis, coagulation, thyroid and HbA1c	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]		X[g]		X	
Serology												
Vital signs		X[j]	X[g]	X[g]	X[g]		X[g]		X[g]		X	
ECG[k]		X[j]	X[g]	X[g]	X[g]		X[g]		X[g]		X	
Gallbladder examination[l]			X[n]				X[n]				X[n]	
MRI of liver and kidney volume and total liver cyst volume			X[n,p]				X[n,p]				X[n,p]	
Administration of IMP[q]	X	X	X	X	X	X	X	X	X	X		
eGFR sampling (creatinine, cystatin C)		X[g]	X[g]		X[g]		X[g]		X[g]		X	
[redacted]												
Plasma samples for octreotide measurement		X[j]									X	X
Immunogenicity		X[g]	X[g]		X[g]		X[g]		X[g]		X	X
PLD-S			X[g]		X[g]		X[g]		X[g]		X	
PLD-I			X[g]		X[g]		X[g]		X[g]		X	
PGI-S			X[g]		X[g]		X[g]		X[g]		X	
PGI-C			X[g]		X[g]		X[g]		X[g]		X	
SF-36			X[g]		X[g]		X[g]		X[g]		X	

	Extension Period[a]											Safety FU Period[p]
	D393	D449	D533	D617	D701	D785	D869	D953	D1037	D1121	D1205	D1265
Procedure/Assessment	**W57**	**W65**	**W77**	**W89**	**W101**	**W113[b]**	**W125**	**W137[b]**	**W149**	**W161[b]**	**W173 EOT**	**W181 Safety FU**
PLD-Q			X[g]		X[g]		X[g]		X[g]		X	
[redacted]												
CGI-S			X		X		X		X		X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X[w]

AE: adverse event; [redacted]; BMI: body mass index; [redacted]; CGI-S: Clinical Global Impression of Severity; D: Day; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOT: End-of-Treatment; FU: Follow-Up; HbA1c: hemoglobin A1c; [redacted]; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PGI-C: Patient Global Impression of Change; PGI-S: Patent Global Impression of Severity; PLD-I: Polycystic Liver Disease Impact; PLD-Q: Polycystic Liver Disease Questionnaire; PLD-S: Polycystic Liver Disease Symptoms; [redacted] SAE: serious adverse event; [redacted]; W: Week.

w For new SAEs considered related to IMP and follow-up of AEs not resolved at Week 173.

7.2 Screening and Baseline Procedures and Assessments

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria, before entering the trial. 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 Investigator or designated trial personnel will explain the nature of the trial and its risks and benefits to the patient. The patient must voluntarily provide written informed consent on an ethics-approved ICF, prior to any trial-related procedures are performed. The consent process must be documented in the patient's medical record, and include confirmation 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.

7.2.2 Demographics

Age, sex, race and ethnicity will be recorded at screening.

7.2.3 Medical History

Relevant medical history within 5 years before screening and any clinically significant medical history more than 5 years before screening will be collected based on available medical records and patient interview. Data will include PLD-related history data and medical history related to gallbladder diseases. The Investigator will evaluate all findings on medical history for clinical significance. Historical liver and kidney volumes, the latter only in patients with confirmed ADPKD, will be collected if available in medical records.

7.2.4 Medication/Treatment History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) and non-pharmacological treatments taken by the patients during the 3 months before screening will be recorded in the source documentation as medication history. Pharmacological and non-pharmacological treatments taken prior to the 3 months before screening should be recorded as medical history if relevant as per the Investigator's opinion, except for history of sclerotherapy which will be recorded if occurring within at least 6 months before screening. The Investigator will determine if the prior medication(s) affect the patient's eligibility to participate in the trial.

Treatment history for PLD and related symptoms, including prophylactic treatment, will be recorded and followed up during the course of the trial.

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. Clinically significant findings that were present prior to signing of the ICF must be included on the Medical History eCRF page. 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 Serology

Samples to assess hepatitis B surface antigen, hepatitis C virus antibodies (PCR required for hepatitis C virus antibody-positive patients), human immunodeficiency virus and human immunodeficiency virus antibodies will be taken at screening.

7.2.7 Contraceptive Requirements

Women of childbearing potential must agree to use an acceptable method of birth control as defined in the ICF from screening and throughout 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 (has had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before 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 a non-hormonal intrauterine device or hormonal intrauterine device not containing estrogen.
- Use of oral contraceptives not containing estrogen.
- 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 Assessments of Liver and Kidney Volume and Total Liver Cyst Volume

MRI of the abdomen and pelvis will be performed to capture images of the kidney and liver within 4 weeks prior to Day 1 Visit (Table 3). Also historical MRI assessments can be considered as the baseline images for this trial if they fulfil the imaging and schedule requirements.

For the determination of patient eligibility at screening (i.e., htTLV ≥1800 mL/m), the site will calculate htTLV according to preferred method (i.e., local clinical practice or central reading) either using the MRI at screening or based on available historical imaging data.

The images will be sent to a central imaging laboratory for blinded, independent reading to determine the liver and kidney volumes and the total liver cyst volume. The volumes will be calculated as per central imaging laboratory recommendations. Imaging parameters will be recorded in the source documents and eCRF. To minimize the risk of inter- and intra-subject variation in MRI, minimum scanning parameters will be provided to each site to comply with the central imaging laboratory requirements.

The processes for image collection transmission of images to the central imaging laboratory will be described in a site manual. The central review and determination of liver and kidney volumes and total liver cyst volume will be further described in an imaging charter.

At screening, Week 77, Week 125 and Week 173/End-of-Treatment the scheduled MRI can be used for the safety assessment of the gallbladder if captured images are of satisfactory quality (Section 7.6.7).

7.3.1.1 Reporting of Incidental Findings

If incidental findings are detected on the images that may be important for further clinical evaluation, this needs to be reported in the eCRF (as medical history if the finding occurs at screening, otherwise as an AE). Patients will be informed of any relevant incidental finding during the trial, as judged by the Investigator. Findings must be handled according to normal clinical practice and followed up as determined by the Investigator.

7.3.1.2 Assessments of Selected Muscle and Adipose Tissue Areas

Scheduled MRI scans will also be used for determination of selected areas of muscle and adipose tissues where available and at time points indicated in Table 3.

7.3.2 Estimated Glomerular Filtration Rate

Blood samples for assessment of the eGFR will be taken at time points indicated in Table 3. The eGFR will be assessed by the CKD-EPI cystatin C equation using serum concentrations of creatinine and cystatin C. Details of the assessments will be provided separately.

7.3.3 Patient Reported Outcomes

PROs for assessment of patients' PLD-related symptoms, impact on functioning and well-being, health-related quality of life and satisfaction include:

- PLD-S Measure
- PLD-I Measure
- PGI-S
- PGI-C
- SF-36
- PLD-Q
- [redacted]
- [redacted]

- Patient Reported Outcome Validation Battery

The PROs should be administered in the patient's local language. Patients should be given enough space and time to complete the questionnaires.

The Investigator should not encourage the patient to change responses reported in the questionnaires. If a patient refuses to complete a questionnaire, this should be documented in the source records. A patient's refusal to complete trial questionnaires should not be captured as a protocol deviation.

The PROs will be completed as indicated in Table 3 and should preferably be completed at the beginning of the visit before any tests or treatments are performed and before the patient receives results from any tests to avoid biasing the patient's perspective.

7.3.3.1 Polycystic Liver Disease Symptoms

The PLD-S is a PRO currently under development to assess patient reported symptoms of PLD. The measure was developed following FDA guidance for the development of PROs, [redacted] (41). [redacted]

7.3.3.2 Polycystic Liver Disease Impact

The PLD-I is a PRO currently under development to assess patient reported impacts of PLD. The measure was developed following the FDA guidance for the development of PROs, [redacted] (41). [redacted]

7.3.3.3 Patient Global Impression of Severity

The PGI-S assessment is a self-rated measure to assess the patients' overall perception of their condition. The PGI-S for the Symptom measure is a 1-item questionnaire that asks the patient to rate the frequency of their overall symptoms over the past week. The PGI-S for the Impact measure is 4 items assessing the frequency of the impact of their PLD over the past week on overall quality of life and for each of the PLD-I measure domains (physical functioning, day to day activities, emotional well-being). The PGI-S questions use a 5 option Likert scale ranging from none at all to all of the time. The Patient Global Impression scale is the PRO counterpart to the Clinical Global Impressions scale, which was published in 1976 (42). A modified version of the PGI-S will be used.

7.3.3.4 Patient Global Impression of Change

The PGI-C is a self-report measure asking the patient to rate the efficacy of treatment (change in frequency of occurrence) since the start of trial treatment. The PGI-C for the Symptom measure is 1 item assessing the overall change in frequency of experiencing PLD symptoms and the PGI-C for the Impact measure is 4 items assessing change in frequency of experiencing overall impact on overall quality of life and for each PLD-I domain (physical functioning, day to day activities and emotional well-being). The PGI-C questions use a 5 option Likert scale ranging from much less often to much more often. The Patient Global Impression scale is the PRO

counterpart to the Clinical Global Impressions scale, which was published in 1976 (42). A modified version of the PGI-C will be used.

7.3.3.5 Short Form-36

SF-36 is a widely used standardized measure of health status (43). SF-36 will be used to assess self-perceptions of general health functioning across multiple dimensions (including general, physical, and emotional/psychiatric functioning). Higher scores indicate better quality of life. It comprises a physical component summary and a mental component summary, both for which a higher score indicates better health status.

7.3.3.6 Polycystic Liver Disease Questionnaire

The PLD-Q was developed to capture patient-reported frequency and degree of discomfort for 16 different PLD associated symptoms (20, 21). The score of each patient-reported symptom included in the PLD-Q can be calculated by adding a frequency (Likert scale; 1=never, 6=always) and discomfort (Likert scale; 0=not at all, 5=a lot) score of each symptom. Total scores will be transformed into a score ranging from 0 to 100 points, where a higher score represents a higher symptom burden. A modified version of the PLD-Q will be used.

7.3.3.7 [redacted]

[redacted]

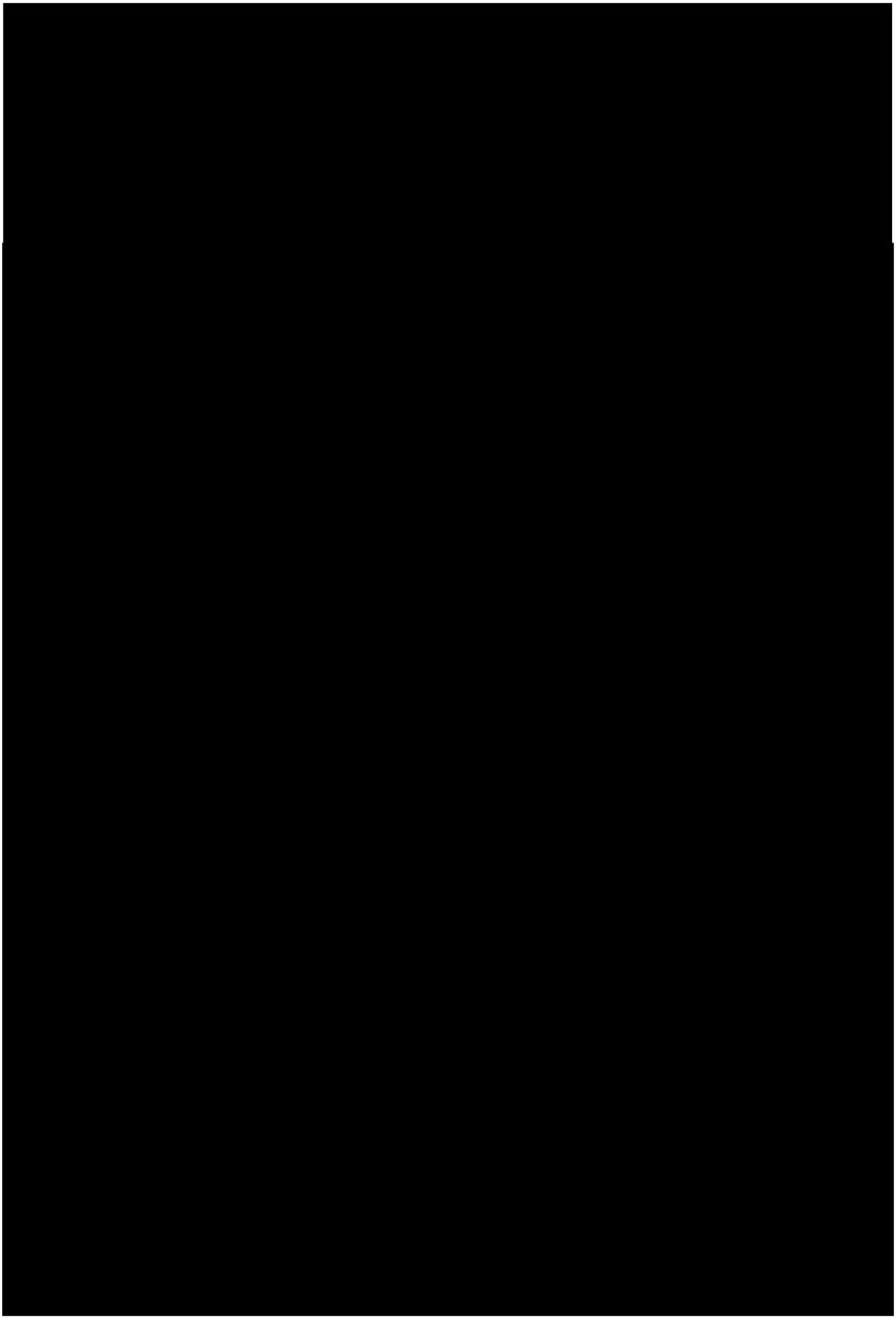
7.3.3.8 [redacted]

[redacted]

7.3.3.9 Patient-Reported Outcome Validation Battery

In order to psychometrically validate the PLD-S and the PLD-I, additional PRO measures/individual items needed to conduct the psychometric testing will be included in the trial as a validation measures battery. The additional measures were chosen from published, validated measures and will assess patient symptom burden as well as the impact of disease on patient functioning and well-being to evaluate the concurrent validity for both the domains and the total score of the PLD-S and PLD-I as well. Additionally, measures/items required to assess known groups validity, retest reliability and assist in the interpretation of clinically meaningful difference for the measures, scores are included. The validation battery will be administered to patients/clinicians before other clinical assessments are completed.

[redacted]



[redacted]

7.3.4 Clinical Global Impression of Severity

The CGI-S scale provides an overall assessment of the current severity of the patient's symptoms. It is 1 of 3 domains of the clinician-rated instrument Clinical Global Impression scale (42), which is one of the most widely used assessment instruments in psychiatry. A modified version of the CGI-S will be used. The CGI-S will be completed at the time points indicated in Table 3.

7.4 Pharmacokinetic Assessment

7.4.1 Blood Collection and Handling

Blood samples for evaluation of plasma concentrations of octreotide will be collected from all patients at the time points indicated in Table 3. In exceptional cases where a blood sample for plasma octreotide concentration assessments cannot be taken, e.g., for logistic or patient personal reasons, this may be considered acceptable after agreement with the Sponsor.

Blood samples will be taken by either direct venipuncture or indwelling cannula inserted in a forearm vein.

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 of approximately [redacted] ng/mL.

7.5 Pharmacodynamic Assessment

7.5.1 Blood Collection and Handling

[redacted]

[redacted]

7.5.2 Analytical Method

[redacted]

7.6 Safety Assessments

7.6.1 Adverse Events and Serious Adverse Events

7.6.1.1 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 (33).

An **AESI** is defined as an AE that, regardless of severity of causal relationship, is specifically of scientific and/or medical concern to the Sponsor's product or program, and for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such AEs may require further investigation in order to understand and characterize them.

AESIs are predicted by the underlying PLD disease, the mechanism of action of CAM2029, or observation with other substances in the same class as octreotide. Many but not all selected events have been observed in non-clinical studies and/or clinical trials with CAM2029 and are defined based on the continuously ongoing review of the safety data.

The selected AESIs are listed under the following mechanistic groups:

- Arrhythmogenic potential and QT prolongation AEs
- Gallbladder related AEs
- Gastrointestinal related AEs
- Injection site reactions
- Hyperglycaemia related AEs
- Liver and renal cyst infection
- Pyelonephritis

AESIs will be collected through routine AE collection.

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.
- Elective or pre-planned treatment, for a pre-existing condition unrelated to the indication under investigation that did not worsen.
- Admission to a hospital or other institution for general care, not associated with any deterioration in the condition.

Other Reportable Information

Other reportable information describes the circumstances around the use of an IMP that potentially could provide knowledge of an IMP. These circumstances may or may not be associated with AEs or adverse drug reactions. Such information must be recorded, reported and followed up as indicated for an SAE (see Section 7.6.1.3). This includes:

- Pregnancy during exposure to a trial treatment. If a pregnancy is confirmed, 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 pregnant partner after obtaining informed consent.
- Medication errors
- Lactation exposure to an IMP
- Misuse, abuse or overdose of an IMP
- Inadvertent or accidental exposure to an IMP
- Any other use of the IMP outside what is describe in this protocol.

7.6.1.2 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 (see Section 7.6.1.3 for reporting of SAEs). AEs will be

assessed from the time of signing the ICF until completion of all trial procedures and discharge from the trial. This includes any new event, sign or symptom occurring in the period between screening (after signing the ICF) and the first IMP administration on Day 1. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

Abnormal laboratory values shall be recorded as AEs if assessed as clinically significant by the Investigator. Laboratory abnormalities that are associated with an already reported medical condition will not be reported as separate AEs but will be used to assess the associated medical condition (e.g., increased neutrophil levels in case of reported infection or increased glucose in a patient with diabetes).

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

Information to be collected includes trial treatment, type of event, time of onset, dosage, Investigator-specified assessment of seriousness, severity and relationship to trial treatment, and time of event resolution, as well as any required treatment or evaluations, and outcome. 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 or the patient's participation in the trial ends, whichever comes first (see further details in Section 7.6.1.7).

The 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 thereafter should not be reported as an AE. However, if it deteriorates at any time during the trial, it should be recorded as an AE.

7.6.1.3 Reporting of Serious Adverse Events

Any AE that meets any of the SAE criteria (Section 7.6.1.1) must be reported to the Sponsor immediately (within 24 hours after the Investigator has become aware of the occurrence of the SAE), using the SAE eCRF page. If the eCRF page is unavailable, a paper copy of the SAE report form (available in the site binder) should be used, following the same timelines as for the electronic system. The Investigator will assess whether there is a reasonable possibility that the trial treatment caused the SAE and must sign the SAE report. Other reportable information as defined in Section 7.6.1.1 should also be reported using the eCRF and followed up as indicated above for an SAE.

The following contact information is to be used for paper-based reporting of SAEs and other reportable information:

Email: SAE@camurus.com

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 IEC/IRB directly, as per IEC/IRB requirements.

7.6.1.4 Assessment of Severity

Severity is defined as a measure of the intensity of an AE or SAE and will be assessed according to the NCI 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.

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. An AE characterized as intermittent requires documentation of onset and duration of each episode.

7.6.1.5 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

7.6.1.6 Assessment of Causality

The Investigator will assess the relationship to IMP 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 that follows a clinically reasonable response on IMP discontinuation (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Possibly related**: An AE with a reasonable time sequence to the administration of the IMP, but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug IMP discontinuation may be lacking or unclear.
- **Not related**: An AE with a temporal relationship to drug administration that 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.

7.6.1.7 Follow-Up of Adverse Events

All AEs should be followed until they have reached a final outcome (see Section 7.6.1.5) or the patient's participation in the trial ends, whichever comes first.

SAEs and Grade 3 (or severe), non-serious AEs that are assessed as "possibly related" or "probably related" to the IMP and 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.

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 that are spontaneously reported by a patient to the Investigator after the patient has completed the clinical trial and for which a reasonable possibility of a causal relationship to the

IMP is assessed by the Investigator ("possibly" or "probably" related), should be reported to the Sponsor by the Investigator, regardless of the time that has elapsed (post-trial events).

7.6.2 Anticipated Risks and Safety Concerns of the Trial Drug

The most frequent ADRs reported during octreotide therapy include GI disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported ADRs in clinical trials with octreotide administration were diarrhea, abdominal pain, constipation, nausea, flatulence, headache, cholelithiasis, hyperglycemia and injection-site reactions. Other commonly reported ADRs were dizziness, biliary sludge, thyroid dysfunction (e.g., decreased thyroid stimulating hormone), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycemia (35).

7.6.2.1 Cardiovascular System

Bradycardia has been reported in patients treated with octreotide with a frequency ranging between 1% and 10% (35). 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.

7.6.2.2 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 Sandostatin® IR. The prevalence of gallstones in the general population (aged 40 to 60 years) is about 5 to 20% (35). If gallstones do occur, management should be provided according to clinical guidelines.

7.6.2.3 Glucose Metabolism

Because of its inhibitory action on growth hormone, glucagon, and insulin release, octreotide may affect glucose regulation. Post-prandial glucose tolerance may be impaired. In some instances, persistent hyperglycemia may be induced as a result of chronic administration. Hypoglycemia has also been reported (35).

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 IR administration resulted in increases in post-prandial glycemia in some subjects.

7.6.3 Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will be performed at screening and during the trial at the time points outlined in Table 3.

A central laboratory will be used to analyze 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 at screening must be reviewed before enrollment to assess the patient's eligibility for the trial.

Laboratory values that are out of normal range must be evaluated for clinical significance. Clinically significant abnormalities known at time of signing the ICF should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Medical Monitor before 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 for laboratory assessments will be taken after the assessment of vital signs and ECG (as described below).

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

The assessments in Table 4 will be performed:

Table 4: Clinical laboratory tests

Test category	Test name
Hematology	Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red blood cell morphology, platelets, red blood cells, WBC, WBC with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Biochemistry	Albumin, ALP, ALT, AST, amylase, bicarbonate, calcium, chloride, creatinine, cystatin C[a], creatine kinase, GGT, lipase, plasma glucose, inorganic phosphorus, magnesium, potassium, sodium, total bilirubin (direct bilirubin and indirect bilirubin only in patients with total bilirubin >2×ULN), total cholesterol, low-density lipoprotein, high-density lipoprotein, total protein, triglycerides, blood urea nitrogen or urea, uric acid
Urinalysis	Urine dip-stick analyses at site (bilirubin, blood, glucose, ketones, WBC, pH, protein, specific gravity); further urinalysis (e.g., urine culture) by central laboratory, if indicated
Coagulation	Prothrombin time or INR, activated partial thromboplastin time
Thyroid	T3 (free), T4 (free), TSH
Additional tests	HbA1c

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; HbA1c: hemoglobin A1c; INR: international normalized ratio; TSH: thyroid stimulating hormone; ULN: upper limit of normal; WBC: white blood cells

a Only collected at specific visits as specified in Table 3

Pregnancy Tests

Women of childbearing potential will have a serum beta-human chorionic gonadotropin 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 before 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 tests will be performed by dipstick locally. A positive pregnancy test requires immediate interruption of IMP treatment until the pregnancy is confirmed via a serum pregnancy test performed by a central laboratory. If confirmed positive, the patient must be withdrawn from the trial.

7.6.4 Immunogenicity Assessments

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

7.6.5 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 measured before performing ECG and collecting blood samples.

Clinically significant findings that are known at the time of signing the ICF must be included on the Medical History eCRF page. Significant findings that begin or worsen after signing of the ICF must be recorded on the AE page of the eCRF.

7.6.6 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. The combined QTcF values from triplicate ECGs will be averaged to provide a single value for each patient. ECGs will be recorded at screening and at the time points outlined in Table 3.

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 before blood samples for PK and clinical safety laboratory assessments.

The ECG assessments pre-dose and at the 24-hour time point 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 ≥481 msec is observed, the procedures for QT-prolongation management described in Section 17.1.2, Appendix 1 must be considered.

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 clinical database.

Clinically significant abnormalities that are known at the time of signing the ICF should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Sponsor before 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.

7.6.7 Gallbladder Examination

Patients with symptomatic cholelithiasis at screening will be excluded from participating in the trial (see Section 5.3).

The gallbladder examination will be performed at screening, Week 77, Week 125 and at End-of-Treatment (Week 173) for all patients. These examinations can be performed at the trial site or at a local hospital. Information on the presence and location of gallstones, gallbladder sludge or other findings will be recorded on the appropriate eCRF page.

Scheduled MRI examinations of the liver and kidneys may be used for the safety assessments of the gallbladder at screening, Week 77, Week 125 and at End-of-Treatment (Week 173). If these MRI scans do not include satisfactory images, ultrasound of the gallbladder will be used.

Historical gallbladder imaging assessments performed within 4 months before Day 1, may be used as baseline measurement. If such a gallbladder ultrasound or MRI is available and includes satisfactory information on present gallstones, gallbladder sludge or other findings, the scheduled screening examination does not need to be performed.

Gallbladder examinations may also be performed at other time points during the trial if it is clinically indicated in patients showing symptoms of cholelithiasis. In those cases, ultrasound is the imaging technique of first choice.

Patients who have had a complete gallbladder removal do not need to undergo gallbladder examinations.

7.7 Data Monitoring Committee

A DMC will be established for this trial. The DMC will include 3 physicians, including 1 hepatologist. Up and until safety data from the last patient in the Double-Blind Treatment Period have been reviewed, the DMC will conduct periodic reviews of safety data and will continuously review all ADRs with CTCAE grade 3 and all AEs with CTCAE grades 4 or 5. The DMC will recommend actions to the Sponsor, as appropriate. The DMC will be informed to what extent the data and analyses provided to them have been quality controlled. Members of the DMC will not be involved in other trial-related tasks.

The DMC will be decommissioned after the safety data from the Double-Blind Treatment Period have been reviewed. The Sponsor will then be responsible for the continued safety monitoring during the remainder of the Open-Label Extension Period.

The DMC procedures are described in the DMC Charter.

8 STATISTICAL CONSIDERATIONS

8.1 Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a SAP, which will be completed prior to database lock for the primary endpoint analysis. 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. A separate analysis plan for the psychometric validation of the PLD-S and PLD-I will be submitted prior to database lock for the primary endpoint analysis.

8.2 Determination of Sample Size

In Hogan 2020, the comparison between pasireotide and placebo over 12 months resulted in a treatment difference in reducing htTLV of approximately 235 mL/m, or 9 to 10% expressed as percent change from baseline (50). The RSDs with the two analysis approaches were approximately 170 mL/m and 8%.

With 20 patients per treatment arm, the power is 80% if the true treatment difference is 165 mL/m (approximately 70% of the difference seen in the Hogan trial). This calculation is based on an assumed RSD of 180 mL/m using a t-test with a significance level of 5% (two-sided). With the same assumptions, the smallest observed treatment difference to give $p < 0.05$ is approximately 115 mL/m. If the 2 CAM2029 treatment arms are combined in the comparison to placebo, the number of patients in the comparison will be 40 versus 20. Assuming the same treatment difference, 165 mL/m, the power is approximately 90%. For a treatment difference of 141 mL/m, the power for the combined comparison would be approximately 80%.

With an assumed 15% drop-out rate the total number of patients required in the trial will be 69.

8.3 General Considerations

Categorical variables will be summarized using numbers and percentages of patients in each category, where the denominator for calculation is the underlying analysis set unless otherwise stated.

Continuous variables will be summarized with descriptive statistics, including number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate.

For all efficacy endpoints, descriptive measures and 95% CIs for the difference in change from baseline between the treatment groups will be presented, unless otherwise specified.

Safety parameters will be presented descriptively.

The statistical analyses will be performed using version 9.4 or later of the SAS® statistical software package.

8.4 Patient Disposition

All patients screened and enrolled will be accounted for. All post-enrollment withdrawals will be summarized by reason for withdrawal from the trial. Patients who are screened but not enrolled will be listed.

8.5 Protocol Deviations

Major protocol deviation criteria will be established prior to each database lock.

8.6 Analysis Sets

8.6.1 Intention-to-Treat Analysis Set

The ITT analysis set will consist of all patients who were 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 full analysis set comprises all patients in the ITT analysis set who were administered at least 1 dose of the IMP.

8.6.3 Per Protocol Analysis Set

The per protocol 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. Detailed criteria defining this analysis set will be documented in the SAP.

8.6.4 Pharmacokinetic Analysis Set

The PK analysis set comprises all patients who were administered at least 1 dose of CAM2029 and for whom at least 1 post-dose plasma octreotide concentration result is available.

The PK analysis set will be used for the analyses of PK data.

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 analyses will be based on the safety analysis set.

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 and overall. All relevant demographic and baseline characteristics will be summarized using descriptive statistics.

8.7.2 Medical History

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

8.8 Prior and Concomitant Medications and Treatments

Prior and concomitant medications will be summarized by ATC classification second level (alphabetically), and the ATC classification fourth level (in decreasing order of frequency).

Prior and current medications or treatments of PLD or its related symptoms, including prophylactic treatment, will be listed, and summarized descriptively.

8.9 Efficacy Endpoints and Analyses

8.9.1 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.

Sensitivity analyses evaluating the impact of missing data will be performed and further described in the SAP.

8.9.2 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline to Week 53 in htTLV as determined by MRI volumetry. In the analysis of the primary efficacy endpoint, the primary comparison will be between the average effect of the 2 CAM2029 doses compared to placebo. In addition, the 2 doses of CAM2029 will be compared with placebo separately, see Section 8.10.

The primary efficacy endpoint will be analyzed using an ANCOVA model with fixed factor for treatment and baseline htTLV as covariate, within the framework of a multiple imputation method. Point estimates and the associated two-sided CI with 95% confidence level will be calculated for the difference in change. The absolute change analysis will be the primary analysis. In this ANCOVA model the average of the treatment effect of the 2 doses of CAM2029 (10 mg once weekly and 10 mg every 2 weeks) will be compared to placebo, i.e., the contrast for the treatment difference is (0.5 0.5 0) – (0 0 1) where the 2 CAM2029 doses are given by the 2 first terms and placebo by the last. Additionally, each of the doses of CAM2029 will be compared with placebo separately, as described in the SAP.

The primary endpoint analysis will be performed when the last patient has completed the Double-Blind Treatment Period (Week 53).

The items that define the primary estimand are the following:

1. Treatment condition: The primary treatment condition of interest is the average effect of the CAM2029 treatment (10 mg once weekly and 10 mg every 2 weeks) vs placebo treatment. Thereafter, the treatment conditions of interest are the effects of:
    - CAM2029 10 mg once weekly vs placebo
    - CAM2029 10 mg every 2 weeks vs placebo
2. Target population: Patients in the ITT analysis set as defined by the inclusion/exclusion criteria in the trial.
3. Variable (endpoint): The variable addressing the primary clinical question is change from baseline in htTLV as assessed at Week 53.
4. Handling of intercurrent events: Intercurrent events will be handled through a combination of a treatment policy strategy and a hypothetical strategy depending on other treatment received and therapeutic interventions conducted while still in the trial:
    - IMP treatment discontinuation: Patients who discontinue treatment with IMP and do not receive another SRL or have any therapeutic interventions with the intention to reduce the liver size while still in the trial, will be analyzed according to a treatment policy strategy, i.e., observations collected after IMP discontinuation will be included in the analysis as they are collected.

- For patients who discontinue treatment with IMP and start receiving another SRL or have any therapeutic intervention with the intention to reduce the liver size while still in the trial, only observations collected prior to the start of the SRL will be included in the analyses. Observations collected after the start of the SRL and the therapeutic intervention will be handled using the method described below:
    - Use of another SRL: Patients who receive an SRL other than the trial IMP while still in the trial, will be handled according to a hypothetical strategy. I.e., any measurements of htTLV following start of any other SRL administration will be set to missing and not be used in the analysis. This hypothetical strategy is motivated by the fact that no approved alternative SRL treatment for PLD is available in most countries.
    - Therapeutic interventions: Patients undergoing therapeutic intervention with the intention to reduce the liver size while still in the trial will be handled according to a hypothetical strategy. I.e., measurements of htTLV following this intercurrent event will be set to missing and not used in the analysis. This strategy is motivated by the fact that such interventions may directly impact the primary endpoint without being related to the effect of the IMP.
    - Missing values: If the htTLV cannot be determined at Week 53, either due to start of another SRL treatment or after a therapeutic intervention with the intention to reduce the liver size after IMP discontinuation or values are missing for other reasons, missing values will be imputed using the multiple imputation method described in the SAP.

d) Population level summary for comparison between treatment conditions*:* Mean change from baseline to Week 53 in htTLV.

The proposed *primary estimand* is the entity defined to address the effect of treatment with CAM2029 in reducing the progression in htTLV in PLD patients without any alternative treatment being available and with a diagnosis as defined by the inclusion and exclusion criteria.

Missing values

If the status of the htTLV cannot be determined at Week 53, either due to start of another SRL treatment and/or a therapeutic intervention with the intention to reduce the liver size after IMP discontinuation, or if values are missing for other reasons, then the missing values will be imputed using the multiple imputation method described in the SAP. Missing htTLV data at Week 53 will be imputed using multiple imputation assuming that data are missing at random within the groups used for imputation..

The imputation will be done within treatment arms defined by the randomized treatment. For these continuous endpoints, [redacted]. Results from the ANCOVA model with fixed factors for treatment and baseline as covariate on each imputed data set, will be combined using Rubin's rule (51).

8.9.2.1 Sensitivity Analyses

The following sensitivity analyses will be performed on the primary endpoint:

- Last observation carried forward analyzed in an ANCOVA with fixed factors for treatment and the baseline value as covariate, i.e., missing data will be imputed using last observed values post-baseline.
- A mixed model repeated measures model will be used to estimate the change from baseline.

- The primary endpoint will be analyzed using the same ANCOVA model with fixed factor for treatment and baseline htTLV as a covariate based on observed cases without imputation or handling of intercurrent events.
- If a significant difference can be detected from the primary analysis, a tipping point multiple imputation analysis as described in Ratitch et al. (2013) will be applied (52). A tipping point analysis is a means of exploring the influence of missingness on the overall conclusion by investigating a broad range regarding the missingness mechanism (from less conservative to more conservative, i.e., it will include scenarios where dropouts on CAM2029 have worse outcomes than dropouts on placebo). The analysis finds a (tipping) point in this range, at which conclusions of effect vary from being favorable to the treatment with CAM2029 to being unfavorable. Based on such a tipping point, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point.

Sensitivity analyses will be described in detail in the SAP.

8.9.2.2 Supplementary Analyses

The following supplementary analyses will be performed on the primary endpoint:

Supplementary analyses will be described in detail in the SAP.

8.9.3 Secondary Efficacy Endpoints

8.9.3.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is change from baseline to Week 53 in the PLD-S measure score and this endpoint will be analyzed with the same methods as for the primary endpoint. In the analysis of the key secondary efficacy endpoint, the main comparison will be between the average effect of the 2 CAM2029 doses compared to placebo. In addition, the 2 doses of CAM2029 will be compared with placebo separately, see also Section 8.10.

8.9.3.2 Other Secondary Efficacy Endpoints

For the secondary efficacy endpoints listed below, the analyses will be described in detail in the SAP:

- Change from baseline in htTLV as determined by MRI volumetry
- Change from baseline in PLD-S measure score
- Change from baseline in height-adjusted total kidney volume as measured by MRI volumetry
- Change from baseline in total liver cyst volume determined by MRI volumetry
- Change from baseline in eGFR, assessed by the CKD-EPI cystatin C equation using serum concentrations of creatinine and cystatin C
- Change from baseline in PLD-I measure score
- Change from baseline in CGI-S score
- Change from baseline in PGI-S score
- PGI-C score by visit
- Change from baseline in SF-36 score
- Change from baseline in PLD-Q score

Point estimates and the associated 95% CI will be calculated for the difference in change at all time points. In the analysis of the secondary efficacy endpoints, the main comparison will be between the average effect of the 2 CAM2029 doses compared to placebo. In addition, the 2 doses of CAM2029 will be compared with placebo separately.

8.10 Adjustments for Multiplicity

Two doses of CAM2029 are analyzed in the trial. In order to protect the overall significance level, the following closed order testing procedure will be used:

1. The effect of the combined CAM2029 treatment groups compared to placebo on change in htTLV at Week 53
2. The effect of treatment with CAM2029 10 mg weekly compared to placebo on change in htTLV at Week 53
3. The effect of treatment with CAM2029 10 mg every 2 weeks compared to placebo on change in htTLV at Week 53

Each test will be performed on the 5% significance level starting with the first test in the list and stopping the testing procedure at the first test for which the p-value is larger than 0.05.

8.11 Safety Endpoints and Analyses

8.11.1 Adverse Events

Summary tables for AEs will include only AEs that started or worsened after the first administration of IMP, i.e., TEAEs. An overview of all TEAEs including severity, relationship to the IMP, SAEs and TEAEs leading to IMP discontinuation, trial withdrawal or death will be presented by treatment arm and trial period.

TEAEs will be summarized by treatment arm and trial period, 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 the number of TEAEs. Furthermore, TEAEs will be summarized according to severity, relationship, outcome, and seriousness.

SAEs, AESIs, and TEAEs leading to IMP discontinuation or trial withdrawal 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.

8.11.2 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 considered.

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

For laboratory tests where grades are not defined by CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology and biochemistry tests:

- Summary tables of observed values and percentage change from baseline at each assessed visit for each standard continuous laboratory parameter.
- 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 laboratory tests where grades are defined by CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE:

- Shift tables using the low/normal/high/ classification to compare baseline to the worst on-treatment 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.

8.11.3 Vital Signs

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

8.11.4 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. In addition, a listing of these subjects/patients will be produced.

8.11.5 Physical Examination

Data on physical examination will be tabulated and listed. Abnormal values will be flagged.

8.11.6 Gallbladder Examination

Gallbladder imaging results details will be listed.

8.12 Pharmacokinetic Analyses

The PK analysis set will be used for all analyses in this section unless specified otherwise.

Descriptive statistics (n, m [number of non-zero concentrations], arithmetic mean, coefficient of variation percentage mean, standard deviation, median, geometric mean, coefficient of variation percentage geo-mean, minimum and maximum) for octreotide concentration will be presented at each scheduled time point by CAM2029 dose regime.

Individual concentration-time profiles will be displayed graphically by CAM2029 dose regime on the linear and semi-log view. In addition, the arithmetic mean (± standard deviation) concentration-time profiles will be displayed graphically on the linear and semi-log view. All individual plasma concentration data for CAM2029 will be listed.

PK/efficacy analyses: The relationship between octreotide exposure and efficacy endpoints may be explored.

[redacted]

Plasma concentration data generated from this trial (PK analysis set) will be used together with data from other clinical trials in a population PK assessment. Patient demographics and baseline data (e.g., age, sex, race, ethnicity, body weight, body mass index) and relevant laboratory assessments will be explored as covariates, if appropriate. The broad principles outlined in the FDA "Guidance for Industry: Population Pharmacokinetics" (53) will be followed during the population PK analysis along with any applicable internal Guidance and Standard Operating Procedures. The results from the population PK analysis will be presented in a separate report.

8.13 Exploratory Endpoints and Analyses

[redacted]

8.14 Sub-Group Analyses

Sub-group analyses will be conducted to check the homogeneity of results across different sub-groups of patients, if possible, for sex and age. Additional sensitivity and sub-group analyses will be included in the SAP.

8.15 Extent of Exposure and Treatment Compliance

Exposure and compliance will be calculated per patient and summarized.

8.16 Interim Analyses

No interim analyses are planned prior to the primary analysis database lock.

9 DATA HANDLING AND QUALITY ASSURANCE

9.1 Source Data and Source Documents

The Investigator must maintain patient medical 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, except for external data (e.g., ECG and clinical laboratory results), which may be transferred electronically. 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 that describes all functions, processes, and specifications for data collection, cleaning and validation, will be created. The data management plan will also describe the activities concerning the 2 database locks during the trial; the first after the last patient has completed all assessments related to Week 53 Visit (end of the randomized Double-Blind Treatment Period) and the second after last patient last visit in the trial (Week 81 Visit in the Safety Follow-Up Period). Such a description will ensure that relevant persons remain blinded after the first database lock until the end of the trial (Section 6.5.2).

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

10 MONITORING PROCEDURES

10.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to ensure adherence to the protocol, ICH GCP (54) 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. Considering the current situation with COVID-19, monitoring may need to be performed remotely and monitoring visits may be performed through telephone and/or video calls. The contract research organization will investigate if alternative measures for review of ICFs and medical records can be implemented.

The Investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents 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 the 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 or randomization number will appear on these copies.

The Investigator should notify the Sponsor without any delay of any announced 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 or randomization number. When the Sponsor receives the patient's personal data, it can therefore no longer be attributable to the patient without a key that will be maintained by the Investigator only. 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.

The following arrangements have been implemented by the Sponsor to comply with data protection regulations:

- Arrangements to comply with the applicable rules on the protection of personal data; in particular organizational and technical arrangements implemented to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and personal data processed.
- Measures implemented to ensure confidentiality of records and personal data of subjects.
- Measures implemented in case of data security breach in order to mitigate the possible adverse effects.

The arrangements and measures above include, for instance, that all personal data will be stored in safe databases, and the number of persons with access to the personal data is very limited. The Sponsor has implemented policies and procedures to ensure lawful processing of personal data and to comply with the General Data Protection Regulation (EU 2016/679).

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 before 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 before IEC/IRB approval/favorable opinion. The Investigator is expected to take any immediate action required for the safety of any patient included in this trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor must be notified of this action, as well as the IEC/IRB and/or regulatory authorities, as required.

11.2 Deviations from the Protocol

Investigators will apply due diligence to avoid protocol deviations. 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. The contract research organization will maintain a log of protocol deviations. 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 at a given clinical site. The Sponsor also reserves the right to terminate the entire trial or temporarily interrupt enrolment. Should the termination of a given clinical trial site or the whole trial 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 protect the patients' best interests. Regulatory authorities and IECs/IRBs will be informed.

Once the 52-week data from the randomized, Double-Blind Treatment Period of the trial are made available, the Sponsor will assess the benefit/risk ratio for the continuation of the Open-Label Extension Period. If the benefit/risk ratio is not positive, the trial will be terminated early.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Independent Ethics Committee/Institutional Review Board and Regulatory Authority Authorization/Approval/Notification

Before starting this trial, the clinical trial protocol, the Patient Information and ICF, and other documents, as applicable, will be submitted to the IEC/IRB and/or regulatory authorities (in accordance with local regulations) for evaluation. The trial will not start before the IEC/IRB and/or regulatory authorities give written approval or a favorable opinion, as required. Any amendments to the protocol will require IEC/IRB and/or regulatory authority approval as required before implementation, except for changes necessary to eliminate an immediate hazard to patients.

12.2 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, Regulation (EU) No 536/2014, and other applicable regulatory requirements (54, 55).

12.3 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 that are relevant to the patient's decision to participate. Each patient will be informed that the monitor(s), quality assurance auditor(s) mandated by the Sponsor, and 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. The patient will also be informed of their right to receive information about the general outcome and the results of the trial.

The patient must be given ample time to consider participation in the trial before consent is obtained. The Investigator must also answer the patient's questions regarding the trial. The process of obtaining informed consent must be documented in the patient's medical records. The ICF must be signed and dated by the patient and the Investigator who provided trial information to the patient, before the patient is exposed to any trial-related procedure, including screening tests for eligibility.

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 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 a written re-consent will be obtained.

12.4 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 consolidated guideline (54), 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 that 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 25 years after the completion or discontinuation of the trial, unless local regulations or institutional policies require a longer retention period, if no further instructions are given by the Sponsor.

No trial site document may be destroyed without a 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 but for a minimum of 25 years.

15 REPORTING AND PUBLICATION

15.1 Clinical Trial Report

A clinical trial report will be prepared upon completion of the Double-Blind Treatment Period, i.e., after last patient completes Week 53 Visit (time point for the primary endpoint).

Interim clinical trial reports may be prepared in between the completion of the Double-Blind Treatment Period and the completion of the Open-Label Extension Period.

A final clinical trial report will be prepared upon completion of the Open-Label Extension Period.

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 to allow the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of trial results. For multi-center trials, it is mandatory that the first publication is based on data from all centers, and that the data are analyzed and submitted as stipulated in the protocol.

Thus, no Investigator or institution may publish any results from the trial conducted at their site before such a first multi-center publication is made that covers the data from all sites.

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

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**.**

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17 APPENDICES

17.1 Appendix 1 Dose Delay and Discontinuation Guidance

17.1.1 Follow-Up on Potential Drug-induced Liver Injury Cases

Patients who were discontinued due to hepatic-related discontinuation criteria in Section 6.10.1 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/international normalized ratio and alkaline phosphatase.
- A detailed history should be collected, including relevant information such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors.
- Further testing for acute hepatitis A, B, C, or E infection and liver imaging (e.g., biliary tract potential metastases) may be warranted.
- 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 identified alternative cause for liver function test abnormalities should be considered as “medically significant”, thus, meeting the definition of SAE (Section 7.6.1.1) and reported as an SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

17.1.2 Specific Management Recommendations for Cases of QTcF Prolongation

Table 5: Dose interruptions 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. Analyze 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 electrolyte analyses 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: Males: 450 msec to 480 msec Females: 470 msec to 480 msec	No dose interruption recommended.
Grade 2 Average QTcF: 481 msec to 500 msec	Pause IMP. Perform repeated triplicate ECGs approximately 1 hour after the first QTcF of ≥481 msec. If QTcF <481 msec, restart IMP. If QTcF remains ≥481 msec, repeat ECG as clinically indicated until the QTcF returns to <481 msec. Restart IMP. If QTcF ≥481 msec remains or recurs, consider discontinuing IMP. 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 Average 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 repeated 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 ≤500 msec. Repeat ECG as clinically indicated until the QTcF returns to <481 msec.

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

SPONSOR PROTOCOL SIGNATURE PAGE

Protocol Title: A randomized, placebo-controlled, double-blind, multi-center trial to assess efficacy and safety of octreotide subcutaneous depot (CAM2029) in patients with symptomatic polycystic liver disease

This clinical trial protocol Version 9 has been reviewed by the Sponsor of the trial. The contents of the protocol reflect and describe the current understanding of the benefits and risks of the product as well as the objectives and design of the trial.

Sponsor's Signatory

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Camurus AB

Signature: [redacted]
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Name and Title | Signature and date

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Email: [redacted]

Name and Title | Signature and date

COORDINATING INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized, placebo-controlled, double-blind, multi-center trial to assess efficacy and safety of octreotide subcutaneous depot (CAM2029) in patients with symptomatic polycystic liver disease

This clinical trial protocol Version 9 has been reviewed by the Coordinating Investigator of the trial. To my understanding, the contents of the protocol reflect and describe the current understanding of the benefits and risks of the product as well as the objectives and design of the trial.

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