Clinical Trial Protocol

CamKid

Effect of Camostat for Kidney Protection in Chronic Kidney Disease

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1 GENERAL INFORMATION

1.1 Title

Protocol Title: Effect Camostat for Kidney Protection in Chronic Kidney Disease

Short Title: CamKid

Danish Title: Camostat til beskyttelse af nyrefunktionen hos patienter med kronisk nyresygdom

1.2 Time Plan

	Month	**Year**
Protocol finished	November	2023
Approval from CTIS	February	2024
Approval from GCP-unit	April	2024
Inclusion of participants	August	2024
Completed inclusion of participants	September	2025
End of study	October	2025
Data analysis completed	October	2026
Manus completed	February	2027
Publication	April	2027

1.3 List of Abbreviations

ACEi	Angiotensin Converting Enzyme inhibitor
ARB	Angiotensin II-receptor blocker
CKD	Chronic didney disease
CM	Camostat Mesilate
eGFR	Estimated Glomerular Filtration Rate
ENaC	Epithelial sodium channel
IMP	Investigated Medical Product
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
PK	Pharmacokinetics
SLGT-2	Sodium Glucose Co Transporter-2
TIA	Transient Ischemic Attack
U-ACR	Urine Albumin/Creatine Ratio
U-hCG	Urine Human Choriogonadotropin
uPA	Urokinase-type plasminogen activator

2 BACKGROUND INFORMATION

2.1 Background

Chronic kidney disease (CKD) affects 10-15 % of the global population. Prevalence and mortality have remained stable through the latest three decades in contrast to conditions like cardiovascular disease and cancer where the decrease in mortality rate has been substantial [1]. CKD is associated with increased risk of hypertension, cardiovascular disease, metabolic bone disease, and premature death. As CKD progresses to end-stage kidney disease, expensive renal replacement therapies like dialysis or kidney transplantation are needed. Proteinuria is an important prognostic factor for CKD progression and cardiovascular morbidity and mortality. Reduction of proteinuria is associated with slower disease progression [2]. While there are currently limited treatment options available to slow down progression of CKD, including ACE inhibitors (ACEi), angiotensin II receptor blockers (ARB), and SGLT2 inhibitors, there is a need for improved treatment alternatives in the fields of CKD.
Patients with CKD and proteinuria have expanded extracellular volume [3], increased salt-sensitivity of blood pressure and respond to dietary sodium restriction suggesting impaired sodium excretion [4]. We propose a causal relation between proteinuria and progression of CKD. The common mediator is aberrant filtration of serine protease most significantly plasmin but also kallikrein and prostasin. They have in common the ability to proteolytically activate both the epithelial sodium channel (ENaC) and complement system precursors also aberrantly filtered. This unifying concept accounts for sodium retention and for continuous inflammatory input by complement system activation [5,6]. We suggest that these apparent different mechanisms are promoted by a common denominator: aberrant serine protease activity in tubular fluid and that they therefore can be attenuated pharmacologically. Inhibition of soluble serine proteases is hypothesized to slow down CKD progression in patients with proteinuria.

Camostat Mesilate (CM) (Foipan®, Ono Pharmaceuticals, Japan) is a well-established broad serine protease inhibitor in use for decades to treat chronic pancreatitis and postoperative reflux esophagitis in Japan [7]. Preclinical data indicate that CM suppresses the proteolytic activation of ENaC and decreases blood pressure, reduces proteinuria and improves renal injury markers [8-10]. We propose that CM will mitigate CKD progression, hypertension, and cardiovascular disease in CKD patients with proteinuria.

Research conducted by applicant lab has identified is aberrant filtration of urokinase-type plasminogen activator (uPA) and plasminogen from plasma to urine in various diseases with albuminuria (preeclampsia, diabetes, hypertension and kidney transplant glomerulopathy) [8,9]. In tubular fluid, plasminogen is activated to plasmin, which subsequently activates ENaC proteolytically in the distal nephron, impairing sodium excretion and free water clearance [10-13]. Probably, contributing to hypertension since ENaC inhibition by Amiloride mobilizes excess sodium and water and lowers blood pressure in patients with diabetes and albuminuria [14,15]. Sets of proteases have been identified in urine in proteinuria and many derive from complement and coagulation cascades [16], such as kallikrein, plasmin, prostasin, urokinase, MASPs (proteases in the lectin pathway of the complement system). Plasmin is the most abundant protease in proteinuria [17]. Plasmin may activate

complement factors at sites of coagulation [18]. We propose that continuous activation of these proteases in tubular fluid promotes inflammation and kidney injury in proteinuria.
Our *in vitro* data show that plasmin in urine promotes formation of the anaphylatoxins C3a and C5a, C3b and membrane attack complex (sTCC, MAC, measured as C5b-9; Isaksson and Palarasah et al.). Deletion of C3a receptor protects against kidney fibrosis in murine models [19,20]. Deletion of plasminogen protects mice from kidney fibrosis [21]. Taken together, inhibition of proteases from these cascades may interrupt detrimental intratubular complement pathways in the kidney. Various drugs have been developed showing reversible inhibitory effects on trypsin, plasmin, plasma-kallikrein, and thrombin. CM is an orally bioavailable synthetic serine protease inhibitor. CM is a registered drug in Japan available since 1985 for treatment of pancreatitis and reflux esophagitis. Upon oral administration, CM and its active metabolite (GBPA) inhibits trypsin, kallikrein, thrombin and plasmin, and C1r and C1 esterases in the complement system. CM and GBPA circulate at 10-30 ng/ml 2 hours after intake of 100 mg in humans [22].

Published available data on Camostat leading to the hypotheses
CM lowered proteinuria in 20 patients with proteinuria from various etiologies [23]; in patients with nephrotic syndrome [24] and in patients with diabetes and nephrotic proteinuria [25,26]. No renal adverse effects were reported. In preclinical studies, CM prevents podocyte injury and lowers proteinuria in rats with metabolic syndrome [27]. Furthermore, CM lowered renal tissue plasmin activity [28], and showed natriuretic and antiproteinuric effect [22]. CM is eliminated in the urine (89-95 %, Pubchem). The studies on proteinuria are from Japan, they are explorative, open label and small scale. To our knowledge, pharmacodynamic mechanistic hypothesis-driven studies have not been conducted in CKD patients. Many registered ongoing trials test the efficacy of CM in Covid-19 disease. A Danish study pioneered this and reported no adverse renal or cardiovascular effects [29].

2.2 Aim
The overall aim of the project is to mitigate progression of CKD of any course and lower cardiovascular morbidity and mortality in CKD patients with proteinuria by repurposing a known pharmaceutical. The specific objectives are to test whether Camostat Mesilate, a serine protease inhibitor, possess previously undiscovered renoprotective effects by inhibiting serine protease activity and suppressing complement activation within the renal tubules.

This will be accomplished through an initial interventional pilot study that will serve as the foundation of a future long-term clinical interventional study. This preliminary study is designed as an exploratory, non-randomized, interventional, pharmacodynamic study in CKD patients with proteinuria and **healthy** controls, aiming to evaluate the effect of Camostat Mesilate in CKD patients with proteinuria and in healthy controls.

2.3 Hypothesis
In patients with CKD and proteinuria on a fixed normal sodium intake, administration of Camostat Mesilate (200 mg x3/day for 4 days) will enhance fluid excretion, mobilize body water, reduce body weight and extracellular volume, and increase sodium excretion compared to healthy controls.

Secondary, Camostat Mesilate will inhibit urinary protease activity, prevent aberrant proteolytic activation of the ENaC gamma subunit and the formation of soluble C5b-9 in urine, consequently leading to a reduction in albuminuria.

2.4 Treatment

CM is an orally bioavailable synthetic serine protease inhibitor. It has been a registered drug in Japan since 1985, primarily used for the treatment of pancreatitis and reflux esophagitis. Notably, CM is very well tolerated and has no known drug-drug interactions [31].

2.4.1 Pharmacokinetics (PK) of Camostat Mesilate (CM)

Upon oral administration, CM rapidly undergoes hydrolysis in plasma to 4-(4-guanidinobenzoyl-oxy) phenylacetic acid (GBPA), which is further degraded into 4-guanidinobenzoic acid (GBA). CM and GBPA have similar biological activity, while GBA is inactive [30]. The absorption fraction after oral dosing has not been documented.

The Japanese Summary of Product Characteristics (SmPC) [31] references a study involving five healthy, fasting adults who received a single oral dose of 200 mg CM. In this study, GBPA had a T_{max} of 40 minutes, C_{max} of 87.1 ng/mL, AUC 10.400 ng*min/mL and $T_{½}$ of 100 minutes. Another study of four patients with complete gastrectomy given a single dose of 100 mg CM showed similar plasma concentration changes, including a C_{max} of 30 ng/mL.

In another study, four healthy Caucasian males received a single dose of 40 mg CM as an intravenous infusion over 12 hours [32]. The parent compound was undetectable in plasma, suggesting rapid degradation. PK parameters for the active metabolite, GBPA, included a T_{max} of 300 minutes (after infusion start), C_{max} of 89.4 ng/mL, C_{ss} of 83.6 ng/mL, AUC of 966 ng*h/mL, and $T_{½}$ of 1.0 hour.

In a study assessing pancreatic function, twelve healthy individuals (6 males and 6 females, median age 24.5 years) were administered 500 mg of CM four times daily for four weeks. C_{ss} for GBPA at the end of week 1-4 were 19600 ng/ml, 18600 ng/ml, 19000 ng/ml and 14400 ng/ml [33].

An ongoing phase 1/2 trial is evaluating PK in 18 subjects following single oral doses of 100mg, 200 mg and 300 mg of CM, respectively [34], however this paper states that doses up to 900 mg daily has been used previously. Specific data has yet to be published.

CM is primarily metabolized to GBPA and then to GBA by carboxylesterase and arylesterase [31]. Neither the parent compound nor its metabolites affect the activity of CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. GBA is mainly renally excreted (>95%).

Kidney function

The primary metabolites of CM are primarily excreted through the kidneys, with GBA being the predominant one and to a much lesser extent GBPA. After a single oral administration of 200 mg CM to five healthy adults, most of these metabolites were excreted within 5-6 hours [31]. No PK studies have been identified that included patients with CKD. However, the TACTIC trial, aimed at studying the effect of CM on chronic pancreatitis in a Western population, excluded patients with CKD stage IV (eGFR < 30 ml/min/1.73m^2) [34]. This suggests that previous studies may have documented the safety of CM in patients with milder degrees of renal impairment.

Interactions with other drugs
No interactions with other drugs have been reported for CM, GBA, or GBPA. These compounds are not metabolized by cytochrome P450 enzymes (CYP).

2.4.2 Safety Profile for Camostat Mesilate

CM is a serine protease inhibitor that seems to modulate the activity of ENaC. In patients with CKD and proteinuria, ENaC is proteolytically activated by serine proteases aberrantly filtered to tubular fluid. CM suppresses this proteolytic activation of ENaC, leading to reduced blood pressure, decreased proteinuria, and attenuation of renal injury progression [22-28].

According to the SmPC [31], CM is indicated for remission of acute symptoms of chronic pancreatitis (600 mg/day) and postoperative reflux esophagitis (300 mg/day). A total of 3.806 patients were evaluated in the Drug Use Investigation, and the following adverse reactions were reported:

- Abnormal laboratory test results (1.3-1.8 %)
- Hepatic function abnormalities (elevated AST and ALT - 0.3 %)
- Rash (0.4 %)
- Pruritus (0.2 %)
- Nausea (0.1-0.3 %)
- Abdominal discomfort (0.2 %)
- Diarrhea (0.2 %)

Clinically significant adverse reactions (incidences unknown, but rare):

- Shock and anaphylactic symptoms (decreased blood pressure, dyspnea, pruritus)
- Thrombocytopenia
- Hepatic function disorder or jaundice
- Hyperkaliemia

Reported adverse effect are rare (less than 3%) and generally mild, including symptoms like pruritus, increased thirst and appetite and lightheadedness) [34].

A phase 1/2 study in the United States investigated the safety of CM as a treatment for chronic pancreatitis [34]. The phase 1 study examined the pharmacokinetics and safety CM doses of 100, 200 and 300 mg doses and demonstrated safety in 18 subjects. The phase 2 study was a double-blind, randomized, parallel-group, dose-ranging study currently ongoing to further assess safety and efficacy of CM compared to placebo. As of May 2019, 63 out of 78 subjects have completed the study, with only few serious adverse events (SAEs) reported, none of which were directly linked to treatment [34].

Two case reports have emerged, one involving autoimmune hepatitis possibly triggered by drug-induced liver injury related to CM treatment. Discontinuation of the drug did not result in complete remission, but low-dose corticosteroids effectively treated the liver function [35]. Another case study

reported eosinophilic pneumonia, likely caused by a 10-day treatment with CM. Eosinophil levels in the blood and infiltration into alveolar space improved upon cessation of the drug [36].

Relevant monitoring of treatment should be based on the knowledge about the reported clinically significant adverse reactions, which include hyperkaliemia, hepatic function disorder or jaundice, thrombocytopenia, eosinophilic pneumonia, and shock/anaphylactic symptoms.

Safety in patients with reduced renal function or end-stage renal disease
Human data regarding CM treatment and renal insufficiency are limited but generally reassuring. Three studies have been identified that address the safety of CM administration in patients with varying degrees of renal insufficiency:

1. Onbe et al. (J Diabet Complications 1991) [24] studied eight patients with nephrotic syndrome and diabetic nephropathy who received 600 mg of CM daily for four weeks. The study demonstrated reduced proteinuria, with stable creatinine clearance throughout the study.
2. Ikeda et al. (J Diabetes Complications 1999) [25] examined three patients with nephrotic syndrome and diabetic nephropathy who were given 600 mg of CM daily for four weeks. The study reported reduced proteinuria with no reported side effects.
3. Matsubara et al. (Clin Nephrol 1989) [23] conducted a study involving 17 patients with heavy proteinuri due to various nephropathies who received 600 mg of CM daily for four weeks. The study observed a reduction in urine protein excretion from the second week onwad, with no changes in serum creatinine during the study.

Collectively, these studies suggest the safety of CM administration in patients with varying degrees of renal insufficiency, with no evidence of harm to renal function or increased risk of adverse drug reactions.

2.4.3 Potential Benefits
Oral CM treatment is expected to significantly inhibit serine proteases and complement factors in tubular fluid in patients with CKD and proteinuria. This inhibition is anticipated to reduce salt and water retention and inflammation, ultimately slowing the progression of renal impairment and potentially improving cardiovascular outcomes in CKD patients. CM, although not on the European pharmaceutical market, has been used safely in Japan for decades. Repurposing CM for treatment of CKD patients represents a cost-effective and safe option compared to developing new medications.

2.4.4 Overall Benefit/Risk Conclusion
Currently, the available treatments to delay kidney disease progression include SGLT-2 inhibitors and ACEi/ARBs. CM is predicted to act additively by targeting a mechanism not addressed by ACEi/ARBs and SGLT-2 inhibitors. CM is expected to reduce proteinuria, reduce kidney tissue inflammation, and inhibit tubular complement activation by suppressing tubular serine protease activity. The primary risk of hyperkalemia, thrombocytopenia and hepatic functions abnormalities has been studied and appears manageable.

2.4.5 Rationale for dose selection

The approved doses for CM are 100 mg three times daily for postoperative reflux esophagitis and 200 mg three times daily for chronic pancreatitis symptoms.
Some studies have employed much higher doses of CM without severe adverse effects, including nine patients with severe oral carcinomas who received up to 7.2 g daily for several months [37] and a study in healthy individuals using 2 g daily for four weeks [38].

Since there is limited data on CM use in patients with CKD, doses that are safe within the limits of the SmPC will be used. A dialy dose of 600 mg divided into three doses has been used in previous studies involving CKD patients.

3 STUDY PURPOSE AND OBJECTIVES

3.1 Purpose

The overall purpose of the study is to evaluate the potential benefits of Camostat Mesilate in CKD patients with proteinuria focusing on fluid balance, kidney injury markers, tubular protease activity and complement activation.

3.2 Primary objective

- To evaluate salt and water excretion including total body water content and blood pressure.

3.3 Secondary objectives

- To evaluate tubular serine protease activity and complement activation in patients CKD with proteinuria.
- To evaluate whether proteolytic activation of ENaC plays a role in normal physiological regulation.

4 STUDY DESIGN

4.1 Endpoints

Primary endpoints
Urine sodium excretion Water excretion BCM/weight Home blood pressure
Secondary endpoints
Tubular complement activation Urine C3a, MAC-sC5b-9, C3dg, MBL Urine protease activity Zymography

Protease activity assay

Urine microvesicles:
- gammaENaC cleavage
- complement deposition (sC5b-9)

24 hours Urine albumin excretion

Plasma concentrations:
- Renin
- NT-proBNP
- Angiotensin II
- Aldosterone

4.2 Design

This trial is a single-center, interventional, non-randomized, open-label pharmacodynamic study aiming to evaluate the effect of CM in both CKD patients with proteinuria and healthy controls. This approach has been chosen as the trial serves as a pilot study, aiming to investigate a novel treatment target in CKD patients. Including healthy control subjects allows for a comparison of the effect of CM on normal physiology versus CKD with proteinuria. By elucidating the differences in drug response between healthy individuals and CKD patients with proteinuria, a better understanding of the therapeutic potential and underlying mechanisms of CM in treating CKD can be gained.

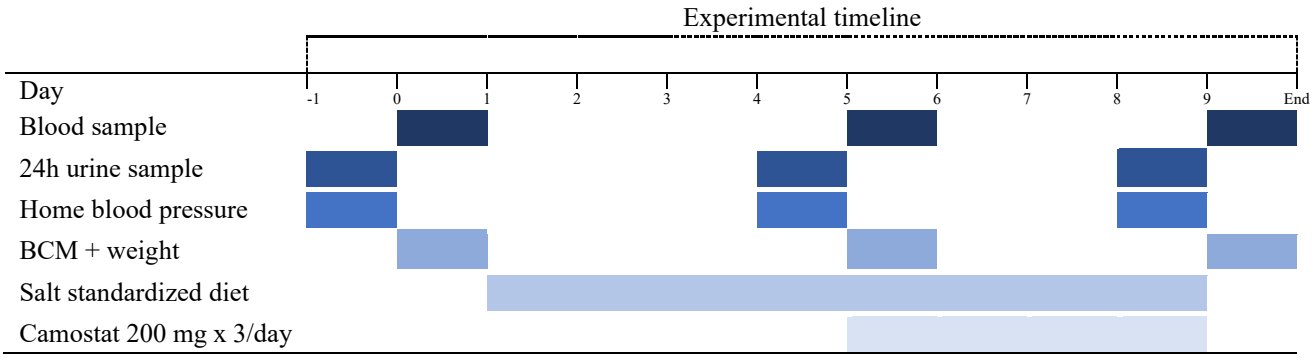


Figure 1: Main study design. BCM: body composition monitor.

4.3 Intervention

The study will include a total of 20 patients with CKD and proteinuria and 20 healthy controls without proteinuria matched for age and gender. Both patients and controls will follow a standardized sodium diet of 150 mmol/day for a duration of 8 days. The diet is specified by a dietitian and prepared by the hospital kitchen. The diet will be distributed to the participants during *Visit 2* and *Visit 3*. It will consist of five meals daily with different energy levels depending on the energy needs calculated from the Harris-Benedict formula. Participant are allowed only to drink tea or water in addition to the beverages included in the diet. On the fifth day of adhering to this diet (*day 5*), administration of oral

Camostat mesylate at a dose of 200 mg x3/day is initiated and will last for four days while the diet is continued. CKD patients will receive the IMP as an add-on to their current treatment regimen.
Blood samples, 24-hour urine samples, home blood pressure, and body composition monitor (BCM) measurement will be obtained at baseline, after 4 days on the diet just before CM treatment (*day 5*) and on *day 9* after completion of 4 days treatment with CM, after which the study is completed.

4.4 Minimizing bias

To minimize potential bias, both CKD patients and healthy controls adhere to a standardized sodium diet, controlling for dietary influences on fluid balance and sodium excretion. This reduces variability and minimize bias associated with dietary sodium intake. Although the trial is open-label and non-randomized, bias is minimized using completely objective measures for both primary and secondary endpoints. These measures include fluid balance, biomarkers, and blood pressure, ensuring an impartial assessment of outcomes. Participants are recruited through specific criteria, and efforts are made to ensure eligibility. This controlled enrollment process helps maintain homogeneity within study groups.

4.5 Recruitment

Patient recruitment will primarily take place at the Department of Nephrology at Odense University Hospital. The recruitment process will involve the following approaches:

1. Identification of eligible patients: Patients meeting the inclusion criteria will be identified through the hospital's electronic patient records. During their routine visits in the outpatient clinic, the treating physician will assess their eligibility based on the inclusion and exclusion criteria outlined in the study protocol. Eligible patients will be provided with recruitment materials as part of their routine outpatient clinic visits.
2. Recruitment of healthy controls: Healthy individuals of similar age and gender will be recruited through advertisements placed at local institutions and through social media platforms. Subjects of interest will be provided with recruitment material identical to the recruitment material provided to eligible patients.

4.6 Screening

Participants who accept to take part in the study will be invited to attend a screening session. During this screening meeting, oral information will be provided, and written informational materials will be distributed. It is recommended that participants bring a relative with them to this meeting. The screening session will take place in a quiet room, free from disruptions.
A minimum consideration time of 24 hours will be offered to participants; however, it is optional, and patients may choose to forgo this consideration period if they wish. No study-related procedures will be conducted until a signed, written informed consent form is obtained from the participants.
A blood and urine sample and a pregnancy test (if relevant) will be collected to obtain current values. From these, inclusion and exclusion criteria are evaluated, and final eligibility are assessed. Only patients who understand and speak Danish will be included in the study.

4.7 Duration/Follow-up

The study period is 11 days. A follow-up visit will be offered one week after the end of the study period. It is optional for the participant to choose a telephone-visit instead.

4.8 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

4.9 Discontinuation of Study

Participants can withdraw from the study, or the IMP as outlined in section 5.4 Subject Withdrawal Criteria.

The study may be prematurely discontinued due to regulatory decisions, changes in the Ethics Committee's opinion, or safety concerns regarding the drug. Additionally, the sponsor has the authority to temporarily suspend or terminate the study due to participant safety, ethical considerations, or serious recruitment challenges.

4.10 Source data

The following documents are defined as source data:

- Informed consent (or power of attorney)
- Prints of study visit notes/information from electronic patient records.
    - Note of each visit in the patient's file
    - Biochemical measurements
- SAE reports

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Patients

5.1.1 Inclusion criteria

Patients:

1. Age ≥ 18 years.
2. A clinical diagnosis of CKD of any course and meet the following criteria at screening:
    a. eGFR ≥ 30 ml/min/1.73m^2
    b. U-ACR ≥ 300 mg/g.
3. Stable antihypertensive treatment 2 weeks before start of investigated medical drug (IMP) and maintain this treatment throughout the study.
4. Office blood pressure at the screening session should be >120/70 mmHg and <150/90 mmHg.
5. Capable of providing a signed informed consent and comply with study requirements.
6. Women with childbearing potential* must have a negative pregnancy test (urine hCG) at spot urine at the screening visit and should use contraception during the study and until one week after completion of study treatment.

5.1.2 Exclusion criteria

1. Treatment with Amiloride, Spironolactone, Aldosterone, or analogues.
2. Treatment with NSAIDs.
3. Hyperkalemia > 5.0 mmol/L at screening.
4. P-bilirubin > 25 umol/L at screening.
5. Ongoing cancer treatment.
6. Treatment with immunosuppressive therapy within 6 months prior to screening.
7. History of organ transplantation.
8. Evidence of current infection (CRP>50 or temperature > 38 C°).
9. Severe hepatic insufficiency classified as Child-Pugh C.
10. Breastfeeding.
11. Congestive heart failure NYHA class IV, unstable or acute congestive heart failure.
12. Recent cardiovascular events < 2 months prior to screening:
    a. Coronary artery revascularization.
    b. Acute stroke or TIA.
    c. Acute coronary syndrome.
13. Allergy or hypersensitivity to the IMP.
14. Addison's disease.
15. Gastric bypass operation.
16. Lactose intolerance since lactose serves as one of the inactive ingredients in the IMP.
17. Participation in other clinical trials within the last 30 days.

5.2 Healthy controls

5.2.1 Inclusion criteria

1. Age ≥ 18 years.
2. Good general health with no significant medical conditions or chronic illness (e.g., diabetes, hypertension, cardiovascular disease, autoimmune diseases, and cancer).
3. Normal kidney function and no proteinuria at screening:
    a. eGFR > 90 ml/min/1.73m^2
    b. U-ACR < 30 mg/g
4. Office blood pressure at the screening < 140/90 mmHg.
5. Capable of providing a signed informed consent and comply with study requirements.
7. Women with childbearing potential* must have a negative pregnancy test (urine hCG) at spot urine at the screening visit and should use contraception during the study and until one week after completion of study treatment.

5.2.2 Exclusion criteria

1. Treatment with any prescription medication except oral contraceptives.
2. Use of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)
3. Hyperkalemia > 5.0 mmol/L at screening.
4. P-bilirubin > 25 umol/L at screening.

5. Evidence of current infection (CRP>50 or temperature > 38 C°).
6. Breastfeeding.
7. History of substance abuse including alcohol.
8. Allergy or hypersensitivity to the IMP.
9. Gastric bypass operation.
10. Lactose intolerance since lactose serves as one of the inactive ingredients in the IMP.
11. Participation in other clinical trials within the last 30 days.

* Women are considered of childbearing potential following menarche and until becoming post-menopausal (12 consecutive months without a menstrual period) unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy or bilateral oophorectomy (According to the Clinical Trial Facilitation Group, 2014-09-15).

5.3 Screen failure

Screen failures are defined as patients who consent to participate in the clinical study and provide an informed consent at visit 1 but subsequently do not meet the inclusion and exclusion criteria. These participants may undergo re-screening once, with a minimum of 4 weeks from the initial visit 1. This process requires new informed and signed consent, a repeated assessment for the study, and a new participant identification number.

5.4 Subject withdrawal criteria

5.4.1 Subject Withdrawal from Study

Subject withdrawal is defined as any living subject who does not complete the final follow-up visit (visit 5) as outlined in this protocol. Reasons for withdrawal include, but are not limited to:

- Subject's request (withdrawal of consent)
- Adverse events (AE) or reactions
- Conditions posing unacceptable risk as determined by Investigators or advisers.
- Sponsor-initiated discontinuation of the study
- Lost to follow-up.

5.4.2 Subject Withdrawal from the Investigational Medicinal Product(s) (IMPs)

Withdrawal from IMP is defined as discontinuation of study treatment with continued follow-up until completion at visit 5. Subjects withdrawing from IMP after at least one dose will undergo safety monitoring with a follow-up visit one week after IMP withdrawal. Reasons for withdrawal from IMP may include, but are not limited to:

- Subject's request (withdrawal of consent)
- Adverse events (AE) or reactions
- Conditions posing unacceptable risk as determined by Investigators.

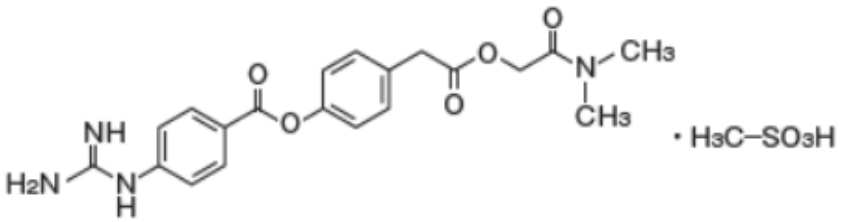
Investigators will attempt to reschedule visits for subjects who miss planned appointments. The eCRF will document the reason for withdrawal, withdrawal date, and the decision-maker (subject or Investigator).
Subjects withdrawn before the end of intervention (visit 4) will not be included in statistical analyses. However, these participants will still be considered as part of the safety analysis for the study. Subjects only missing the final follow-up visit (visit 5) are included in the statistical analyses.

6 TREATMENT OF SUBJECTS

6.1 The Investigational Medicinal Product (IMP) - Camostat Mesilate

Camostat Mesilate will be provided as a film-coated tablet in press-through packages. Each tablet contains 100 mg of Camostat Mesilate.

Chemical name: [4-[2-[2-(dimethylamino)-2-oxoethoxy]-2-oxoethyl]phenyl] 4-(diaminomethylideneamino)benzoate;methanesulfonic acid
International Nonproprietary Name (INN): Camostat
Molecular formula: $C_{20}H_{22}N_4O_5 \cdot CH_4O_3S$
Molecular weight: 494,52
Structural formula:



6.2 IMP dosing modifications

No dosing modifications allowed.

6.3 Drug Supplies, Packaging and Labelling

6.3.1 Camostat Mesilate

The name of the drug is Foipan film-coated tablets 100 mg. It is imported from Japan.
Foipan produced by the company: Ono Pharmaceutical Co., Ltd., 8-2, Kyutaromachi 1-chome, Chuo-ku, Osaka, 541-8564 Japan.
The Pharmacy at Odense University Hospital will make the imports to Denmark according to Danish law.
If necessary, one of the following generic marketed products can be used:

Brand Names

- **Archiment**
  Ohara Yakuhin, Japan
- **Camoent**
  Tsuruhara Seiyaku Pharmaceutical, Japan
- **Camostat Mesilate**
  Daito, Japan; Kyowa Yakuhin, Japan; Medisa Shinyaku, Japan; Nichi-Iko Pharmaceutical, Japan; Nihon Generic, Japan; Nipro, Japan; Ohara Yakuhin, Japan; Takeda Teva Pharma, Japan; Tatsumi Yakuhin, Japan; Towa Yakuhin, Japan; Tsuruhara Seiyaku Pharmaceutical, Japan
- **Camostate**
  Nichi-Iko Pharmaceutical, Japan
- **Camoston**
  Teva Seiyaku, Japan
- **Camotat**
  Kobayashi Kako, Japan
- **Carmozacine**
  Nipro Pharma Nipurofama, Japan
- **Foipan**
  Ono Yakuhin, Japan
- **Kamostaal**
  Towa Yakuhin, Japan
- **Leanac**
  Maeda Yakuhin, Japan
- **Leseplon**
  Tatsumi Kagaku, Japan
- **Libilister**
  Takeda Teva Pharma, Japan
- **Mecilpan**
  Choseido Pharmaceutical, Japan
- **Mospan**
  Daito, Japan
- **Pancrel**
  Kyowa Yakuhin, Japan
- **Raintat**
  Koa Isei, Japan

6.4 Drug Storage and Accountability

The Sponsor and Principal Investigator are responsible for secure and correct storage of the IMP after arrival at study site. The IMP will be stored in a locked medication room within the outpatient clinic at the Department of Nephrology, Odense University Hospital. The storage compartment will be monitored regularly. Records of received, used and remaining quantities of the IMP will be maintained. Any discrepancies must be solved and explained.
Until dispensation to the study subjects, the IMP must be stored as follows:

• Foipan (Camostat mesilate): store at temperature below 25° Celsius

For the trial participants, the IMP should be stored at room temperature.

Participants are required to self-administer the IMP in the comfort of their own homes. The IMP batch provided to each participant is documented in the eCRF. To ensure compliance, participants will be encouraged to set an alarm on their mobile phones at the designated administration times and maintain a diary of the administration. At the final visit, participants will be questioned about their administration, and the investigator will verify by counting the returned tablets. Any deviations from the prescribed dosage regimen will be documented in the eCRF. Any returned IMP will be destroyed.

6.5 Drug administration

CM will be administered from day 5 at a dose of 200 mg x3/day (e.g., at 6 AM, 2 PM, and 10 PM). The intervention period is 4 days. Total number of doses is 200 mg x3 x4 = 2400 mg (=24 tablets).

6.6 Management of overdose

An overdose is characterized as any instance in which a participant has ingested a dose exceeding the maximum target dose specified in the protocol. The approach to managing an overdose should be based on clinical judgment based on symptoms and signs.

In the event of an overdose, the investigator is responsible for:

1. Contact the sponsor to report the overdose incident.
2. Evaluate the participant's condition to determine whether it is necessary to interrupt the study intervention,
3. Closely monitor the participant for any adverse events (AE) or serious adverse events (SAE) and assess laboratory abnormalities as clinically indicated.
4. Record the amount and duration of the overdose eCRF.

6.7 Concomitant Medications

All medications or vaccines that the participant is currently taking at the time of enrollment or receives during the study must be documented in the eCRF. Please refer to exclusion criteria for medications not allowed during the study. Also, it should be noticed, that all antihypertensive and diuretic medication should remain stable during the study period and 14 days before initiation the study.

6.8 Post-Study Care

Following the termination of the study, there are no predefined post-study care. They will resume their routine appointments with their attending physician at the outpatient clinic as usual.

7 ASSESSMENTS AND PROCEDURES

For a detailed specification of study endpoints refer to Section 4.1 (Endpoints).

7.1 Primary Endpoint

Data on the primary endpoint will be collected by the study personnel and/or investigators.

7.2 Secondary Endpoints

Data on the secondary endpoints will be collected by the study personnel and/or investigators.

Schedule of Activities (SoA)	Screening	Preintervention	Salt standardized diet		Intervention period	End of intervention	End of study (1 week after visit 4)
Study days	**-14 to -2**	**0**	**1-4**	**5**	**6-8**	**9**	**(18)**
Visit	**1**	**2**		**3**		**4**	**5**
Informed consent and eligibility							
Orally informed consent	●						
Eligibility (in- and exclusion criteria)	●						
Signed informed consent	●						
Baseline characteristics							
Demographics		●					
Medical history		●					
Physical examination[1]		●					
Anthropometric data							
Weight		●		●		●	
Blood pressure (office)	●						
Home blood pressure[2]		●		●		●	
Body Composition Monitor		●		●		●	
Laboratory evaluations							
u-HCG (if relevant)	●						
Blood samples[3]	●	●		●		●	
Spot urine (albumin/creatine ratio)	●						
24-hour urine[4]		●		●		●	
100 mL spot-urine +20 mL for freeze[5]		●		●		●	
Study intervention and safety							
Salt standardized diet			●	●	●		
Study intervention				●	●		
Dispensation and return of IMP				●		●	
End of study phone call							●
AE/SAE/OE						●	●

Table 1: Schedule of activities - Main study

1. At a minimum assessment of cardiovascular and respiratory systems.
2. Each participant will receive a calibrated blood pressure monitor and will be instructed to record their blood pressure three times in the morning and three times in the evening, following a 15-minute period of rest.
3. Plasma: hemoglobin, leucocytes, platelet count, CRP, albumin, sodium, potassium, hydrogencarbonat, creatinine, carbamide, ALAT, LDH, bilirubin, renin, angiotensin, aldosteron
4. Albumin, total protein, sodium, potassium, creatinine, creatinine clearance
5. Tubular complement activation and urine protease activity

8 ASSESSMENT OF SAFETY

The safety of enrolled participants will be monitored continuously based on statements of Adverse Events (AE) and Serious Adverse Events (SAE). AEs and SAEs will be monitored and recorded from the initiation of the IMP administration until the end of the study, which is approximately one week

after the final dose of the IMP. Following the occurrence of an AE or SAE, participants will receive appropriate follow-up and treatment based on standard guidelines. Adverse events will be reported by both the participant and the investigator, along with any qualified designees who are responsible for detecting, documenting, and recording events meeting the definition of an AE or SAE through in-person visits and telephone contacts. Annually, a safety report will be uploaded into the CTIS.

8.1 Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a trial subject receiving a pharmaceutical product, even if there may not necessarily be a causal relationship with the treatment. An AE can therefore be any undesirable and/or unintended sign or symptom (including deviation from usual laboratory findings) temporally associated with the use of the IMP, regardless of whether a causal link to the IMP is evident.
Abnormal laboratory values or test results are classified as AEs only if they result in clinical signs or symptoms, are considered clinically significant, or require investigation or intervention. Repeated tests will be conducted until deviations from usual laboratory findings return to normal, stabilize, or are no longer clinically significant. If an abnormal test result is determined to be an error, it need not be reported as an adverse event. Such determinations will be made based on the scientific and medical judgment of the investigator (MD).

All AEs will be recorded and assessed in accordance with the principles of Good Clinical Practice (GCP) and the latest requirements of the Medicines for Human Use (Clinical Trials) Regulations.

Each AE must be assessed and categorized according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). These details will be recorded on the AE form within the CRF, providing the following information:
1. The severity grade (mild, moderate, severe)
2. Its relationship to the IMP (suspected or not suspected)
3. Duration (including start and end dates, or indication if the AE is ongoing at the final examination)
4. Whether it qualifies as a Serious Adverse Event (SAE)
5. Actions taken in response to the IMP
6. Outcome

8.2 Serious Adverse Events (SAE) and Serious Unexpected Suspected Adverse Events (SUSAR):

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence or effect that, at any dose, meets any of the following criteria:
- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in a congenital anomaly or birth defect.
- Results in persistent or significant disability or incapacity.

Some medical events may place the patient at risk or require intervention to prevent any of the above-mentioned consequences. Such events are referred to as "important medical events" and should also be categorized as "serious" in accordance with the definition. The decision of whether an event is "serious" is made by the investigator based on medical judgment. The investigator must assess causality independently, considering factors such as timing and other relevant information. A planned hospitalization will not be considered an SAE. To determine whether a serious adverse related event (SAR) is unexpected and, therefore, qualifies as a Suspected Unexpected Serious Adverse Reaction (SUSAR), the most recent product summary for Foipan (Camostat mesilate) is used. An adverse event is unexpected if its specificity and severity are not described in the latest product summary.

8.2.1 Pregnancies

Pregnancy, although not itself a serious adverse event, will also be reported on a SAE form and be followed up to determine outcome, including spontaneous or voluntary termination, details related to the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. All information pertaining to pregnancy should be recorded on a dedicated Clinical Trial Pregnancy Form.

8.3 Reporting of Adverse Events

All adverse events will be reported and assessed in the appropriate eCRF.

8.4 Reporting of Serious Adverse Events (SAE)

Throughout the entire study period, all serious adverse events/reactions will be reported and assessed. Participants will be questioned at each visit/telephone call after initiation of IMP administration. The investigator is required to report all SAEs to the sponsor within 24 hours of becoming aware of their occurrence. The initial report will be followed by detailed written reports.

8.5 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

The sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is promptly recorded and reported to the EudraVigilance database, and in any case no later than seven days after the sponsor becomes aware of such a case. For other serious SUSARs, this information will be reported within 15 days. Additionally, any follow-up inquiries from authorities will be addressed within eight days.

8.6 Annual Safety Report

An annual Safety Report will be submitted through CTIS. This safety report will adhere to the format of the Development Safety Update Report (DSUR). It will specify the reporting timeframe and provide a concise summary of all documented serious events, including both Serious Adverse Events (SAEs) and Serious Unexpected Suspected Adverse Reactions (SUSARs). Furthermore, the safety report will include an up-to-date benefit/risk evaluation.

9 STATISTICS

9.1 Statistical Methods

The statistical methods employed will include descriptive statistics, such as means and standard deviations, for continuous variables, and frequencies and percentages for categorical variables. Inferential statistical tests will be used to compare outcomes between groups.

9.2 Interim analysis

Interim analyses are not planned for this study.

9.3 Sample Size

The total number of subjects planned to be enrolled is 20 CKD patients with proteinuria and 20 healthy controls. The sample size is chosen based on feasibility and the availability of eligible participants. This study is primarily designed as a pilot study exploring the effects and pharmacodynamic features of the IMP, and the sample size is not determined by statistical power calculations. However, the selected sample size is considered sufficient to observe potential trends and provide preliminary insights into the effects of the intervention.

9.4 Trial power

Since this study is designed as a pilot and not powered to detect specific effect sizes or differences between groups, it may have limited statistical power to detect smaller, yet potentially clinically relevant, effects. Therefore, it should be interpreted with this limitation in mind.

9.5 Level of Significance

The level of significance to be used for hypothesis testing is set at $p < 0.05$. A p-value of less than 0.05 will be considered statistically significant.

9.6 Reporting Deviations from the Statistical Plan

Any deviations from the original statistical plan will be documented and justified in the final study report. The protocol may also be updated to reflect these deviations if necessary.

9.7 Selection of Subjects for Analyses

The selection of subjects to be included in the analyses will be of all participants who have completed the study according to the prescribed protocol until the end of intervention (visit 4). This includes both CKD patients with proteinuria and healthy control subjects. This approach ensures that all relevant data are included in the analysis, providing a comprehensive assessment of the intervention's effects within the study population.

9.8 End of study

The trial will be completed when 20 CKD patients and 20 healthy controls are included in the trial. Withdrawn participants will not be replaced.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Based on approval from the regional Ethics Committee, the Sponsor hereby affirms that the Investigators and the involved institutions in the clinical trial will permit trial-related monitoring, auditing, and inspection by regulatory authorities. This includes granting direct access to source data and study documents for review by The Danish Medicines Agency, The Ethics Committee, and their collaborators.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The clinical trial will be conducted in accordance with the trial protocol, the Regulation, and the principles of Good Clinical Practice (ICH-GCP).

The Investigator holds the responsibility for ensuring the study's conduction, documentation, and completion in accordance with the protocol. The study is monitored by the GCP-Unit at Odense University Hospital.

12 ETHICS

12.1 Ethical Conduct of the Study

The study will be reported to the Clinical Trials Information System (CTIS). All necessary approvals from regulatory authorities will be awaited before initiating the study. The study will adhere to the approved protocol, and any deviations from the protocol will be documented and reported as required. The study will be conducted in accordance with the Declaration of Helsinki, principles of Good Clinical Practice (GCP), the Regulation (EU) No. 536/2014, and national ethical guidelines and law.

12.2 Informed Consent

The investigator is responsible to provide each potential participant with information about the background, purpose and potential risks of the study. Additionally, participants will be informed about their rights to privacy including protecting their personal information. To confirm that the participants have understood the provided information, they will be asked to recap their understanding. After appropriate consideration time, the investigator will obtain written informed consent from each participant. A copy of the Informed Consent Form (ICF) will be provided to the participant, and the original signed copy of the ICF will be maintained by the investigator. And subject to inspection as needed. Furthermore, participants will be explicitly informed that they have the right to withdraw their consent at any time.

12.3 Access to data

To identify eligible participants, a review of laboratory data stored in the Electronic Patient Journal (EPJ) will be conducted, focusing on data related to eGFR and urine albumin/creatinine ratio. These data will be used to assess the eligibility of potential participants based on patient lists within the outpatient clinic. Once signed informed consent has been obtained, the Sponsor, Investigator, the GCP unit, Ethics Committees, and regulatory authorities will be allowed access to the source data.

12.4 Ethical Considerations

The IMP, Camostat mesilate (CM), is not currently marketed in the EU, but has been used safely in Japan for decades. CM is known to be a safe and well-tolerated medication, with the most common side effects reported as abnormal biochemistry (1-2%), rash (0.4%), nausea (0.3%), pruritus (0.2%), and abdominal discomfort (0.2-0.4%). Furthermore, existing evidence from CM administration in patients with varying degrees of renal insufficiency suggests no harm to renal function or an increased risk of adverse drug reactions.

During the study, participants will undergo the collection of several blood and urine samples, which may cause minor discomfort and inconvenience. Additionally, participants in the main study will be required to commit significant time and adhere to clinical visits, 24-hour urine collection, 24-hour blood pressure measurements, and compliance with a standardized sodium diet. However, participants will benefit from closer doctor contact compared to standard outpatient clinic visits.

Currently, available treatment options to delay progression CKD are limited. This study may contribute valuable knowledge regarding the efficacy and safety of the IMP in a disease area that needs improved treatment options and a deeper understanding of disease mechanisms. As the target mechanism of CM is not yet fully explored, any beneficial effects discovered could be additive to existing pharmacological treatments. Regardless of the study results, it will contribute with important knowledge on the efficacy of the IMP and contribute to the broader understanding of disease mechanisms in CKD.

13 Data Handling and Record Keeping

13.1 Trial Master File and Source Data

According to requirements from the GCP-unit, a Trial Master File will be created, containing source data including the protocol and its amendments, all correspondence with regulatory authorities including the Danish Medicines Agency, the Ethics Committee, and the Danish Data Protection Agency, informed consent documents, staff curriculum vitae, forms, delegation logs, and other relevant documents and correspondence. All source documentation will be securely stored under the responsibility of the Principal Investigator. The Principal Investigator will maintain complete and accurate records to ensure comprehensive documentation of the trial's execution and enable subsequent data verification.

13.2 Use of Case Report Forms (CRF)

The Sponsor is responsible for maintaining an updated and accurate electronic CRF (eCRF) designed to accurately record all study-related observations and data using the REDCap database. Recording in the eCRF should generally occur following each study visit. Data entry into the eCRF should be done comprehensively and carefully to ensure correct data interpretation. The eCRF have a logging system that logs the date, time, and action taken in the eCRF, and the person responsible for this action. If any corrections are introduced, previous text or data will remain logged in the eCRF logging system for transparency and traceability. The eCRF will only be considered complete once all data, including any missing, incorrect, or inconsistent entries, have been accounted for.

13.3 Data handling

All personal data and study materials are protected in compliance with national law, the EU General Data Protection Regulation (GDPR), and the Data Protection Agency. Blood samples and subject-specific documents are supplied with a unique study identification code to prevent direct subject identification. After study completion, Study data will be stored in coded form for a duration of 25 years in accordance with the recommendations of CTR nr. 536/2014. After this period, the data will be securely destroyed.

13.4 Computer Systems

Data processing will be conducted using a validated computer system that complies with regulatory requirements. For this study, source data will be sourced from medical records. Laboratory results (blood and urinary samples) will be extracted from the electronic medical record and added to the eCRF. Data regarding blood pressure, body water measurements, body weight, height, medication administration, and side effects will be directly recorded in the eCRF.

13.5 Data Entry

To enter, review, or correct study data, all personnel must log into the RedCap computer system using their confidential username and password.

13.6 Data Validation

Validation will be performed via review of the data in the eCRF to ensure accurate and reliable data. The CRF will be reviewed and signed by the investigator.

13.7 Biological material

Throughout the study, participants will undergo blood sampling four times, with a maximum of 50 mL blood distributed in 6 sample tubes at each blood sampling session. The total blood volume collected throughout the study will not exceed 200 mL. Additionally, four fresh urine samples, each approximately 120 mL, will be collected, totaling a maximum of 500 mL. Moreover, there will be a total of three instances of 24-hour urine collection.

13.8 Research biobank

In collaboration with Open Patient Data Explorative Network (OPEN), a research biobank will be established. This biobank will house blood and urine samples collected from study participants. Most of these samples will undergo immediate analysis, while some will be stored for later analysis during the study period.

Sample analysis will be conducted at the laboratories of Odense University Hospital (OUH), the Department of Cardiovascular and Renal Research at the University of Southern Denmark or the Department of Clinical Pharmacology, Aarhus University Hospital.

Any surplus biological material remaining after the study's conclusion will be securely stored for a period of 15 years. The storage is for potential use in future research studies. Access to the research biobank will be regulated by the principal investigator.

The biological samples will be stored in the biobank at Department of Clinical Biochemistry at OUH. The samples will be pseudonymized and the sample code list (code key) will be securely stored separately from the samples and will be under the custody of the sponsor and principal investigator. They will be responsible for maintaining the link between the pseudonymized samples and their original participant identities.
For analysis samples will be transferred in pseudonymized form to laboratories with restricted access where they will be analyzed. Remaining material will be brought back for storage in the biobank.
The primary objective of this biobank is to support research directly related to the objectives of this trial. However, it will also serve as a resource for potential future, unspecified research, after approval from the Danish Ethics Committee and renewed informed consent of the participants. Participants will receive information about this biobank during the oral information session and will be provided with written materials.

14 FINANCING AND INSURANCE

The study is initiated by the sponsor. Non-commercial funding finances the medication. There is no involvement from industry partners in the project. There will not be any remuneration during the project, however travel expenses will be refunded.
In accordance with the relevant national regulations, subjects enrolled in the study are under The Danish Patient Insurance that covers all study subjects as guaranteed by The Danish Act on the Right to Complain and Receive Compensation within the Health Service administered by The Patient Assurance Association.

15 PUBLICATION POLICY

Following the completion of the study, the trial results, regardless of whether they are positive, negative, or inconclusive, will be published promptly and in a professionally responsible manner. This publication will be conducted in compliance with the Act on Processing of Personal Data. In cases where the results cannot be published in a journal, they will be published in another way. It is the responsibility of the investigator to maintain the confidentiality of study data ant to consult with the sponsor prior to the submission of any study data for publication.
At this stage, a final list of authors cannot be determined; however, all researchers who have met the Vancouver criteria for authorship will be included in the final publication.
Furthermore, the summary of the results must be submitted to the CTIS portal without undue delay and no later than one year after the trial has concluded.

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