Multifactorial intervention to reduce cardiovascular disease in T1D

A prospective, randomised, open-labelled, multi-center study

Title

Multifactorial intervention to reduce cardiovascular disease in T1D

Short title

The Steno 1 study

Setting

Steno Diabetes Centers and 14 partner clinics in Denmark

EU CT number: 2023-505794-32

Principal investigator

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Investigators

Listed in Appendix 1

Study sites:

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Sponsors medical advisors for the trial: Peter Rossing

This trial will be carried out in accordance with the protocol and current statutory requirements/legislation.

Timeline for the trial

Project initiation	**March 2023**
Protocol finished	January 2024
Approval from CTIS	May 2024
First patient first visit (FPFV)	July 2024

Last patient last visit (LPLV)	July 2029
Data analysis	August 2029
Conference presentation and publications[a]	End of 2029

a) Baseline and intermediate outcome will be presented and published during the study.

This clinical trial will be conducted in compliance with the protocol, with this regulation and with the principles of good clinical practice.

Table of content

Abbreviations

ACEi	**Angiotensin-Converting Enzyme inhibitors**
AE	**Adverse Event**
ADA	**American Diabetes Association**
ARB	**Angiotensin II Receptor Blocker**
CGM	**Continuous Glucose Monitor**
CKD	**Chronic Kidney Disease**
CVD	**Cardiovascular Disease**
DFU	**Directions for use**
DKA	**Diabetic Ketoacidosis**
DN4	**Douleur Neuropathique en 4 Questions**
DPN	**Diabetic peripheral neuropathy**
EASD	**The European Association for the Study of Diabetes**
EMA	**European Medicines Agency**
ESKD	**End Stage Kidney Disease**
eGFR	**Estimated Glomerular Filtration Rate**
EQ5D	**European Quality of Life 5 Dimensions**
GLP-1RA	**Glucagon Like Peptide 1 Receptor Agonist**
GCP	**Good Clinical Practice**
HF	**Heart failure**
HFrEF	**Heart Failure with reduced Ejection Fraction**

HHF	**Hospitalization for Heart Failure**
IMPD	**Investigational Medicinal Product Dossier**
IRB	**Institutional Review Board**
IEC	**Independent Ethics Committee**
ITT	**Intention-To-Treat**
MACE	**Major Adverse Cardiovascular Endpoints**
MFI	**Multifactorial Intervention**
MNSI	**Michigan Neuropathy Screening Instrument**
MODY	**Maturity-Onset Diabetes of the Young**
NRS	**Numerical Rating Scale**
nsMRA	**Non-Steroidal Mineralocorticoid Receptor Antagonist**
PAID5	**The Problem Areas in Diabetes Scale 5**
PCSK9i	**PCKS9 inhibitor**
PI	**Principal Investigator**
PROBE	**Prospective Parallel-group randomized, Open Blinded endpoint evaluation**
RAAS	**Renin Angiotensin Aldosteron System**
RCTs	**Randomized Controlled Trials**
RSI	**Reference Safety Information**
SAE	**Serious Adverse Event**
SDCC	**Steno Diabetes Center Copenhagen**
SDCO	**Steno Diabetes Center Odense**
SDCA	**Steno Diabetes Center Aarhus**

SDU	**University of Southern Denmark**
SGLTi	**Sodium-Glucose Cotransporter Inhibitor**
SGLT2i	**Sodium-Glucose Cotransporter-2 Inhibitor**
SmPC	**Summary of Product Characteristics**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
T1D	**Type 1 Diabetes**
T2D	**Type 2 Diabetes**
UACR	**Urinary Albumin-to-Creatinine Ratio**

Summary

Background: Individuals with type 1 diabetes (T1D) are at high risk for cardiovascular disease (CVD). Even with optimal glycaemic control, the risk is doubled compared to healthy individuals. Treatment of type 2 diabetes (T2D) is based on multifactorial intervention (MFI). The development of new drug classes has had profound impact on treatment guidelines through a documented reduction in mortality and morbidity in individuals with T2D. MFI acknowledges the need for interventions directed towards several risk factors for CVD, and not focus merely on glucose levels. A fundamental change in risk management with a strong focus on MFIs to lower CVD risk in individuals with T1D and comorbidity of CVD, Chronic kidney disease (CKD), Heart failure (HF) or obesity, has the potential to improve morbidity and survival in T1D.

Objective: The aim of the Steno 1 study is to test a strategy of intensified care based on MFI in individuals with T1D at high risk of CVD with ambitious treatment targets compared to standard of care, while simultaneously investigating the safety and efficacy of 40 mg finerenone in individuals with T1D in risk of CV death and hospitalization for heart failure (HHF). We hypothesize, that intensive treatment based on MFI reduces major adverse cardiovascular endpoints (MACE), hospitalization for heart failure (HHF), progression of kidney disease and mortality.

Design: This study uses a PROBE design (prospective, parallel-group randomised, open, blinded endpoint evaluation), as it will not be possible to mask the MFI. The study is a superiority trial.

Patient population: High-risk individuals with T1D of >10 years duration (>40 years of age with presence of either CKD, CVD, HF, obesity or a >10% 5-year CVD risk determined by the Steno T1 Risk Engine). Participants are recruited from Steno Diabetes Centres or partner clinics which will constitute the sites.

Randomisation: Participating sites will be randomised. Before initiation of the study, we will form two strata (large patient pool, intermediate- small). Within each stratum, participating sites will be randomised to either group A or group B. Group A will receive current guideline-recommended standard of care and group B will receive the multifactorial risk based intensive therapy. Participants are allocated to sites based on geography (current affiliation) and not based on phenotype.

Intervention: For the intensively treated group, the MFI will be determined by the risk profile and risk markers of each individual aiming for ambitious treatment targets for CVD risk factors (glucose, blood pressure, lipids) and the participants will be allocated to supplementary therapy of semaglutide, sotagliflozin and finerenone according to clinical characteristics and a prespecified algorithm.

Endpoints: The primary endpoint is to determine whether an intensified strategy based on MFI is superior to standard care with respect to development of MACE+HHF (composite of time to first non-fatal myocardial infarction, first non-fatal stroke, cardiovascular death or first hospitalization for heart failure). Secondary endpoints are to 1) determine whether MFI is superior to standard care with respect to all-cause mortality, or a composite endpoint of renal function (end-stage kidney disease (ESKD) (dialysis, renal death, transplantation) or >50% sustained decline in eGFR), or on the composite endpoint CV death and HHF compared to standard of care, 2) to determine whether MFI including the use of SGLT2i and GLP1RA leads to an increased frequency of diabetic ketoacidosis compared to standard of care.

Timeframe: First patient first visit July 2024. Last patient last visit July 2029.

1. Background information

1.1 List of all investigational medicinal products:

The study evaluates a strategy of intensified multifactorial intervention which in addition to the ambitious targets for CVD risk factors include the following products used based on participant characteristics according to a prespecified algorithm (figure 1).

GLP-1RA treatment: Semaglutide (Ozempic) once weekly subcutaneously individually stepped highest tolerable dose according to standard guidelines aiming at 1 mg/week. Indication: Persons with BMI>27 kg/m^2, persons with BMI>25 kg/m^2 and ischemic heart and vascular disease and/or stroke, and persons with >10% increased 5-year risk of atherosclerotic cardiovascular events as determined by the Steno Type 1 Risk Engine.

SGLTi treatment with sotagliflozin 200 mg once daily. Indication: Persons with a diagnosis of CKD (UACR >30 mg/g and/or eGFR <60 ml/min/1,73 m^2), persons with a diagnosis of HF, and persons with >10% increased 5-year risk of atherosclerotic cardiovascular event as determined by the Steno T1 Risk Engine.

Finerenone (Kerendia): 10-20 mg once daily titrated to 20-40 mg. Indication: As add-on in persons with persistent albuminuria (>30 mg/g) despite RAS blockade and sotagliflozin or for persons with a diagnosis of HF (Except HFrEF (Heart Failure with reduced Ejection Fraction)).

1.2 Introduction

Individuals with T1D are at high risk for CVD. Even with optimal glycemic control, their risk is doubled compared to healthy individuals (1) . In Denmark, people with T1D have up to 10 life-years lost in comparison to the general population (2) . In the 2019 guideline for prevention of cardiovascular disease issued by the European Society of Cardiovascular disease, individuals with T1D of more than 20 years duration are classified as having “very high risk” of CVD. In Denmark, the Steno Type 1 Risk Engine can be used to estimate the cardiovascular risk of an individual with T1D to guide the decision to recommend treatment (3). Unfortunately, we have found that less than 40% of the adult T1D population in Denmark are treated with basic cardioprotective drugs as statins for lipid-lowering and renin-angiotensin system inhibitors for hypertension and kidney protection, despite having an overall increased CVD risk (4).

Although insulin treatment of T1D has changed, new cardio-renal protective medications have not been introduced for the management of T1D. In contrast, treatment of type 2 diabetes (T2D) is based on multifactorial intervention (MFI). The development of new drug classes as sodium glucose co-transporter 2 inhibitors (SGLT2i), GLP-1RA and nonsteroidal mineralocorticoid receptor antagonists (nsMRA), has had profound impact on treatment guidelines based on documented reductions in mortality and morbidity in individuals with T2D (5–16). Multifactorial intervention acknowledges the need for interventions directed towards several risk factors for CVD, as opposed to focusing merely on glucose levels. This approach was first tested at Steno Diabetes Center with the Steno 2 study, where the major part of the risk reduction could not be attributed to a reduction in HbA_{1c}, but rather a concerted effect of reducing all risk factors (17). Therefore, a fundamental change in risk management with a strong focus on multifactorial interventions to lower CVD risk in individuals with T1D and comorbidity of CVD, CKD, HF or obesity, has the potential to improve morbidity and survival in T1D.

Traditionally, HbA1c has been the marker used for estimating glucose levels, with its close correlation to mean blood glucose. There is a substantial body of evidence linking increases in HbA1c with diabetes-related complications. Yet, patients with identical HbA_{1c} values can have vastly different complications rates—for example, only 11% of the variation in retinopathy risk may be explained by total glycemic exposure in the DCCT cohort (18). With the increasing use of continuous glucose monitoring (CGM) especially among people with type 1 diabetes, there is a growing opportunity to acquire a more nuanced understanding of the effects of various glucose metrics, including time spent in different glucose ranges and glucose variability. Currently, there are no longitudinal intervention studies to establish an association between glycemic variability and the progression of cardiovascular risk and morbidity, going beyond other interventions such as reduced HbA1c and treatment with cardioprotective drugs.

Diabetic peripheral neuropathy (DPN) is the most common complication to diabetes mellitus, but the pathophysiology remains unknown. However, the major risk factors for developing DPN are closely associated with cardiovascular risk factors such as hypertension, hypercholesterolemia, obesity, and smoking (19,20). It is therefore likely that targeting these risk factors will reduce the

incidence of DPN, which would ultimately reduce the burden of major complications such as neuropathic pain, loss of protective sensation, foot ulcers, and amputation (21).

1.3 Targets for intervention

Chronic kidney disease (CKD) and albuminuria in T1D are risk factors not only for end stage kidney disease (ESKD) but also for CVD. Annual incidence of albuminuria is between 1.3% -3.8% and incidence of developing impaired kidney function (eGFR <60 ml/min/1.73 m^2) is between 2–4% per year (22). The cumulative incidence of CKD is about 21% (23). Large meta-analyses of observational and randomised trials in T2D indicate that a 30% reduction from baseline levels of elevated albuminuria, leads to a reduced risk of CVD and CKD, but dedicated studies in T1D are lacking. Both SGLTi and treatment with the new non-steroidal mineralocorticoid receptor antagonist finerenone (24,25), have documented effects on individuals with T2D and CKD, but it remains to be established whether these drugs have the same effect in T1D. The SGLTi were approved in Europe and Japan as adjunctive therapy for improved glycose control in persons with T1D between 2019 and 2021 but was withdrawn again from the European market. Since then, there has been an ongoing discussion and weighing of the potential benefits on the heart and kidneys in high-risk persons with T1D and the risk of DKA. It is assumed, that the major risk reductions in the risk of CVD and kidney failure seen in the large randomised controlled trials (RCTs) in persons both with and without T2D will be the same in T1D, but we lack large RCTs to show it. Smaller studies have been conducted, showing a clinically relevant effect on albuminuria in persons with T1D and albuminuria (26).

Heart failure (HF) in T1D has an incidence of 5.6 per 1000 patient years (27), which is more than 3 times that of the general population. Also, HF increases risk of CVD, CKD and hospitalization for HF. Treatment options follow conventional HF treatment, with the important exception of SGLTi. Since SGLTi have demonstrated impressive effects on heart failure in individuals with and without T2D (28–30), it is expected that persons with T1D could also benefit from these agents. However, the lack of studies in T1D and the potential risk of diabetic ketoacidosis(31), has hindered the use in persons with T1D, but proper identification of the right persons to receive this treatment could lead to safe use where the benefit outweighs the risks (32).

The risk of *Ischaemic heart disease* in T1D depends to a large extent on the presence of different factors such as cardiovascular risk factors (elevated LDL-cholesterol, hypertension, and smoking), factors more specific to diabetes (HbA_{1c}, and micro- and macroalbuminuria) and non-modifiable factors such as age, family history and sex. In T1D optimal levels of modifiable risk factors are associated with lower risk of CVD(33). In a meta-analysis involving 166,027 persons with T1D and matched controls from the general population, the overall relative risk for coronary heart disease was 9.38 (95% CI 5.56, 15.82), and for myocardial infarction 6.37 (95% CI 3.81, 10.66), compared with controls without diabetes(34). A large Swedish study estimated the risks of ischaemic heart disease according to diabetes duration and demonstrated high relative risks in persons with T1D with onset at an age of 10 years and younger compared with matched control participants from the general population. The relative risks were lower among those with onset after 20 years of age and overall, with highest risk in women(35). Targeting the modifiable risk factors for ischaemic heart disease will contribute to a lower risk as described in the sections below.

Obesity (BMI>30 kg/m^2) is becoming increasingly prevalent in T1D. More than half of the adult population with T1D is overweight or obese(36), today 16.7% of the adults with T1D at Steno Diabetes Center Copenhagen have a BMI above 30 kg/m^2. Like people without diabetes, the risk of death increases with increasing BMI mostly driven by CVD(37). There is scarce evidence evaluating non-pharmacological weight loss interventions in T1D. A retrospective nested-control study in persons with T1D showed that lifestyle-induced weight loss improved glycaemic control and reduced insulin doses compared with a control group(38). Evidence of weight loss during treatment with a GLP-1RA in T1D is intriguing with body weight reductions of 2.2% to 6.6% with a significant effect already after 4 weeks' treatment(39–43). There are currently no studies evaluating the effect of GLP1-RA on incidence of CVD in T1D, but the results from T2D hold promise for a reduction in CVD risk.

Dyslipidemia is contributing to the cardiovascular risk in T1D. However, only limited data are available to document the effect of lipid lowering medication on cardiovascular risk in individuals with T1D. Subgroup analysis of the limited number of individuals with T1D included in the lipid lowering trials indicates a similar risk reduction(44,45). Therefore, there is potential for a substantial cardiovascular risk reduction in individuals with long-duration of T1D with high

cardiovascular risk (but without history of CVD or CKD) by lowering the treatment goal to the suggested goal of 1.4 mmol/L(46). If the benefit of lipid lowering treatment is similar to what is observed in other high-risk populations, an additional 0.4 mmol/L lowering of LDL cholesterol will provide a ≈8% relative risk reduction(44).

Blood pressure is an independent risk factor for CVD in T1D. A recent meta-analysis of 344,716 persons treated with blood pressure lowering agents demonstrated a clear reduction in CVD risk irrespectively of baseline blood pressure level (47). A 5 mm Hg reduction of systolic blood pressure reduced CVD risk by 10%, with reductions in risk of stroke, HF, ischemic heart disease, and cardiovascular death. The SPRINT trial indicated a benefit of intensive blood pressure treatment with lower treatment targets than those currently recommended(48). It is likely that stricter blood pressure targets in T1D could reduce CVD risk. If the effect is similar to other populations, a lowering of the target for systolic blood pressure by 10 mmHg could translate into a 20% relative risk reduction.

1.4 Benefits and risks

As has been seen in studies in T2D, many benefits of an intensified treatment and MFI can be anticipated in study participants, i.e., improved glucose control, weight loss and a reduction in overall cardiovascular risk.

Among immediate risks for participants, there is a minimal risk of infection at the puncture site after venous puncture related to blood sampling.

Regarding treatment with GLP-1RA: The treatment with GLP-1RA in T1D is usually well tolerated with generally mild tolerable primarily expectable gastrointestinal site effects, however with a slightly increased risk of hypoglycaemia and hyperglycaemia with ketoacidosis(39,40). However, two Danish studies investigating the effect of GLP-1RA on glycaemic control in T1D did not show any sign of increased risk of diabetic ketoacidosis (DKA)(41,49). Participants will be equipped with a ketone measuring device and instructed to measure ketone levels in case of current symptoms (malaise, fever, nausea, loss of appetite, diarrhea, stomach ache). Participants will be carefully selected and educated in the risk of this treatment and will have the usual access to the clinic along with instructions to follow local procedures if needed. DKA is a very serious complication but

with information and education we believe that the likelihood of this event to occur is very small. If ketone levels rise or the participant should develop acidosis, emergency treatment of DKA can be initiated immediately via the local emergency department.

The investigators will ensure that participants are:

- Adherent to prescribed diabetes regimen
- Willing/able to perform all prescribed diabetes self-management tasks
- Performs blood glucose monitoring or uses continouous glucose monitor (CGM) as prescribed
- Willing/able to perform ketone testing as prescribed
- Has received education/training in ketone testing and interpreting/acting upon test results
- Will be adviced on how to procure ketone testing materials.
- With no or moderate use of alcohol judged by the treating physisian;
- No use of illicit drugs
- Not diagnosed with congestive heart failure NYHA class IV
- Caution should be exercised when using semaglutide in participants with diabetic retinopathy.

Investigators are instructed to observe the need for reduction between 10-20 % in insulin dose after initiation of GLP-1RA treatment.

<u>Regarding treatment with SGLTi:</u> In the previous placebo-controlled trials on SGLTi for T1D, the risk of DKA was found to be between 2-4%. In a recent retrospective observational study in Denmark estimating the incidence of DKA in Denmark in persons with T1D treated with SGLTi we found zero events of DKA (16). Participants will be equipped with a ketone measuring device and instructed to measure ketone levels if there is concurrent symptoms (malaise, fever, nausea, loss of appetite, diarrhea, stomach ache). Participants will be carefully selected and educated in the risk of this treatment and will have the usual access to the clinic along instructions to follow the local emergancy procedures if needed. DKA is a very serious complication, but with information and education we believe that the likelihood of this event to occur is very small. If ketone levels rise or

the participant should develop acidosis emergency treatment of DKA can be initiated immediately via the local emergency department.

The investigators will ensure that participants are:

- Adherent to prescribed diabetes regimen
- Willing/able to perform all prescribed diabetes self-management tasks
- Performs blood glucose monitoring or uses CGM as prescribed
- Willing/able to perform ketone testing as prescribed
- Has received education/training in ketone testing and interpreting/acting upon test results
- Has received written instruction on how to respond to elevated ketone levels.
- Has access to ketone testing materials.
- No or moderate use of alcohol;
- No use of illicit drugs
- Not having an ALAT X 3 the upper normal limit
- Upon medication commencement in a stable condition i.e. is not hospitalised due to surgery or acute medical illness
- Scheduled with relevant follow-up appointments including blood samples if receiving treatment with digoxin

The risks of genital infections and diarrhea in randomised trials are approximately 8-9%. If these events occur, relevant treatment can be initiated immediately by contact to the clinic.
SGLTi treatment *should not* be offered to participants on insulin pump therapy, to reduce risk of ketoacidosis. Investigators are instructed to observe the need for adjustment in insulin dose after initiation of SGLTi treatment.

<u>Regarding treatment with finerenone:</u> From the pooled FIDELITY analysis finerenone has been well described in more than 6500 persons with type 2 diabetes and CKD in the FIDELIO-DKD and FIGARO-DKD, trials demonstrating reductions in UACR and decreased risk of adverse kidney and CV events (24,25,50). Similar studies have not been conducted in type 1 diabetes. In the upcoming FINE-ONE trial, they aim to assess the efficacy and safety of finerenone, in addition to the standard of care consisting of ACEi or ARB treatment, compared with placebo in people with type 1 diabetes

and CKD (51). The hypothesis underlying the FINE-ONE trial is that finerenone will reduce UACR, and based on mediation analyses of the T2D studies with finerenone it is expected that this will lead to a reduction in CKD progression in persons with type 1 diabetes. (52–54). Treatment with finerenone carries a small risk for increase in hyperkaliemia. In the FIDELIO-DKD/FIGARO-DKD trial the incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (2.3/1.2%) than with placebo (0.9/0.4%)(24,25). In the Steno1 trial serum potassium and estimated glomerular filtration rate (eGFR) will be measured to determine if finerenone treatment can be initiated and participants will have their serum potassium levels measured after 4 weeks to secure whether it is safe to continue the treatment and increase dose according to the titration algorithms used for type 2 diabetes with CKD.

The investigators will ensure that participants are:

- Not treated with any strong inhibitors of CYP3A4 (i.e. itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin nefazodone)
- Not diagnosed with Addison's disease
- Instructed not to consume grapefruit juice while treated with finerenone

Regarding hypoglycemia and severe hypoglycemia: SGLTi and GLP1-RA treatments can affect glucose levels, SGLTi however without increasing the risk of hypoglyceamia. If the investigator finds it necessary the participants will be instructed to reduce daily insulin doses when treament with SGLTi and GLP1-RA are initiated. The particpants will be informed on the effect on blood glucose.

2. Study population

High-risk individuals with T1D of >10 years duration (>40 years of age with presence of either CKD, CVD, HF, obesity or a >10% 5-year CVD risk determined by the Steno T1 Risk Engine). Participants are recruited from the Steno Diabetes Centres or the 15 partner clinics, and will continue in usual clinical care during the study, even if the center is randomised to intensive therapy, as this should be incorporated pragmatically in the usual clinical routine. As always additional visits may be added for control of riskfactors and titration of medication at the discretion of the investigator.

The original Steno T1 Risk Engine for CVD outcome was developed using clinical data from patients treated at Steno Diabetes Center Copenhagen which was linked to relevant national health registers for the period January 1st 2001 to September 30th 2013. To evaluate risk using the Steno Type 1 Risk Engine, it requires specific inputs, including: age, sex, diabetes duration, HbA1c, systolic blood pressure, presence of microalbuminuria or macroalbuminuria, eGFR and current smoking and regular exercise .The Steno Type 1 Risk Engine has been described in detail in a previous paper (3). Prior to patient recruitment, the Steno T1 Risk Engine will be recalibrated using the same data sources as for the original development but updated to year 2022.

2.1 Selection of trial subjects and criteria for inclusion in and exclusion from the trial

Inclusion criteria

1. Male or female persons ≥40 years old with T1D (diagnosis before age 30 with insulin from onset or if diagnosis after 30 years of age insulin from onset and DKA or positive autoantibodies (in accordance with local guidelines), or confirmed, at the investigator discretion by the available medical records) during >10 years.
2. Presence of chronic kidney disease (UACR >30 mg/g or eGFR < 60 ml/min/1.73 m^2) **OR** history of cardiovascular disease (previous myocardial infarction, stroke or angina) **OR** history of heart failure **OR** obesity grade 2 and 3 (BMI>35 kg/m^2) **OR** 5-year CVD risk >10% according to Steno Type 1 Risk Engine.
3. Fertile females must use highly efficient chemical, hormonal and mechanical contraceptives during the whole study and at least 2 months after cessation of study drug. The following contraceptive methods are approved: IUD or hormonal contraception that inhibits ovulation, i.e. pills, implantations, transdermal patches, vaginal ring or depot injection. Alternatively, be in menopause (i.e. must not have had regular menstrual bleeding for at least one year), have undergone bilateral oophorectomy or have been surgically sterilized or hysterectomised at least 12 months prior to screening.
4. Ability to communicate with the investigator and understand informed consent.
5. Given written informed consent.
6. For the CGM sub-study: Using CGM at inclusion, as part of their usual diabetes treatment.

Exclusion criteria

1. T2D, Maturity-onset diabetes of the young (MODY), secondary diabetes.
2. History of pancreatitis.
3. Body mass index < 18.5 kg/m^2
4. Females of childbearing potential who are pregnant, breast-feeding, intend to become pregnant or are not using adequate contraceptive methods.
5. Known or suspected abuse of alcohol or recreational drugs.
6. Participant in another drug-intervention study.
7. CKD stage 5.
8. For the sub-study on CGM if for some reason the participant chooses no longer to use CGM

2.2 Recruitment

The recruitment of eligible participants can be by either of the two methods described below.

1.

The first act of recruitment is when a medical doctor affiliated with the clinical trial (if it is not the PI, it will be a medical doctor who has a written agreement with the PI) identifies potential participants during a routine visit at the outpatient clinic. During the routine visit the doctor has access to the medical record and is therefore able to assess eligibility for inclusion in the study. The potential participant will be orally informed about the study and will be given written information about the study (Steno1_participantinformation) containing a weblink/QR code leading to a website with an informative video* and a telephone number to call if interested in participating in the trial. The brochure "Your rights as a participant in a clinical trial with medical products, will be handed out. The medical doctor will ask for consent to contact the potential participant after 14 days by telephone if he/she has not contacted the site within these 14 days. This consent will be documented in the electronic health records. This to follow up on whether or not he or she wishes to participate in the study. At this telephone call performed by a designated study nurse or medical doctor an inclusion visit will be scheduled if the participant wishes to participate. At the inclusion visit a medical doctor (if it is not the PI, it will be a medical doctor who

has a written agreement with the PI) will ensure before the potential participant gives consent that the information given is understood.

It will be emphasised that participation is voluntary, and that consent can be withdrawn at any time without consequence for the participant and that the potential participant will have the opportunity to consider final participation for as long as they want and that they have the right to minimum 24 hours. If the potential participant wants to participate the participant will sign the informed consent papers, or an invitation via Digital Post (borger.dk, e-boks.dk, and Mit.dk) will be send and allow the potential participant to fill out an informed consent electronically. When the informed consent is registered a questionnaire will be presented. Regardless, whether the questionnaire is answered, a digital copy of the informed consent will be sent to the participant via Digital Post. The informed consent will be signed by a medical doctor (if it is not the PI, it will be a medical doctor who has a written agreement with the PI).

2.

Due to the pragmatic nature of this trial, included sites are also able to recruit eligible participants by the following methods instead of using the run-in visit: Information on eligible participants at the including site who fulfils inclusion criteria, is disclosed to the investigators by the head of clinic at the including site. The same written participant information as mentioned above will be sent to eligible participants scheduled to a routine visit within the next 3-6 months, with the brochure: "Your rights as a participant in a clinical trial with medical products". A designated study nurse or medical doctor will inform the medical doctor who is scheduled to see the patient at the next routine visit, that this patient is a potential participant for the Steno 1 trial (if it is not the PI, it will be a medical doctor who has a written agreement with the PI). At the routine visit the potential participant will be orally informed about the study and asked if he/she would like to participate. Before the potential participant gives consent to participate it will be assured that the information given is understood and emphasised that participation is voluntary, and that consent can be withdrawn at any time without consequence for the care of the participant and that the potential participant will have the opportunity to consider final participation for as long as they want and that they have the right to minimum 24 hours. If the potential participant wants to participate the participant and medical doctor will sign the written informed consent during the routine visit on

paper. An invitation via Digital Post (borger.dk, e-boks.dk, and Mit.dk) will also be send and allow the potential participant to fill out an informed consent electronically. Because of potential delay from sending the informed consent electronically to the participant receives it, we will obtain informed consent on paper at the routine visit. The participant will also be asked to fill out the informed consent electronically, because it gives the participant the advantage of having an electronical copy in e-boks and it is also possible to have it registered on Sundhed.dk if the participant wishes so. When the informed consent is registered electronically a questionnaire will be presented. Regardless, whether the questionnaire is answered, a digital copy of the informed consent will be sent to the participant via Digital Post. *Appendix 3.

For both recruitment methods, some sites will offer eligible participants who have read the written information the option to attend either an online group information meeting with other interested eligible participants or a private online meeting. A medical doctor (if it is not the PI, it will be a medical doctor who has a written agreement with the PI) will provide oral study information via a secure virtual meeting. Only pre-registered individuals will be admitted after verifying their identity using their MitID. In group meetings, those who wishes to participate will be scheduled for an individualised follow up meeting to secure the potential participant has understood the given information, and for personalised discussions, including personal health related information. After attending an online information session, eligible participants will receive the informed consent form via Digital Post (borger.dk, e-boks.dk, and Mit.dk) for electronic signature. Eligible participants are also informed that they have a minimum of 24-hour consideration period to consider their decision. After signing, a digital copy of the consent form will be made available to participants. In cases of technical failures, participants will have the option to attend an in-person visit to complete consent procedures. Additionally, if a participant requests a physical information meeting at the site, and wishes to sign the consent form on paper, this option will also be available.

2.3 Patient withdrawal or treatment termination

- Withdrawal of informed consent

Termination of treatment with continued follow up of patients to the extent possible and at least in registers:

- For the CGM sub-study: If participants for some reason stop using CGM
- Pregnancy will lead to termination of study drugs and other medications not approved for use in pregancies (such as statins, ACE inhibitors, SGLTi, GLP1 and finerenone)
- Diabetic ketoacidosis if occuring during SGLTi or GLP1 RA treatment will lead to termination of these medications (unless there is another plausible explanation for the DKA)
- Hyperkalemia (5.5 mmol/l) during treatment with finerenone will lead to a treatment pause, when potassium is <5.0 mmol/l finerenone may be started again using 10 mg as initial dose at the discretion of the investigator and with control of potassium 4 weeks after initation or increase in finerenone doses
- Safety concerns judged by the investigator
- Non-compliance with the study protocol judged by the investigators
- Unacceptable adverse effects in the discretion of the investigator.
- Withdrawal on participants request will be accepted at any time without further justification or consequence to regular treatment at the clinic.
- Withdrawn patients will not be replaced.

2.4 Compliance

General compliance with any provided interventions (GLP1 RA, SGLT2i or nsMRA) will be monitored as use of study drugs throughout the study period.

3. Trial plan and trial design

3.1 Aim and hypothesis

The aim of the Steno 1 study is to test a strategy of intensified treatment using a multifactorial intervention in individuals with T1D at high risk of CVD with ambitious treatment targets, while simultaneously investigating the safety and efficacy of 40 mg finerenone in individuals with T1D in risk of CV death and hospitalization for heart failure (HHF). We hypothesize that the multifactorial

intervention reduces major adverse cardiovascular endpoints (MACE), hospitalization for heart failure (HHF), ESKD and mortality.

3.2 Study endpoints

Primary endpoint

- First major adverse cardiovascular events (MACE), and first hospitalization for heart failure (HHF). The primary efficacy analysis will analyse if a multifactorial intervention strategy is superior to standard care with respect to time to first event of the composite endpoint of first non-fatal myocardial infarction, first non-fatal stroke, cardiovascular death or first hospitalization for heart failure five years after inclusion of the first patient.

Secondary efficacy analyses

- Will determine whether a multifactorial intervention is superior to standard care with respect time to a composite endpoint of renal function (end-stage kidney disease (ESKD) (dialysis, renal death, transplantation) a sustained eGFR <15 ml/min/1.73 m^2 or >50% sustained decline in eGFR from baseline) compared to standard of care (sustained means change in eGFR sustained for at least 30 days).
- To determine the effect of multifactorial intervention is superior to standard of care with respect to the individual components of the composite endpoints.
- To determine whether a multifactorial intervention is superior to standard care with respect to all-cause mortality.
- To determine the effect of multifactorial intervention on the composite endpoint CV death and HHF.

Safety

- To determine whether a multifactorial intervention including the use of SGLTi and GLP-1RA leads to an increased frequency of diabetic ketoacidosis compared to standard care.
- To evaluate the safety and tolerability of a multifactorial intervention in this population.
- Number of subjects with hyperkalemia (serum potassium > 5.5 mmol/L).
- Number of subjects with severe hyperkalemia (serum potassium > 6.0 mmol/L).
- Number of subjects with hospitalization for hyperkalemia.

- Number of subjects discontinuing permanently or temporarily due to hyperkalemia.

Exploratory endpoints

- To assess the association between CGM-values in relation to the primary endpoint.
- To assess the association between CGM-data and HbA1c.
- To assess the association between glucose variability and MACE + HHF.
- To assess progression to diabetic retinopathy (degree 0 to degree 1-4)
- To assess 2-step or more progression of diabetic retinopathy (degree 0 to degree 2-4, degree 1 -> degree 3-4, degree 2 -> degree 4).
- To assess progression to proliferative diabetic retinopathy (degree 0-3 to degree 4)
- To determine the effect of the MFI on the development and progression of painful and painless DPN.
- To determine whether a multifactorial intervention is superior to standard of care in reducing the total number of lower extremity amputations.
- To determine whether a multifactorial intervention is superior to standard of care in reducing the total number of hospitalisations.
- To determine whether a multifactorial intervention is superior to standard care with respect to sustained reduction in kidney function (>30% decline in eGFR as well as >40% decline in eGFR).
- To determine whether a multifactorial intervention is superior to standard care with respect to quality of life as measured with the EQ5D questionnaire and diabetes-related emotional distress as measured with the PAID5 questionnaire.
- To assess the association between glucose variability (CGM-data) and the development of painful and painless DPN
- To determine the cost-effectiveness of the multifactorial intervention against the standard of care.

Intermediary outcomes (after 1 year of intervention)

- To determine whether a multifactorial intervention reduces urinary albumin to creatinine ratio (UACR) compared to standard of care.

- To determine whether a multifactorial intervention reduces HbA_{1c} levels compared to standard of care.
- To determine whether a multifactorial intervention reduces LDL cholesterol levels compared to standard of care.
- To determine whether a multifactorial intervention reduces BMI compared to standard of care.
- To determine whether a multifactorial intervention reduces NT-proBNP levels compared to standard of care.
- To determine whether a multifactorial intervention reduces hsCRP levels compared to standard of care.

Intermediary outcomes (after 3 years of intervention)

- To determine whether a multifactorial intervention reduces estimated 5- and 10-year cardiovascular risk as assessed using the Steno T1 Risk Engine compared to standard of care.
- To determine whether a multifactorial intervention reduces urinary albumin to creatinine ratio (UACR) compared to standard of care.
- To determine whether a multifactorial intervention reduces decline in eGFR compared to standard of care.
- To determine whether a multifactorial intervention reduces HbA_{1c} levels compared to standard of care.
- To determine whether a multifactorial intervention reduces LDL cholesterol levels compared to standard of care.
- To determine whether a multifactorial intervention reduces BMI compared to standard of care.
- To determine whether a multifactorial intervention reduces vibration perception (biothesiometry score) compared to standard of care.
- To compare incidence of diabetic ketoacidosis between the groups.

End of study (5 year) outcomes

All outcomes (primary, secondary, exploratory) will be compared between groups.

Long term follow-up (5 and 10 years after end of study, register based)

- Cardiovascular events (MACE+HHF) in both groups.
- Overall survival between the groups.
- Number of individuals developing the composite kidney endpoint and the individual endpoint ESKD in both groups.
- Number of lower extremity amputations between the groups.
- Incidence of diabetic ketoacidosis between the groups

3.3 Trial endpoints

Once yearly untill end of study endpoints will be registered in RedCAP from the electronic health records.

3.4 Trial design

This study uses a PROBE design (prospective, parallel-group randomised, open, blinded endpoint evaluation), as it will not be possible to mask the multifactorial intervention. The participants will know which treatment group they have been assigned to and so will their treating health care professionals. The endpoints will be reviewed in a blinded fashion by a data and safety monitoring board throughout the study, while the rest of the involved parties will remain unaware of the data until the trial's conclusion. This is a superiority trial. The study will end five years after the inclusion of the first participant.

3.5 Randomisation

Randomisation on center level was chosen as the intervention of the trial is more naturally implemented on a health care facility level, as the trial involves the implementation of a broad new treatment regime, and to avoid contamination, that the implementation of the new treatment regime affects the treatment of the participants in the control group. Before inititation of the study, we will form two strata (large patient pool, intermediate-small). Within each stratum, participating centers will be randomised to either group A or group B. The stratification is performed to ensure approximately equal numbers of patients in group A and B (55) and to ensure an approximate equal allocation to group A and B of sites of similar size. In accordance with this

allocation strategy, the two largest centers will be assigned to the large patient pool stratum, while the remaining centers will be grouped into the intermediate-small stratum. The randomization will be generated by an external statistician. Group A will receive current guideline-recommended standard of care and group B will receive the multifactorial risk based intensive therapy. Participants follow usual care at the sites they attend, thus they are allocated to centers based on geography and not based on phenotype. Hence, there is no reason to believe the variation between patients within a center is different than between patients from different centers. As a consequence, the centering is assumed not to affect the power or the sample size needed to conduct the study.

The randomisation of centers will be performed as close to study initiation as possible, but before the inclusion of the first participant as there will be a continuing inclusion of participants. To mitigate potential bias, participating centers are encouraged not to disclose to participants whether they belong to group A or B untill after obtaining written consent.

3.6 Description of the multifactorial intervention

For the intensively treated group, the multifactorial intervention will be determined by the risk profile and risk markers of each individual, see figure 1 below. The composition of the intervention will be guided by presence of CKD, CVD and obesity and will also comprise more ambitious treatment targets for blood pressure and lipid levels. This will lead to a sequence of added pharmacological treatments, to be added at study visits. As a participant may well have more than one risk profile, there may be overlaps between the interventions.

All trial medication will be provided to participants free of charge.

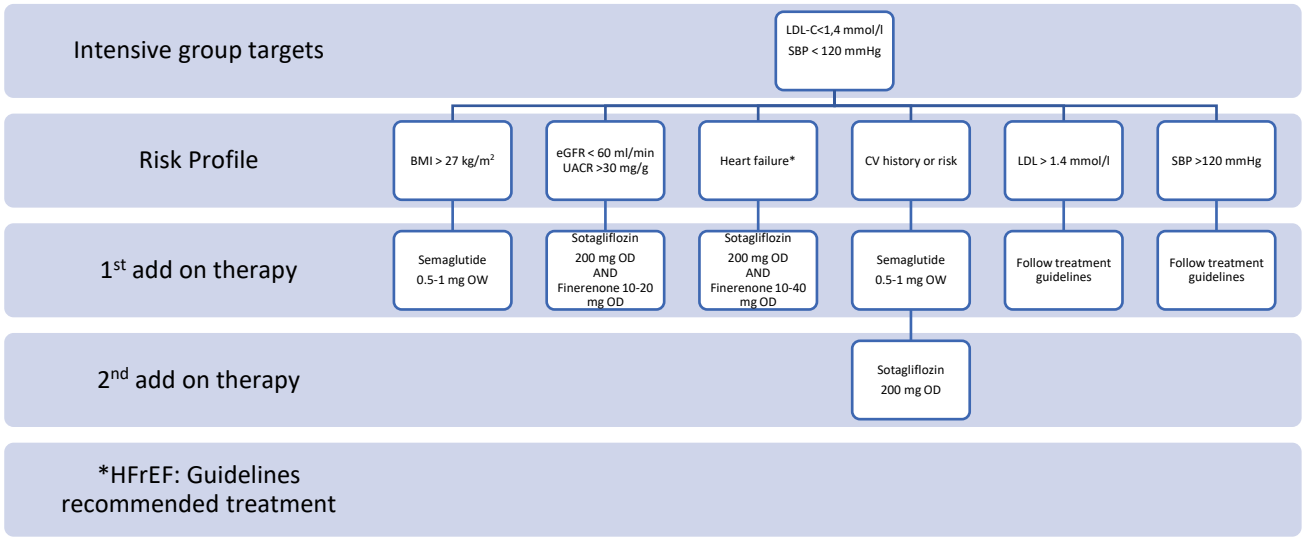

Figure 1. Multifactorial treatment algorithm.

3.7 Description of the standard intervention

During the entire study period the standard intervention will follow current Danish and international (American diabetes association (ADA)/the European association for the study of diabetes (EASD)) guidelines to ensure best practice for the standard of care group. For this reason similar risk factors will be treated as in the intensive group, however to a less ambitious treatment target for blood pressure (SBP <130-140 mmHg) and cholesterol level (LDL<1.4-2,5 mmol/l) and will not include the use of SGLTi, finerenone or GLP-1RA. If the future versions of the guidelines are updated and the drug classes become recommended, the standard intervention group will follow the old guidelines, and the study will continue. If a participant requests to be treated according to the updated guidelines recommending the specific drug classes, they will be discontinued from the study.

4. Study treatments

Investigational medicinal products are the GLP1-RA semaglutide 0.25-1.0 mg once weekly, the SGLT1/2 inhibitor sotagliflozin 200 mg and the ns-MRA finerenone 10 – 40 mg daily.

4.1 Investigational Medicinal Products (IMPs)

Study brand name	Ozempic	Sotagliflozin	Finerenone
Generic name and dose	Semaglutide 0.25-1 mg	Sotagliflozin 200 mg	Finerenone 10/20/40 mg
Dosage form	Injection	Tablet, film-coated	Tablet, film-coated
Route of administration	Subcutaneous	Oral	Oral
Dosing instructions	0.25-1 mg once weekly	1 tablet once daily	1 tablet once daily

Table 1 Investigational medicinal products

4.2 Status of development of the IMPs

Semaglutide is a glucagon-like peptide-1 receptor agonist with demonstrated cardiovascular benefit in persons with type 2 diabetes or obesity and a history of CVD. Semaglutide is currently being tested in persons with type 2 diabetes and CKD and the trial ((56)) has been stopped early because of efficacy but results have not been presented.

Sotagliflozin is a sodium-glucose cotransporter-1 and 2 inhibitor. It is an antihyperglycemic agent that decreases renal glucose absorption and increases urinary glucose excretion. Sotagliflozin has shown cardiovascular and renal benefit in persons with type 2 diabetes.

Finerenone is a non-steroidal mineralocorticoid receptor antagonist with demonstrated cardiovascular and renal benefit in persons with type 2 diabetes and CKD. Finerenone is currently being tested in non-diabetic CKD and in persons with type 1 diabetes.

All IMPs are authorized medications. Sotagliflozin is not marketed in Denmark. Semaglutide, sotagliflozin and finerenone are not approved for type 1 diabetes in the EU.

Initially pharmaceutical companies possessing marketing authorization for SGLT2i in Europe, were approached to explore the potential of collaboration. They did not consent to a collaboration.

In response, we reached out to Lexicon, a company with prior experience in T1D research, specifically with their SGLTi (57). Lexicon demonstrated an interest in establishing a collaborative partnership to advance our understanding of SGLTi treatment in individuals with T1D. Consequently, an agreement for collaboration was successfully reached.

4.3 Description and justification of dosage

According to the randomisation sites which are allocated to intensive treatment with multifactorial intervention will in addition to intensive risk factor control with standard medications apply the algorithm illustrated in figure 1 and the intensive strategy with MFI will include open label medications according to phenotype. As the medication is provided open label there will be no need for a code break procedure and there is no placebo.

Semaglutide

In this study we will use Semaglutide 1.34 mg/ml / Ozempic. The drug product provided is a clinic version of the marketed product. The clinic variant of the cartridge is produced with an army green closure cap compared to a dust green closure cap in the marketed Ozempic® product. Ozempic® is marketed in different pen variants for different intended dosing regimens. The push button and cartridge holder are light grey, and the pen can be found in both a 1.5 ml and 3 ml variant, dependent on the country. The clinic pen can be found in one variant to support 0.25 mg, 0.5 mg and 1 mg doses in a 1.5 ml variant. The push button and cartridge holder are light brown. Neither closure cap nor the pen is in contact with the product and the differences in colours have no impact on the stability of the product. Novo Nordisk A/S does not provide support for needles.

Individually stepped highest tolerable dose according to standard guidelines aiming at 1 mg/week. Eligible participants will be initiated on Ozempic 0,25 mg s.c. once weekly. After 4 weeks the participant will either be seen by their regular nurse/doctor or by telephone and if Ozempic is tolerated, dose will be increased to 0.50 mg and again after 8 weeks the dose will be increased to 1.0 mg/week. Directions for use (DFU) will be provided by Novo Nordisk A/S and will be handed out to the participant at first dispensing visit.

Sotagliflozin

In this study, we will use sotagliflozin 200 mg film-coated tablets. It contains the active substance sotagliflozin. The dose and route of administration are according to the marketing authorization. Initiation requires eGFR >20 ml/min/1.73m^2 whereas initiated medication can continue also in participants where eGFR declines below 20 according to KDIGO guidelines for the use of SGLTi.

Finerenone

In this study, we will use finerenone 10,20 or 40 mg film-coated tablets. It contains the active substance finerenone. In this study, finerenone 10-20 mg will be used as authorized in the European Union (EU) for type 2 diabetes with CKD. For the 40 mg dose participants with HF with or without CKD will be treated with finerenone 20 - 40 mg daily if eGFR > 60 ml/min/1.73m^2 and 10 to 20 mg daily if eGFR is <60 ml/min/1.73m^2. Participants with CKD without HF will be treated with finerenone 20 mg daily if eGFR > 60 ml/min/1.73m^2 and 10 to 20 mg if eGFR is <60 ml/min/1.73m^2. Serum potassium and estimated glomerular filtration rate (eGFR) will be measured to determine if finerenone treatment can be initiated:

Initiation of finerenone treatment:

Potassium (mmol/L)	**If treatment can be initiated:**	
≤ 4.8	Finerenone 10 mg treatment can be initiated in patients with eGFR >25 ml/min/1.73m^2	Finerenone 20 mg treatment can be initiated in patients with eGFR >60 ml/min/1.73^2
> 4.8-5.0	Finerenone treatment can be initiated with additional serum potassium monitoring within the first four weeks based on patient characteristics and serum potassium level.	
> 5.0	Finerenone should not be initiated.	

Continuation of treatment

Serum potassium and eGFR have to be remeasured four weeks after initiation, dose increase or restart of finerenone treatment. After that, serum potassium must be remeasured periodically and as needed based on patient characteristics and serum potassium levels.

Current serum potassium (mmol/L)	**Current finerenone dose (once daily)**	
	10 mg	**20 mg (if eGFR>60 ml/min/m^2)**
≤ 4.8	Increase to 20 mg	Increase to 40 mg
> 4.8 to5.5	Maintain 10 mg	Maintain 20 mg
> 5.5 to <6.0	Withhold Finerenone.	Down-titrate to 10 mg
≥6.0		Withhold Finerenone

Table 2 Finerenone dosing and potassium monitoring

The Summary of Product Characteristics (SmPCs)/Investigational Medicinal Product Dossier (IMPD) will be used as the reference document for the study medication.

4.4 Packaging and labelling of the medicin

Sotagliflozin will be provided by Lexicon, **Finerenone** by Bayer AG and **Semaglutide** by Novo Nordisk A/S.

Semaglutide will be labelled in accordance with EU CTR Annex VI.

Sotaglilozin and finerenone will be delivered in bulk packaging and additional labelling applicated following GMP-guidelines and CTIS regulation (EU) NO 536/2014.

4.5 Accountability procedures for the supply and administration of medicinal products

Study-drug for use at the participating sites will be delivered from Lexicon, Novo Nordisk and Bayer to Region Hovedstadens Apotek, and handled, if needed repackaged and labelled by authorized staff according to local regulation and GMP-guidelines at Region Hovedstadens Apotek. Specifically, semaglutide will not be repackaged or relabelled.

Study medication is received at the study sites by a designated person, handled safely and correctly, and kept in a secured, controlled, and monitored location, as dictated by local regulations. The investigator or delegate shall maintain records of the delivery to the trial site and the inventory at the site. The study medication will be stored according to the instructions specified on the drug labels, with access limited to authorized study staff.

If concerns regarding the quality or appearance of the investigational product arise, the investigational product will not be dispensed.

Study medication will be dispensed by the PI or delegate at each participating site. Documentation for participant-specific dispensing and returns will be maintained throughout the study.

4.6 Trial duration

The total study duration will be 5 years, counted form the day of the first included participant. Thus, the study is not event-driven, but interim analyses are planned to assess either futility or overwhelming efficacy during the study. The expected duration of the individual trial subject's participant in the trial will depend on the date of their first visit. Participants recruited when the trial is initiated will be followed in the trial for five years, participants recruited after 1 year will be followed for four years and so forth. End of trial will be 5 years after first patient first visit.

	Run-in	**Telephone**	**Study specific visits**				**Minimum 1 pr year (telephone,virtually or in person)**		**Annual visits (year 1-4)**	**End of study**
			Inclusion	If semaglutide is initiated	If finerenone is initiated	If sotagliflozin is initiated				
Week	-8 til -1	-8-1	0	4+8+12 (after initiation)	4 (after initiation or up-titration)	4 (after initiation)				5 years
Informed consent			x							
Blood samples			x		x		x		x	x
Urine samples			x						x	x
Biobank samples			x						x	x

	Run-in	**Telephone**	**Study specific visits**				**Minimum 1 pr year (telephone,virtually or in person)**		**Annual visits (year 1-4)**	**End of study**
Dispense of study medication			(x)	(x)	(x)		(x)		(x)	
Questionnaires			x[a]						x	x[a]
Safety monitoring				x	x	x	x		x	x
Endpoints									x	x
CGM-data			x				x		x	x
Retinal-fundus photography			x							x

Table 3 Study visits, [a]neuropathy questionaires (inclusion and end of study)

Blood samples: Estimated glomerular filtration rate (eGFR), p-sodium, p-potassium, p-creatinine, p-haemoglobin,

Urine samples: Urine albumin-creatinine ratio (UACR)

Biobank samples: 20 ml urine and 28 ml blood for future research. Four ml blood to analyse pro-brain natriuretic peptide (NT-proBNP), high sensitive C-reactive protein (hsCRP).

Questionnaires: The Problem Areas in Diabetes Scale 5 (PAID5), European Quality of Life 5 Dimensions (EQ5D), Michigan Neuropathy Screening Instrument (MNSI), Douleur Neuropathique en 4 Questions (DN4), Numerical Rating Scale (NRS) of pain in the feet (0-10).

Safety monitoring: with focus on drug specifik side effects, hypoglycemia, gastrointestinal side effects (semaglutide), hyperkalemia, table 2 (finerenone), hypoglycemia, ketoacidosis (sotagliflozin) and cardiac or kidney events or any infections.

Endpoints: MACE, HHF, dialysis, renal death, kidney transplantation, a sustained eGFR <15 ml/min/1.73 m2, death, eGFR values, UACR values. Diabetic ketoacidosis, extremity amputations, BMI, biothesiometry.

CGM-data: Data wil be uploaded and collected prior to visit. If data is not uploaded automatically the following will be collected manually from devices: time-in-range (TIR), time-above-range (TAR), time below range (TBR), mean sensor glucose, standard deviation (SD) on mean glucose, coefficient of variation (CV).

5. Visit description

Run in

The Run in visit will be performed as described in section 2.2 Recruitment.

Study specific visits

Inclusion: Patients will provide digital written consent, contribute samples to the biobank, CGM data collection, collect retinal-fundus photography and commence treatment. Questionnairs are send electronically as soon as the particant have signed the electronically informed consent.

From the patient records we will collect data on:

- In- and exclusion criteria
- Medical history: Personal data (birthday, gender, ethnicity), current medication, comorbidity, tobacco and alcohol use, hypoglycemia awareness.
- Diabetes status: duration, treatment, complications
- Clinical variables: Weight, height (BMI), blood pressure, heart rate.
- Electrocardiogram if available.
- Calculation of Steno Risk Engine score

The study visits will be modified according to the additional medication provided according to figure 1:

Treatment with semaglutide: Three study-specific visits approximately 4 weeks apart, focusing on safety monitoring (focus on gastrointestinal symptoms and hypoglycemia) and up-titration.

Treatment with finerenone: A study-specific visit 4 weeks after initiating treatment, monitoring potassium levels and safety. Up-titration according to potassium levels. After increase in finerenone doses p-postassium will be monitored after 4 weeks (table 1)

Treatment with sotagliflozin: A study-specific visit 4 weeks after starting treatment, monitoring safety (focus on hypoglycemia and blood ketone measurements).

If a participant qualifies for both sotagliflozin and semaglutide, a mandatory two-month interval must be observed between the two treatments before adding the second one. This precaution is implemented to reduce the risk of ketoacidosis.

Visits

Participants will be seen as a minimum twice per year. They will be seen in person at their annual visits and in person, by telephone or virtually at the visits in between. Before these visits the participants will have blood samples drawn. At the visits they will be asked in a structured way if there have been any cardiac-, kidney or diabetic ketoacidosis events or any infections. Since the participants are all persons with type 1 diabetes and various comorbidities, we will expect the majority to have regular visits 2-4 times per year before the inclusion in the study and that the

frequency of these visits will continue during the study and expected to be higher in periods with medication adjustments. These visits will provide safety monitoring and dispense of study medication.

Annual visits

Annual status visits with measures aiming for eGFR (CKD-EPI) and albuminuria. Assessments of neuropathy and retinopathy (at the interval prescribed by the local ophthalmologist) will also be recorded.

During each visit, all treatment goals will be evaluated, and medication will be adjusted.

Any new outcome (CV events, HHF, kidney endpoints, adverse events of interest) will be recorded and reported in REDCap.

As a standard practice during routine annual visits, the majority of the participating sites will measure blood pressure, weight, eGFR, p-haemoglobin, electrolytes, p-creatinine, lipids, HbA1c, p-TSH, p-ALAT, p-alkaline phosphatase.

End-of-study visit

Will involve biobank samples, questionnaires, safety monitoring, CGM data collection, retinal-fundus photography, and endpoints. Any new outcome (CV events, HHF, kidney endpoints, adverse events of interest) will be collected from the medical records and reported.

Study medication will be provided for GLP1 (semaglutide), SGLTi (sotagliflozin) and nonsteroidal mineralocorticoid receptor (finerenone).

5.1 Methods and measurements

The majority of visits will be included in the annual consultation cycle according to local practice. All routine clinical measurement will continue during the study, and clinical information gathered in the medical records will also be part of the clinical data collected for the study. The glycaemic treatment targets will be determined by the investigator based on hypoglycaemic and

cardiovascular risk independent of the treatment arm. The multifactorial intervention will not affect how the glycaemic control is handled.

6. Source data

Source documents for this study will include hospital records, CGM files, laboratory reports and procedure reports. These documents will be used to enter data in REDCap. Data reported in REDCap derived from source documents must be consistent with the source documents, or the discrepancies must be explained. Some data elements may be entered directly into REDCap (e.g., data not previously written down or electronically registered). For these data elements, REDCap is the source.

7. Compliance monitoring

Throughout the study, the study staff will remind the participants to follow the study procedures and requirements to ensure participant compliance. Documentation for participant-specific dispensing will be maintained throughout the study.

8. Endpoint assessments

All endpoints will be identified in the medical records and registered in REDCap. Additional data is retrieved from laboratory data; or through information received through standard medical practice. The following endpoints will be recorded in REDCap:

All deaths

Hospitalization for heart failure

Cardiac ischemic events (MI and unstable angina)

Cerebrovascular events (stroke)

Kidney endpoints:

– eGFR values <15 ml/min/1.73 m^2 (sustained for >1 measurement with 30-day interval between assessments)

- eGFR values to identify a sustained decline of ≥50% from baseline
- UACR values
- Initiation of chronic dialysis (>90 days, or if patient dies after dialysis initiation)
- Kidney transplantation

Diabetic ketoacidosis

Extremity amputations

Biothesiometry.

8.1 Quality of life and diabetes distress

To assess the impact of multifactorial treatment on quality of life and diabetes distress we will collect questionnaires at the start, the annual visits, and the end of the study. We will use the EQ5D, PAID5, and a validated questionnaire for hypoglycemia.

8.2 Cost-effectiveness analysis (CEA)

To assess the economic impact of the multifactorial treatment compared to standard care we will conduct a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) in conjunction with the study. By incorporating both CUA and CEA, we aim for a comprehensive evaluation of the intervention's cost-effectiveness. CUA offers a broad perspective by assessing the intervention's impact on quality of life and overall longevity, while CEA provides detailed insights into specific cardiovascular outcomes.

We will compare costs and effect over the 5-year intervention period outlined in the trial.

Effect measurements (overall survival, MACE and EQ-5D) and direct intervention costs will be collected within the main study, while remaining data will be obtained from national registers, as shown in Table 2.

The personal identification number (CPR) will be collected and processed by the sponsor, as this is required to obtain registry data and link them with existing study data.

Table 2 Registers utilised

Registers	Data

The National Patient Register (LPR)	Contains detailed information on all hospital admissions, outpatient visits, and emergency room contacts. It will be used to identify and calculate the number of inpatient and outpatient treatments at hospital (both somatic and psychiatric).
The National Health Insurance Service Registry	Contains information on healthcare service covered by the Danish National health Insurance. This includes data on services provided by general practitioners, specialist, psychologist, dentists, and other healthcare professional.
The Register of Pharmaceutical Sales	Track sales of prescription medicine at individual level and is used to calculate the costs of prescription medicine use.
Elderly documentation (Ældredokumentation)	Includes information on the allocated time for home care (comprising practical assistance and personal care in the individual's home), home assistance in nursing home, and the number of visits by home healthcare nurses.

9. Biobank

9.1 Research Biobank

A research biobank will be established at Steno Diabetes Center Copenhagen (SDCC)s containing biological material in the form of blood and urine. All samples are pseudoanonymised using a participant identification number, to which only those in charge of the trial have access. The samples will only be used for the purpose described in the protocol. After the analyses have been carried out and the experiment has been completed, the material will be destroyed by 2030 at the latest.

9.2 Biobank for future research

Participants will be asked for additional blood samples and urine samples for storage and future research. The participation in a future research biobank is voluntary and does not affect participation in the trial. Participants will receive information and will be asked separately for consent to participation in a future biobank (Steno1_participantinformation_futureresearch). The samples for future research will be stored in a freezer for a maximum of 25 years after end of the study at biobank facilities at Esbjerg Hospital/University of Southern Denmark. After 25 years, the samples will be destroyed. The blood sample is for the purpose of future research in markers of diabetes, cardiovascular disease, diabetic complications and their treatment and will only be used after approval from Research Ethics Committee and in agreement with project collaboration partners. Analysis of the pseudoanonymised samples can be carried out abroad (EU, UK, USA). If a participant wants the samples removed from the biobank later on, this will be complied with, but results already made from the biobank material will not be deleted.

The amount of blood and urine obtained per visit for the biobank is 28 ml blood and 20 ml urine.

10.Clinical trial regulations

The trial will be carried out according to the declaration of Helsinki, to the regulations for good clinical practice (GCP) and this protocol. The GCP-unit, Copenhagen University Hospital, will survey the trial. The trial protocol will be submitted to CTIS and approval for data storage will be obtained from the Danish Data protection Board.

11. Safety reporting

All IMPs have undergone thorough testing through extensive clinical trials to ensure their safety. Semaglutide have been evaluated for safety both in populations with and without T2D and has gained approval for both treatment of obesity and T2D (58,59). Sotagliflozin was previously approved by the European Medicines Agency (EMA) as adjunctive therapy for people with T1D based on comprehensive randomised controlled clinical trials (57,60,61). These trials showed an increased risk of DKA of 2-4 % but also a lower incidence of DKA after implementation of an enhanced risk mitigation plan, suggesting that the risk of DKA could be managed with education.

Finerenone has also been extensively studied in large cohorts with T2D and CKD (24,25,50), and is currently undergoing evaluation in trials related to heart failure and in trials including persons with type 1 diabetes and CKD (51). Finerenone has obtained marketing authorization for T2D and CKD and no adverse events directly attributed to T1D have been registered.

11.1 Definitions

Adverse events (AEs)

Adverse events are defined as any untoward medical occurrence in a participant to whom a medicinal product is administered, which does not necessarily have a causal relationship with this treatment.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence in a patient or study participant that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect

Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious;
2. There must be a certain degree of probability that the event is a harmful and undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected; that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the reference safety information (RSI).

11.2 Recording of AEs/SAEs/SUSARS

At planned clinical or telephone study visits, AEs will be assessed and recorded.

Conditions present before exposure to the study drug and anticipated day-to-day fluctuations of these conditions will not be reported as AEs but should be reported as medical history.

Abnormal laboratory test results or safety assessments considered clinically insignificant in the medical and scientific judgment of the investigator will not be reported as AEs.

11.3 Reporting of AEs and SAEs

Reporting of SAEs by the investigator to the sponsor

All SAEs should be reported to the sponsor.

11.4 Follow-up of adverse events

All AEs will be followed until they have abated or until a stable situation has been reached. Participants will be provided with a specific written instruction outlined in “Appendix C” guiding them on the appropriate actions to take, if there are any signs diabetic ketoacidosis. From this instruction they will be directed to contact the designated treatment site responsible for their care. In the event of hospitalisation with ketoacidosis the PI will register it in REDCap. SAEs need to be reported till the end of the study.

11.5 Reporting of SUSARs by the sponsor to the EudraVigilance database

The sponsor will keep detailed records of AEs reported to him/her by the investigator or investigators.

The sponsor will report electronically and without delay to the EudraVigilance database all relevant information about any SUSAR.

The period for the reporting of SUSARs by the sponsor to the European medical agency (EMA) will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;

- In the case of non-fatal or non-life threatening SUSARs, not later than 15 days after the sponsor became aware of the reaction;
- In the case of SUSARs which was initially considered to be non-fatal or non-life-threatening but turned out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, per section 2.4 of Annex III, submit an initial incomplete report followed by a complete report.

11.6 Annual safety report

Regarding investigational medicinal products, the sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of each investigational medicinal product used in a clinical study.

11.7 Temporary halt for reasons of participant safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize participant health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt but not later than 15 days from the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state. The investigator will take care that all participants are kept informed.

11.8 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigators will take appropriate urgent safety measures to protect the participants. In addition, the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay, but no later than seven days from the date the measures have been taken.

11.9 Final safety report

A final report regarding the AEs and SAEs will be uploaded via CTIS and included as part of the clinical study report after end of trial.

11.10 Safety reporting to product owner

The investigator should notify Lexicon, Bayer and Novo Nordisk when reporting SUSARs to health authorities. Reporting must be within day 15 from the investigator's first knowledge about a valid case. If any urgent safety measures are undertaken, the product owners will be informed within 15 days. Lexicon, Bayer and Novo Nordisk will be notified of any pregnancy in a participant within 15 days.

11.11 Reporting parameters for SAEs and SUSARs

When reporting SAEs and SUSARs the following parameters must be recorded: study name, patient identification (subject number, initials, sex, age), event (preferably a diagnosis), investigational medicinal product (IMP), reporter identification (name or initials), causality, outcome.

12 Statistical analyses

Analyses will be performed based on the intention-to-treat (ITT) principle, i.e., using all collected data in the analyses.

Because time of outcome assessment will follow the routine clinical measurements of the participants, the follow-times will vary between study participants and produce an unbalanced design.

Continuous outcomes will be analysed using linear mixed-effects models including a random effect for study center and a nested random effect of study participant (nested within the center). Fixed effects will include treatment group (A or B), time since baseline (study inclusion) and their interaction. To gain power, a baseline corrected model will be used, i.e., all participants will be placed in the control group at baseline in the statistical analysis. An autoregressive covariance pattern will be assumed. Model fit will be evaluated using graphical methods before estimating the treatment effects and if necessary, outcomes will be log-transformed. Estimated mean differences between groups and within group changes will be extracted from the model. For log-transformed outcomes the results will be back-transformed. If distribution assumptions cannot be met by log-transformation, a non-parametric test will be applied.

Binary outcomes will be analysed using a Poisson generalised linear regression model with a random effect for study center and the log of the risk time (follow-up time) as offset. Follow-up time will be from study entry and until first recording of the event in question, death, emigration, or end of follow-up. The follow-up time will be split into 3 months intervals, assuming the incidence rate is constant in each interval. Exposure variables in the model will include treatment group, time since baseline (study inclusion) and their interaction. Estimated incidence rate ratios between groups and within group incidence rates will be extracted from the model. For the primary outcome, 5- and 10-year cumulative risk will be estimated using the conditional survival function (62) to account for the competing risk of non-cardiovascular death.

For the primary outcome, two-sided P-values and 95% confidence intervals will be presented for comparisons (between and within groups). For secondary outcomes, false detection rate correction ad modem Benjamini and Hochberg (63) will be used to control for multiplicity. For explorative outcome assessments, no correction for multiplicity is planned.

The analytical approaches of the economic evaluation will take the form of CEA and CUA, were the base case CEA and CUA compare five-years societal costs with respectively five-years health effect/QALYs. The analysis will be based on individual patient data. The result of the analysis will be expressed by an incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{\Delta\text{Costs}}{\Delta\text{QALY}} = \frac{\text{Costs multifactorial intevention} - \text{Costs standard care}}{\text{QALY multifactorial intervention} - \text{QALY standard care}}$$

A cost effectiveness plane and associated acceptability curve will be produced and evaluated. Sensitivity analyses will assess how variations in key parameters (e.g. cost values, discount rates) affect the analysis results.

The analysis of the primary and secondary outcomes will be performed by a statistician blinded to the group allocation, except om the CEA. Data will be handled and analysed using Excel 2016, Stata version 18.0 or higher, and the statistical software R version 3.6.1 or newer version (The R Foundation for Statistical Computing, www.R-project.org) will be used for the analyses.

12.1 Sample size

The 5-year CV risk estimated by the Steno Risk Engine in a broad high-risk T1D population with a typical phenotype is estimated to be 12.4%. Given a minimally important difference of 4 percentage points for the 5-year cumulated risk of MACE+HFF the expected cumulative risk will be 12.4% in the standard care group and 8.4% in the intervention group. With the following assumptions the total sample size will be 1826 when using a two sample test for proportions: no strata effect (ICC = 0), no effect of heterogenous strata sizes, a two-sided alpha of 5% and a type 2 error of 20%. We expect a combined absolute risk reduction of 4%, resulting in a sample size of 2009 participants. With different assumed absolute risk reductions, the resulting sample sizes will be:

Absolute risk reduction	Sample Size	Including dropouts (10%)
4 %	**1826**	**2009**
3.5%	2592	2851
3%	3276	3604

The overall absolute risk reduction is based on the estimated combined effects of the multifactorial intervention, with guidance from effects seen in studies in T2D.

The recruitment will cease either when the arm with the fewest participants reaches a total of 1000 individuals or five years after the first patients first visit.

12.2 Interim analyses

An interim analysis is planned at 3 years of study duration, as counted from first patient first visit.

12.3 Trial stopping criteria

At the planned interim analysis, the Data and Safety Monitoring Board will assess the provided comparative outcome from the two study groups, to determine whether there is utility or overwhelming efficacy of the intensive treatment versus the standard therapy. Please see

Appendix for detailed Data and Safety Monitoring Board protocol and the section on Study governance.

13 End of study

The total study duration is 5 years.

The study participants will still be followed for long-term outcome through registries for another 10 years. The difference in treatment will however not continue.

Upon completion of the study, participants in the intensive treatment group will terminate their treatment. However, the investigators can discuss continuing parts of the intensive treatment with the participants, according to local practice.

14 Insurance

Subjects are covered by the public patient insurance.

15 Ethics committee

The trial will be conducted in accordance with the Helsinki Declaration, EU Directive on good clinical practice (GCP) and ICH-GCP guidelines after approval by the the Danish Medical Research Ethics Committees, Danish Medicines Agency and the Data Monitoring Board. The trial will be registered on www.clinicaltrials.gov and monitored by the GCP-unit at the University of Copenhagen, Denmark. Permission for third person to have access to patient data will be obtained at screening visit. This will provide access to source data and relevant documents in connection with monitoring, inspections and audits to relevant authorities.

15.1 Ethical considerations

The described study and interventions are all tested, approved and available for the treatment of T2D, and so the participating investigators will have had clinical experience with them, making it easier to identify side effects. Some of the treatments have also been tested in T1D and the literature therefore informs this study protocol and the safety procedures described.

Participants randomised to the standard of care can also be offered the described treatments on an individual basis if deemed necessary by their treating physician or investigator.

15.2 Informed consent

The investigator must

- ensure that the participant is adequately informed both orally and in writing about the nature, purpose, possible risk and benefit of the study.
- ensure that the participant will get information on their rights and will be offered time to consider this and to bring a supporter for the discussion.
- ensure each participant is notified that they are free to discontinue from the study at any time.
- ensure that a copy of the signed consent form is given to the participant by sending to their Digital Post.

16 Financing

This study will be financed by a national Steno Collaborative Grant from the Novo Nordisk Foundation. Furthermore, specific drugs are donated from the pharmaceutical companies Lexicon (sotagliflozin), Bayer (finerenone) and Novo Nordisk A/S (semaglutide). There is no compensation for participants.

17 Study governance

The PI, co-PIs and site representatives (one from each participating clinic) will form a Steering Committee for the study, with the overall responsibility for decisions regarding study conduct. The Steering Committee will be in close collaboration with a *Participant Advisory Panel*, consisting of an individual with T1D from each Steno center (not necessarily participants in the study), that will advise the Steering Committee on final study protocol, study conduct, dissemination of results and so on.

An *External Advisory Board* will be appointed to provide study oversight providing the PI and the Steering Committee with input regarding timelines, recruitment rates and site collaboration at online meetings every sixth month. The External Advisory Board will consist of independent experts with experience from diabetes treatment or clinical trials.

An independent *Data and Safety Monitoring Board* (Appendix 4) will be appointed for the planned interim analysis, consisting of a study statistician and 2 independent clinicians not involved as investigators. Their primary responsibility will be to assess the safety parameters and, if specific criteria are met, make the decision to terminate the trial. Throughout the initial year, safety reports will be submitted for evaluation every three months. Following this initial period, the frequency of safety reporting will transition to an annual basis.

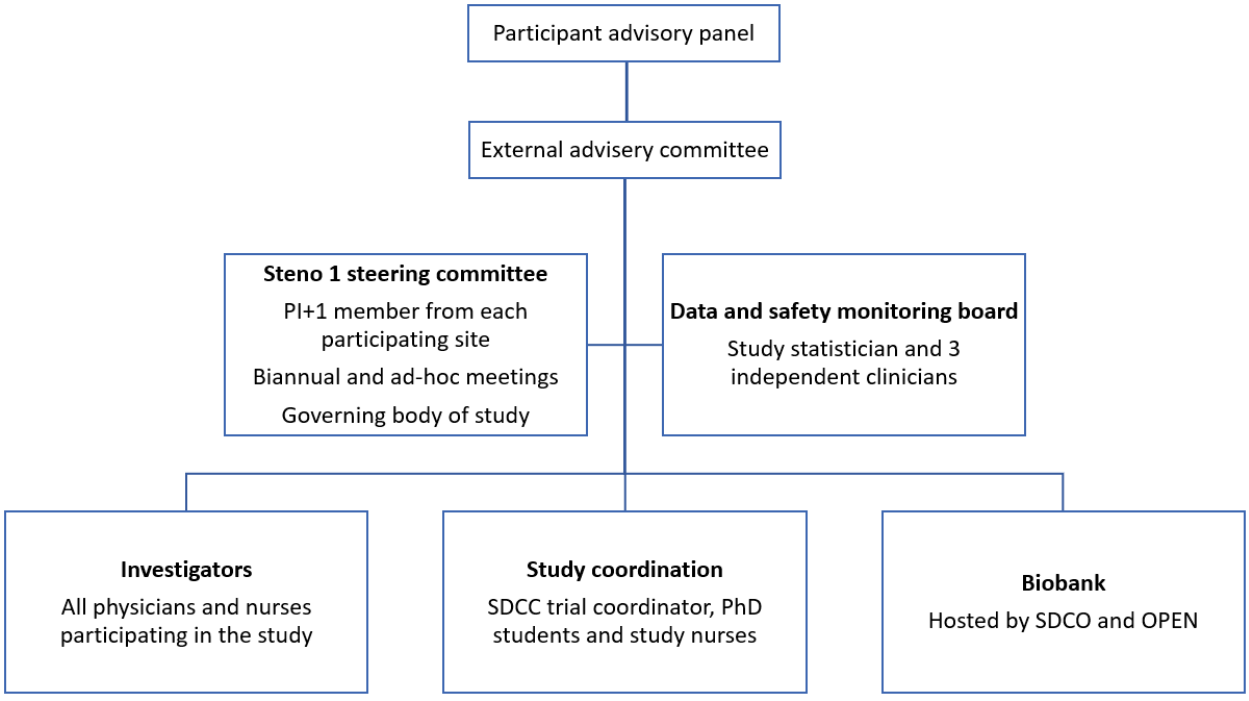

Figure 3. Study governance and committees

18 Communication of results

18.1 Publications

Baseline characteristics and all positive and negative as well as inconclusive study result will be presented at international meetings and published in international peer-reviewed medical journals. The Steering Committee will ensure that all contributing investigators are invited as co-authors or mentioned in acknowledgements in accordance with the Vancouver guidelines. The Steering Committee will also decide author successions on manuscripts.

No later than one year after the trial has ended, the summary of the results will be submitted to the CTIS portal.

19 Data management

19.1 Source data identification and source data verification

All clinical trial information in this trial will be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification. Source data will be stored in a study specific RedCap database.
Sponsor/investigator will provide direct access to source data/documents for trial related monitoring, audit, Institutional review board (IRB)/independent ethics committee (IEC) review, and regulatory inspection.

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Appendix

Appendix1: List of included sites and investigators

Appendix 2: Participant information regarding treatment with sotagliflozin

Appendix 3: Text for informative video

Appendix 4: Data Safety Monitoring Board

Appendix 5: CVD definition