The FibroCAN study

Mineralocorticoid receptor antagonist treatment for diabetic cardiovascular autonomic neuropathy

EU trial no.: 2024-516597-30-00

Sponsor:

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1 Project summary

Background

Diabetic neuropathy (DN) is a common, severe, and untreatable complication of diabetes. As the prevalence of cardiovascular autonomic neuropathy (CAN) is approximately 20%, the condition could affect as many as 100 million of the people living with diabetes in the world leading to increased morbidity and mortality, primarily due to the lack of disease-modifying treatment. CAN and other manifestations of neuropathy is associated with increased formation of fibrosis. This fibrosis formation may be a possible pathway to neuropathy and may present a new possible treatment target. Recently, treatment with mineralocorticoid receptor antagonists (MRAs) such as finerenone has shown to improve autonomic neuropathy in non-diabetic conditions, such as heart and kidney failure, reduce fibrosis and inflammation in addition to possessing cardio- and reno-protective effects. Thus, finerenone may be a potentially effective therapy for the treatment of CAN.

Objective

To assess if finerenone may have an effective disease modifying effect on CAN in a 78-week trial of people with type 2 diabetes and early-stage CAN. In addition, treatment effects on other forms of neuropathy and related pathological (and molecular) mechanisms causing the complication will be explored.

Methods

The study is a two-centre, two-armed, double-blinded parallel randomised placebo-controlled trial assessing 78 weeks treatment with finerenone/placebo on cardiovascular autonomic reflex testing (primary endpoint) in people with type 2 diabetes and early-stage CAN defined as on pathological cardiovascular autonomic reflex test; the E/I ratio.

Implications

This study will test if the previously shown cardio- and reno-protective effects of finerenone extents to a disease modifying effect for CAN. Ultimately, the findings may reveal a new treatment target for CAN.

2 Study centers and participants

Study centers
Steno Diabetes Center Copenhagen (SDCC)
Borgmester Ib Juuls Vej 83
2730 Herlev, Denmark

Steno Diabetes Center Northern Denmark (SDCN)
Mech-Sense
Aalborg University Hospital
9000 Aalborg, Denmark

Information regarding investigators and third parties involved in the study can be found in the Clinical Trials Information System (CTIS).

3 Abbreviations

AE	Adverse event
AR	Adverse reaction
CARTs	Cardiovascular autonomic reflex tests
DNS	Diabetic Neuropathy Symptom
DN4	Douleur Neuropathique en 4 questionnaire
DPN	Diabetic peripheral neuropathy
HRV	Heart rate variability
IENFD	Intraepidermal nerve fiber density
MRA	Mineralocorticoid receptor antagonist
NDS	Neuropathy disability score
SAR	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
SDCC	Steno Diabetes Center Copenhagen
SDCN	Steno Diabetes Center North Denmark
UAR	Unexpected adverse reaction
PT	Post treatment follow-up

4 Background

Cardiovascular autonomic neuropathy (CAN) (1)is caused by damage to the nerves regulating the heart and vessel function and affects people with diabetes by being an independent predictor of cardiovascular mortality and morbidity including arrhythmia, silent ischemia (1-4), and diabetic kidney disease shown by us (5) and others. People with diabetes and CAN have higher mortality rate compared with people without CAN (1, 6-8). Also, poorer measures of CAN have been associated with preclinical coronary atherosclerosis (9) and heart failure(10). Prevalence of CAN in newly diagnosed T2D is up to 20% (11)(12, 13). Presently, it is estimated that 537 million people suffer from diabetes worldwide with an estimated increase of more than 750 million people in 2040(14). These estimates extrapolate to at least 100 million people suffering from CAN presently with an estimated rise to 150 million people in 2040. Thus, preventing CAN may reduce excess morbidity and mortality in diabetes.

Early stages of CAN and other forms of neuropathy have a component of reversibility (12, 15). However, later stages may be irreversible. Prevention of progression to late stages of CAN and reversal of disease are therefore paramount. Several drug trials have failed to show disease-modifying effects on neuropathy. Possible reasons are that most studies have been performed in people with late irreversible stages of CAN. Secondly, CAN is a slow-progressing disease where long-term intervention studies are needed to assess the efficacy of treatment.

Fibrosis assessed by collagen turnover markers such as serum PRO-C6 and C3M have been associated with impaired nerve function in animal models (16, 17) and in people with diabetes (18-20). Neuropathy associated with collagen turnover may be a result of increased fibrosis of the extracellular matrix of nerves but also by pro-fibrotic and pro-inflammatory effects induced by the markers themselves (21). We have recently demonstrated that high serum levels of fibrosis markers are significantly associated with the risk of CAN and peripheral neuropathy (22). Taken together, fibrosis is a part of the pathophysiological mechanisms leading to diabetic neuropathy and could therefore be a future treatment target for the complication.

Mineralocorticoid receptor antagonists (MRAs) may constitute a novel treatment option for CAN. In addition to disease-modifying effects on congestive heart failure, diabetic kidney disease, and cardiovascular disease, MRAs have beneficial effects on autonomic dysfunction. Most human studies on CAN have been performed with the first-generation MRA spironolactone. Here, randomised placebo-controlled trials in people with congestive heart failure demonstrate improvements in autonomic function measured by Holter monitor-derived heart rate variability (HRV) indices after treatment periods varying from 8 to 52 weeks (23-25). Similar results have come from trials in people in hemodialysis after 12 to 24 weeks of treatment (26, 27), indicating that MRAs' effects on autonomic function are not disease-specific. Whether these improvements are mediated through a reduction in systemic inflammation or by direct effects on the central nervous system as shown in animal studies (28) is, not known. Finerenone is a third-generation well-tolerated MRA that has had remarkable

effects on cardiovascular and renal complications in diabetes patients (29) and concomitantly reduces fibrosis and inflammation (30). Finerenone is now approved and used for the treatment of diabetic kidney disease. Thus, finerenone is a readily available drug that could be used to treat or prevent CAN in diabetes.

5 Methods

5.1 Objective & hypothesis

The objective of this study is to investigate the disease modifying effect of finerenone on early CAN in a 78-week doubled blinded, randomized placebo-controlled multi-centre trial of people with type 2 diabetes and early-stage CAN. Treatment effects on neuropathy measures, levels of fibrosis and inflammation and heart function will be explored.

We hypothesize that treatment with the MRA finerenone is efficacious in reversing early CAN and that these effects are associated with a reduction of levels of fibrosis and inflammation. Furthermore, we hypothesize that improved autonomic function can be demonstrated in a 78-week trial by improvements in cardiovascular autonomic reflex tests (CARTs) and resting heart rate variability (HRV), in addition to measures of other forms of neuropathy and cardiac function. As the CART the E/I ratio is often the first to be affected in the progression to definite CAN we hypothesize that people who only have this CART affect have a reversible state of CAN.

5.2 Trial Design

This study is a two-armed double blind randomized control multi-centre trial performed with participant treatment at SDCC and SDCN (Figure 1).

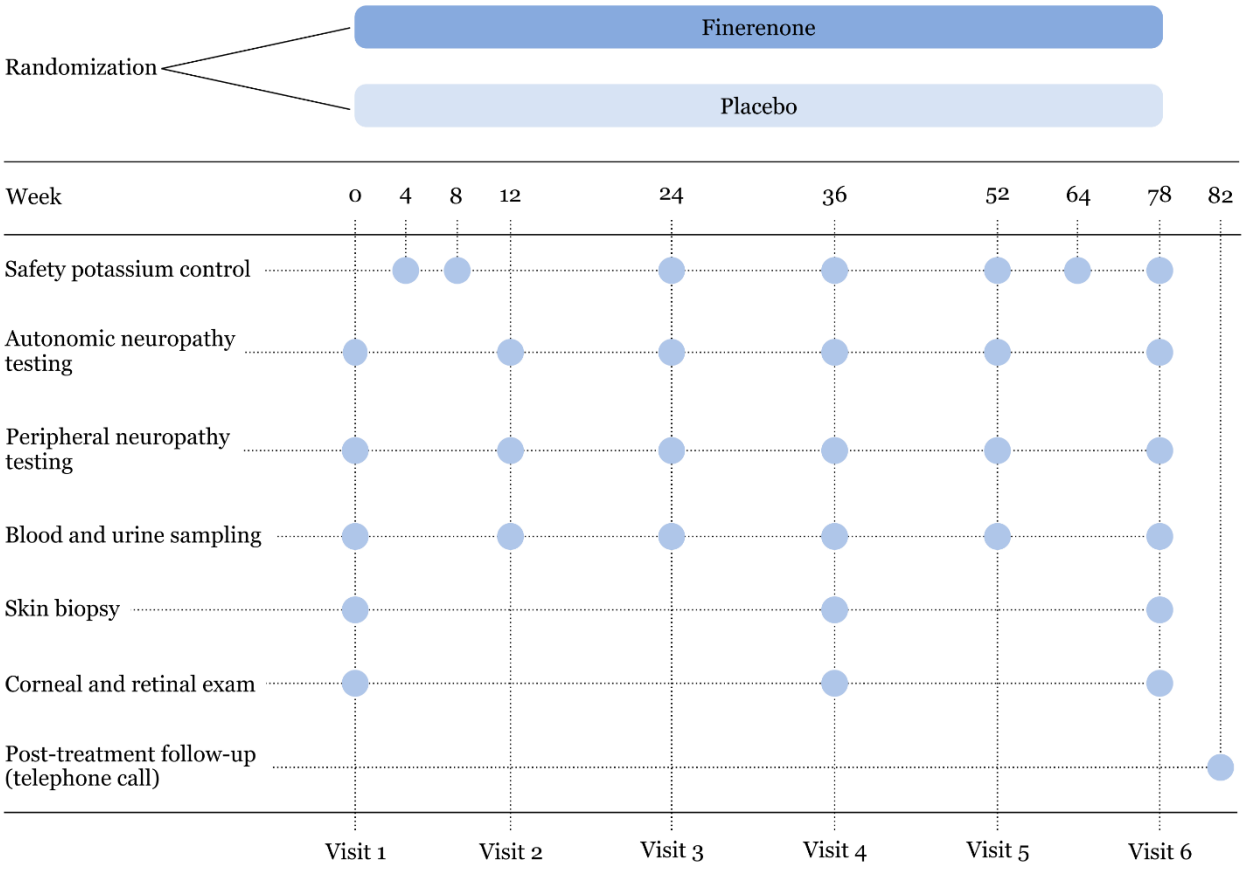

Figure 1 FibroCAN detailed study design and study visits

5.3 Study intervention and study medication titration

Participants will be randomized 1:1 to either finerenone or a matching placebo. The participants will take one tablet daily orally for 78-weeks.

We expect a dose-dependent reduction in neuropathy and hypothesize that 40 mg of finerenone is equipotent to 50 mg of spironolactone, which has shown efficacy in decreasing a CAN measure. Participants will be titrated to 40 mg oral dose following a stepwise titration based on eGFR and with close monitoring of potassium and eGFR. Previous studies have found 40 mg to be safe and well-tolerated, including the FINEART-HF study (31) with 3003 patients on finerenone, utilizing doses up to 40 mg, and a phase 1 program where 80 mg was the highest investigated single dose and 40 mg oral dose was the highest studied multiple-dose regimen (Investigator Brochure). Titration of finerenone will be based on baseline eGFR.

Participants with eGFR > 60

Participants with eGFR > 60 mL/min/1.73m² will start on a 20mg dosage. Medication dosage will be increased to 40 mg after an additional one month if serum potassium < 4.8 mmol/l. If side effects occur at any dosage, the dosage will be reduced to the previous level.

Participants with eGFR < 60 and >25

Participants with eGFR < 60 mL/min/1.73m² (and eGFR < 25 mL/min/1.73m²) will start on a 10mg dosage. Medication dosage will be increased to 20 mg after an additional one month if serum potassium < 4.8 mmol/l. Subsequently, Medication dosage will be increased to 40 mg after an additional one month if serum potassium < 4.8 mmol/l. If side effects occur at any dosage, the dosage will be reduced to the previous level. Additional serum potassium monitoring during the trial will be considered by the study-affiliated medical doctor based on an individual assessment based on patient characteristics and serum potassium levels.

5.4 Trial endpoints

Endpoints are between-group (finerenone vs. placebo) differences in changes of endpoint measures from baseline to 78-week follow-up.

Primary endpoint:

The CART E/I ratio (by the Vagus^{tm} device)

Secondary endpoint:

Cardiovascular reflex tests: R/S ratio, Valsalva manoeuvre (CARTs)

HRV indices (SDNN, RMSSD, Low and high-frequency power) (by the Vagus^{tm} device)

Fibrosis markers (serum PRO-C6 and C3M assessed by ELISA)

Fibrosis markers in skin biopsies (Pro-C6 and C3M by immunostaining (Only week 0, 36, 78)

Exploratory Endpoint:

Inflammation markers (plasma proteomic analyses, O-link platform)

Markers of corneal neuropathy (to quantify the severity of small nerve fibre damage by confocal corneal microscopy)

Cardiac vagal tone (by the eMotion Faros).

Markers of retinopathy (nonproliferativ/proliferative retinopathy and retinal nerve fibre layer thickness by optical coherence tomography)

Markers of peripheral neuropathy:

Sural nerve conduction and amplitude (DPNCheck)
Vibration sensation threshold (Biothesiometry)
Light touch and pain sensation (10 and 75 g monofilament and 40g needle)
Cold and warm sensation of foot and lower leg by (Rolltemp)
Ancle and Patella reflexes (Reflex hammer)
Intraepidermal nerve fiber density (IENFD) (Skin biopsies week 0,36,78)
Questionnaires for painful and painless neuropathy DN4, MNSI.

Markers of autonomic neuropathy:
Sudomotor function of the skin in hands and feet (Sudoscan)
Questionnaires for autonomic neuropathy (Compass-31 and GCSI)
Orthostatic blood pressure testing

5.5 Study visits

During the study the participants will attend six physical study visits at SDCC or SDCN at week 0, 12, 24, 36, 52, and 78 where all study outcomes will be assessed except for skin biopsies and eye examinations (CCM and retinopathy) which will only be performed at week 0, 36 and 78. In addition, safety serum potassium tests will be performed at week 4, 8, 24, 36, 52, 64, 78 and additionally after 4 and 20 weeks if study drug dosage is changed (see overview figure 1). All participants will undergo a post-treatment follow-up via telephone after 4 weeks (+/-5 days) of their last study visit, during which adverse events will be recorded.
At the screening visit demographic and anthropometric measures (Height, weight, BMI, hip- and waist circumference) as well as lifestyle habits will be inquired (alcohol, smoking, exercise levels). At the screening visit 7 ml of blood will be drawn after informed consent is given. The blood will be analyzed immediately to assess exclusion biomarkers: potassium, HbA1c and eGFR (see table in section “9.4 Blood/urine sampling and molecular (fibrosis and inflammatory proteins) testing.”). Results from blood analyses will be assessed by study personnel prior to randomization.

In the trial overview below measures obtained at each visit are listed below.

	Information	Screening	W0	W4	W8	W12	W24	W36	W52	W64	W78
ENROLMENT											
Informed consent	x										
In/exclusion criteria		x									
Demography		x									
Medical history		x									
Biochemistry*											
Screening		x									
Baseline			x								
Follow-up						x	x	x	x		x
SAFETY OUTCOMES											
Serum potassium + eGFR				x	x	x	x	x	x	x	x
Adverse events				x	x	x	x	x	x	x	x
PRIMARY OUTCOME											
E:I ratio (CART)		x	x			x	x	x	x		x
SECONDARY OUTCOMES											
CARTs (other than E:I)		x	x			x	x	x	x		x
HRV indices			x			x	x	x	x		x
Cardiac vagal tone			x			x	x	x	x		x
Fibrosis markers			x			x	x	x	x		x
EXPLORATORY OUTCOMES											
Sudomotor function			x			x	x	x	x		x
Orthostatic blood pressure			x			x	x	x	x		x
Peripheral neuropathy			x			x	x	x	x		x
Questionnaires			x			x	x	x	x		x
Inflammatory markers			x			x	x	x	x		x
Skin biopsy			x					x			x
Corneal neuropathy			x					x			x
Retinopathy			x					x			x

Table 1.
** List of analytes can be found in section 9.4.*

5.6 Randomization and blinding

Participants will be randomized between the screening visit and study visit week 0. Participants will be randomized 1:1 by block randomization with four participants per block. Randomization lists will be made using the online tool at sealedenvelope.com.

The Hospital Pharmacy of The Capital Region of Denmark (Marielundvej 25, 2730 Herlev) will coordinate the randomization process and allocation concealment. The randomization will be based on a computer generated random-number allocation sequence stored at the pharmacy. The randomization sequence will not be available to staff involved in data management, analysis, report writing or patient care until breaking

of randomization code. Envelopes will be sequentially numbered, opaque and closed with tamper-proof seals and will be prepared by adequately trained staff at the pharmacy certified in handling of medicine and un-blinded to the allocation sequence, but not involved in participant contact, data management or data analysis during the trial. Each center will have their participants randomize individually. Sealed codes are marked according to randomization code and distributed according to a pre-described order.

Group allocation will be concealed to patients as well as investigators, and only revealed at the end of trial or if unblinding is needed.

Should the unblinding of a study participant be necessary because of an emergency, a dedicated person at SDCC or SDCN not involved in the study will perform the procedure. Alternatively, the Principal investigator will be able to perform unblinding (as stated in the section "11.1 Unblinding").
Finerenone tablets and matching placebo tablets will be provided by Bayer and shipped to The Hospital Pharmacy of The Capital Region of Denmark (Marielundvej 25, 2730 Herlev) , Denmark where containers will be labeled and distributed to the study sites.

5.7 Adherence to protocol

Drug accountability (pill count) will be performed at physical visits to document adherence to the study protocol. Adverse effects will be recorded at all study visits (as described below).

5.8 Trial termination criteria

The trial will be terminated when:

a) Participant number 100 has completed his/her last visit OR
b) 74 participants have completed a full trial with data on a least the primary endpoint at last follow-up AND the remaining participants in the trial at this time point have completed their trial.

5.9 Study timeline

The trial protocol will be approved by the Medical Research Ethics Committee (MREC) and the Danish Medicines Agency in 2024 with expected first patient first visit (FPFV) in January 2025 and last patient first visit in the end of 2025. Last patient last visit is expected to be in March 2027.

The first papers on unblinded baseline measures of fibrosis, inflammation and neuropathy are expected to be published in mid-2026, whereas the first paper on trial outcomes will be published in around august 2027. Secondary papers in last quarter of 2027 to first quarter 2028 (see figure 2 below).

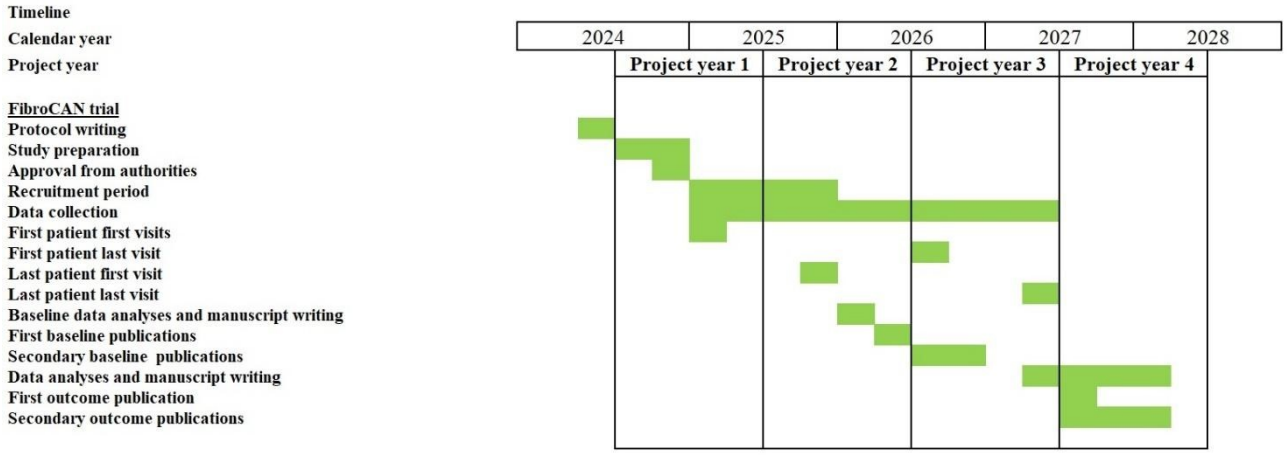

Figure 2 FibroCAN Study timeline

6 Statistical analysis

6.1 Sample size estimation

Previously, 50 mg spironolactone has been shown to increase the resting heart rate variability measures (CAN measure) in the range of 2% (50) to 45% (51) in patients with congestive heart failure. We hypothesize that 40 mg finerenone is equipotent to 50 mg spironolactone. However, to address i) that the present study consists of people with diabetes without heart failure and ii) a high variance of effect sizes in previous studies, and iii) that we will calculate power for an autonomic reflex test (CART), we estimate a modest efficacy of finerenone on the primary outcome (E/I ratio). We conservatively hypothesize that 40 mg finerenone will increase the E/I ratio by 15% compared to the placebo. A 15% increase in CAN measures is clinically relevant as the natural history of CAN is a reduction in all CAN measures over time (5).

From a larger CAN screening study performed at SDCC, we have calculated that people with type 2 diabetes and early CAN have an E/I ratio of 1.13 ± 0.2. Thus, a 15% increase in E/I ratio equals to 0.17. With 90% power and a two-sided significance level of 0.05, the sample size needed to detect this change (with no expected placebo effect) is 37 participants in each group or 74 participants in total. Expecting a dropout rate of 20 % and to accommodate for the inaccuracies of assumptions above we aim for a sample size of 50 participants in each group. Thus, a total of 100 participants will be recruited for the study.

6.2 Demographics and other baseline characteristics

Baseline characteristics and demographics will be presented by treatment group and overall. The characteristics will include, but are not limited to, age, body mass index, hip and waist measures, smoking history, alcohol consumption, medical history including diabetes duration and baseline blood samples.

6.3 Treatment efficacy

Treatment efficacy will be analysed by linear mixed-effect models with visit and treatment as fixed factors and a patient-specific random intercept to account for the correlation of repeated measurements within patients. Analyses will be done as intention-to-treat analyses as the primary analyses and subsequently as per-protocol analyses. The endpoints are analysed as between-group (finerenone vs. placebo) differences from baseline to 78-week follow-up. The endpoints are listed in section 5,4 and with a focus on between-group changes in neuropathy (cardiovascular autonomic neuropathy, peripheral neuropathy and corneal/retinopathy) fibrosis, inflammation markers and other endpoints. We also plan a baseline analysis of baseline measures of endpoints to investigate possible association between fibrosis markers and inflammatory markers to the level of both autonomic and peripheral neuropathy.

Statistical analysis will be performed using appropriate statistical software such as R or SAS. Descriptive statistics will be reported as mean (standard deviation) or median (quartile range) or frequencies and percentages for categorical variables. In between group differences will be analyzed using Fisher's exact test or T-test. A two-sided P-value of 0.05 will be considered statistically significant.

6.4 Safety outcomes

Serious adverse events, changes in serum potassium, and cases of hyperkalemia (moderate >5.5 mmol/L and severe >6.0 mmol/L) will be assessed. This includes the number of subjects hospitalized for hyperkalemia or discontinuing the study drug due to it. Renal function changes (eGFR) will be monitored, along with hospitalizations and drug discontinuations due to worsening renal function. Changes in other lab values will also be recorded.

7 Participant selection

7.1 Inclusion criteria

To be included in this study the participants must fulfill the following inclusion criteria.

- Given informed consent
- Type 2 diabetes defined by WHO criteria
- Aged 40 ≥ at inclusion

- Pathological E/I ratio (Mean value of three measures)

7.2 Exclusion criteria

Participants will be excluded in one or more of the following criteria are met.

- No CAN (no abnormal CARTs)
- Definite CAN (more than one abnormal CART)
- HbA1C >100 mmol/mol
- Treatment with potassium-sparing diuretics (amiloride) or MRAs e.g., spironolactone or eplerenone which cannot be discontinued 4 weeks prior to screening visit. The patient's primary physician, who is not involved in this study, will determine if discontinuation is possible.
- Atrial fibrillation/flutter
- Congestive heart failure (NYHA class 3-4)
- History of cardiac arrhythmia
- Severe forms of respiratory disease including asthma and COPD
- Any nondiabetic cause of neuropathy
- All female subjects of childbearing potential (WOCBP) must have a negative result of a highly sensitive urine HCG (pregnancy test) performed at screening. Subjects of childbearing potential must agree to use a highly effective form of contraception throughout the duration of the study (list of definition on WOCBP and accepted contraception in appendix A).
- Severe hepatic impairment
- Lactose intolerance
- Breastfeeding
- Nephropathy requiring dialysis
- Beta-blocker-use
- Hyperkalemia at screening visit (serum potassium >4.8 mmol/l)
- eGFR < 25 ml/min/1.73m2
- serum potassium > 4.8 mmol/l (at randomization)
- Treatment with strong CYP3A4-inhibitors (e.g. Itraconazol, ketoconazol, ritonavir, cobicistat, clarithromycin) which cannot be discontinued 4 weeks prior to screening visit
- Treament with moderate to strong CYP3A4-induceres (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort or efavirenz) which cannot be discontinued 4 weeks prior to screening visit
- have received chemotherapeutic treatment within last 12 months
- Grapefruit consumption that cannot be discontinued during the study period
- inability to complete study protocol, assessed to investigator

- not able to read, write and/or understand Danish

7.3 Withdrawal criteria

Participants will be withdrawn from the study if:

- The following diagnoses are given during the study
    - Pregnancy
    - Cancer
    - Addison's disease
- The investigator judges it necessary e.g., due to medical reasons or severe non-compliance to the protocol.

Withdrawal on participants request will be accepted at any time without further justification or consequence to regular treatment at SDCC and SDCN. Withdrawn patients will not be replaced.

7.4 Screening of eligible participants

Screening cohorts

Participants will be recruited by the treatment responsible doctor or study personnel affiliated with SDCC or SDCN. Participants will be identified from 1) business intelligence-generated reports identifying specific patients based on relevant ICD-10 codes, 2) cohorts of previous studies (if they have agreed to be contacted regarding other studies in diabetes research) e.g., a recently finalized neuropathy screening study (the DANES study) at SDCC, where participants have agreed to be contacted regarding other studies. Here 899 people with type 2 diabetes were screened for CAN. From the DANES study and a previous CAN screening study, we know that the prevalence of early CAN at SDCC is approximately 26% (32) amounting to 234 type 2 patients from the DANES study eligible for recruitment. Moreover, a backup cohort of 700 people with type 2 diabetes screened for CAN at SDCC in 2013 is available as a secondary source of participants. At SDCN participants will be recruited among former participants from previous studies investigating CAN, where 170 participants have agreed to be contacted regarding clinical studies. Moreover, patients may be recruited from reading recruitment posters placed in the primary sector, out-patient clinics, patient associations, and health community centers (Sundhedshuse). Both centres will recruit 50 participants.

Use of electronic patient records

Potential study participants will be prescreened for inclusion and exclusion criteria by access to their electronic medical record. This assess will be granted by the treatment-responsible doctor at the treatment center. This will be conducted in accordance with Sundhedsloven § 46, stk 1, under the responsibility of the primary

investigator at the respective centers. This pre-screening approach will allow the researchers to avoid, contacting un-eligible persons and thus save time and costs.

7.5 Initial contact to potential study participants

Eligible participants will be contacted by digital post (e-boks) or regular letter by study personnel to enquire if the person is interested in participating. If this is the case, written information about the study will be send. People will be given a 7-day period to respond to the contact. If no response has been recorded, the person will be contacted in writing a second time. After an additional 7 days of no response, study personnel will contact the given person by telephone to ask for interest in participation.

The written material will be sent ('Deltagerinformation') along with the leaflet about the rights of participants in a clinical trial ('Dine rettigheder som forsøgsperson i forsøg med medicin'). The patients will have the possibility to contact the investigators responsible for the study by telephone or e-mail in the time of reflection to inquire about the study.

7.6 Participant information visit

Prior to enrolment participants will be invited to an information visit where they will receive verbal information about the study by a health care professional at the study site in a quiet room. During this information visit, study personnel will inform the potential participant about the purpose of the study and the explain the experimental procedures, the potential benefits/risks and answer all study-related questions. It is underlined that participation is voluntary and the participant can withdraw his/her consent anytime without consequences. All individuals are informed that they can bring an assessor to both the information session and study visits.

All study individuals who participate in the information visit sessions will be allowed time to reflect about their participation, however no longer than 14 days. The information visit and screening visit can be scheduled to the same day if the patient wishes and gives informed consent.

7.7 Screening

Following informed consent, participants will be invited for a screening visit at one of the study sites. This screening visit may be performed at the same day as the participant information visit if the participant whishes this. The screening will be performed by a study-affiliated medical doctor, who will go through medical history, medication and if necessary, examine the participant. If the study-affiliated medical doctor can confirm eligibility the participant will be enrolled in this study. At the screening visit 7 ml of blood will be drawn after informed consent is given. The blood will be analyzed immediately to assess exclusion biomarkers: potassium,

HbA1c and eGFR (see table in section "9.4 Blood/urine sampling and molecular (fibrosis and inflammatory proteins) testing."). Results from blood analyses will be assessed by study personnel prior to randomization.

When the participant has been enrolled, he/she will be randomized to a study arm. Participants will be randomized between the screening visit and study visit week 0 by authorized study personnel as described under "5.6 Randomization and blinding".

8 Study medication: description, handling, and storage

Excessive overactivation of the mineralocorticoid receptors promotes reactive oxygen species (ROS) production, and mediates inflammatory and fibrogenic processes, which can lead to myocardial hypertrophy, ventricular remodeling, glomerular hypertrophy, glomerulosclerosis, and vascular endothelial dysfunction (27, 28). Finerenone is a selective mineralocorticoid receptor antagonist and by blocking the mineralocorticoid receptor the binding of receptor coactivator and the following pro-inflammatory and pro-fibrotic gene transcription is inhibited.

8.1 Packaging and labelling

The study medication will be manufactured, packaged, and distributed in accordance with the principles of Good Manufacturing Practice, under the responsibility of Bayer. Finerenone and matching placebo tablets will be delivered by Bayer to The Hospital Pharmacy of The Capital Region of Denmark (Marielundvej 25, 2730 Herlev). Tablets will be provided in a container labelled with study name, batch number, "study medication", a unique Id number, daily dosing paradigm and contact information. Labeling and secondary packaging will be performed by trained and qualified personnel in The Hospital Pharmacy of The Capital Region of Denmark (Marielundvej 25, 2730 Herlev) according to Annex 13 of the Good Manufacturing Practice guidelines of the European Commission, ICH, GCP guidelines, and local law. No manipulation, repackaging, or relabeling of study medication is permitted after qualified person release by The Hospital Pharmacy of The Capital Region of Denmark (Marielundvej 25, 2730 Herlev). Control of receipt will be done according to the Good Clinical Practice Guideline by qualified personnel at the investigational site. Trained and qualified study site staff will provide each participant with sufficient finerenone or placebo tablets until their next physical visit.

8.2 Biobank Storage

All study medication will be stored in a secure place in a dedicated room under appropriate storage conditions (locked, dark room at room temperature) at each study site. Only authorized study personnel will have access.

All medication will be labeled with information that it is only intended for use in a clinical trial. Left-over and unused study medication will be disposed of according to local and GCP guidelines. A detailed count of the study medication dispersion and storage will be kept.

9 Methods and measures

9.1 Pre-examination restrictions

All testing of CARTs will be performed between 8 and 12 o´clock. Participants will be asked to fast from midnight prior to testing. The participants will be asked to refrain from nicotine, caffeine, and alcohol 8 hours before an examination visit. Participants will be asked to refrain from strenuous exercise 24 hours prior to an examination day.

9.2 Cardiovascular autonomic reflex testing and heart rate variability

Cardiac autonomic reflex tests (CARTs) are the gold standard to assess CAN (33) CARTs are measured using the Vagus™ device (Medicus Engineering, Aarhus, Denmark) that use a 1-lead ECG to obtain R-R intervals. The Vagus™ device is CE-marked and recognized internationally for its role in screening for diabetic autonomic neuropathy (CAN)(34, 35). Prior to testing the participants will see video instruction of how to perform the tests. The participants will be guided though the test by the examinator and information on the screen of the Vagus™-device. Prior to testing the participants will rest in the supine position in a quiet room for 10 minutes. The test will consist of the following tests.

- A 5-minute resting heart rate variability measurement in the supine position.
- The 30/15 ratio: the ratio between the 30th RR-interval (the longest) and the 15th (the shortest) after shifting from lying to standing position.
- The E/I ratio: the ratio of the RR-intervals during expiration and inspiration in a one-minute cycle of deep breathing. (Primary endpoint), (Performed three times).
- The Valsalva ratio: the ratio of the longest RR-interval after a 15 second strained expiration (40 mmHg) and the shortest RR interval during the strained expiration.

All tests will be separated by one minute of rest. The CAN diagnosis is defined as two or more abnormal tests, early CAN by one abnormal test, and no CAN when the obtained tests were within the normal range of the specific age-dependent cut-off values (36).

The following heart rate variability (HRV) indices will be derived from test 5-minute resting HRV:

- SDNN: standard deviation of NN-intervals

- SDANN: standard deviation of the average NN-intervals
- SDNNi: mean of the standard deviations of all the NN-intervals
- RMSSD: Root mean square of successive NN-interval differences
- VLF: very low frequency power (<0.04 Hz)
- LF: low-frequency power (0.04–0.15 Hz)
- HF: high-frequency power (0.15–0.4 Hz)
- Total power (≤ 0.4 Hz)

9.3 Cardiac vagal tone

During the 5-minute resting HRV measurement with the Vagus™ device, the participant will be equipped with a three lead ECG recorder with a sampling rate 8 kHz for 5 minutes using the commercially available system (eMotion Faros, Mega Electronics Ltd, Kuopio, Finland). Cardiac vagal tone is quantified by phase demodulation of high-resolution time domain of RR-intervals.

9.4 Blood/urine sampling and molecular (fibrosis and inflammatory proteins) testing

At each study visit blood and urine will be sampled for basic biochemical measures, inflammation, and fibrosis markers. Blood and urine samples will be collected according to the table below.

Analyses of the following markers will be performed at the StenoLab at Steno Diabetes Center Copenhagen or the department of biochemistry at Aalborg University Hospital, Aalborg: HbA1c, lipids, eGFR, creatinine, potassium, sodium, ALAT, CRP, vitamin B12, hemoglobin, and blood glucose, urine albumin/creatine ratio.

Serum samples will be analyzed for fibrosis markers including but not limited to PRO-C6 and C3M with enzyme-linked immunosorbent assay (ELISA) (Nordic Bioscience A/S Herlev, Denmark).

Inflammation markers will be analyzed with the Olink Proteomic Target 96 Inflammation panel (Olink, Uppsala, Sweden). Samples will be analyzed by BioXpedia A/S

Urine HCG, pregnancy test will be performed at screening visit, W36 and W78 for all women with childbearing potential (WOCBP). All WOCBP will be offered a urine HCG, pregnancy test at every visit. More information in Appendix A.

Assessment	Analytes	Amount
Screening visit	Potassium, HbA1c, eGFR	7 ml for immediate analyses
Baseline biochemistry (week 0)	Markers of fibrosis and inflammation HbA1c, lipids, eGFR, creatinine, potassium, sodium, ALAT, CRP, vitamin B12, hemoglobin, and blood glucose, urine albumin/creatine ratio	Research biobank: 30 ml blood, 6 ml urine ml Future research biobank: 20 ml blood, 5 ml urine.
Follow-up biochemistry (Visit week 12, 24, 36, 52, and 78)	Markers of fibrosis and inflammation HbA1c, eGFR, creatinine, potassium, blood glucose, urine albumin/creatine ratio.	Research biobank: 30 ml blood, 6 ml urine ml Future research biobank: 20 ml blood, 5 ml urine.
Safety visits (Visit week 4, 8, 12, 24, 36, 52, 64 and 78 And after 4 and 20 weeks at study medication dosage change)	Potassium + eGFR	4 ml blood for research biobank

9.5 Corneal neuropathy

Confocal corneal microscopy will be used to assess the following outcomes: corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL), and inferior whorl length (IWL). During CCM images from both central sub-basal nerve plexus and the inferior whorl region will be obtained, and images will be manually quantified. Measures will be obtained by use of the Rostock Cornea Module on the HRT3 platform (Heidelberg Engineering, Heidelberg, Germany).

9.6 Retinopathy

The state of retinopathy will be assessed by fundus photo grading and optical coherence tomography (OCT) using the Topcon DRI OCT Triton or the Topcon 3D OCT2000 (Topcon Corporation, Tokyo, Japan). OCT enables imaging of the layers of the retina measuring their thickness. The average thickness of the retina as well as of thickness of the superior, inferior, nasal, and temporal quadrants will be assessed. Sural nerve conduction and amplitude

9.7 Nerve conduction

Nerve conduction velocity and amplitude of the Sural nerve will be assessed the average of three measures on both the left and right leg by use of the NC-StatR DPNCheck (NeuroMetrix, Inc., Waltham, USA). Age- and height-stratified perception thresholds will be applied for both tests (37).

9.8 Vibration sensation threshold

Vibration perception threshold (VPT) will be measured by using biothesiometry (Bio-medical instruments, Ohio, USA) applied to the distal tip of the first toe on both feet. Cut-off above 25 V and age-sex-height specific cut-offs was applied (38, 39). Biothesiometry measurements will be repeated three times and averaged of the measures will be used.

9.9 Light touch and pain sensation

Ten-gram and 75-gram monofilament (Neuropen, Owen Mumford Ltd, Oxford, UK) will be applied three times at four points on the plantar aspect of the foot (first toe, proximal to the first toe, third toe and fifth toe) in addition to the proximal to the nail on the first dorsal, third and fifth toes on each foot (33). All measures will be obtained on both feet. DPN will be defined as absence of sensation at all locations.

Pain sensation will be assessed by pinprick (Neuropen, Owen Mumford Ltd, Oxford, UK). Pinpricks will be applied proximal to the nail on the first dorsal, third and fifth toes on each foot. DPN will be defined as no pain at any tested location.

9.10 Cold and warm sensation of foot/lower leg

Thermal sensation (25°C and 40°C) will be assessed by applying metal rolls bilaterally on the dorsal side of the first toe, dorsum of the foot and the anterior part of the low leg from 10 centimeter above the lateral malleolus and 10 centimeter proximately by Rolltemp-II (Somedic SenseLab AB)(40). All measures will be obtained on both legs. Abnormal sensation will be defined as bilateral abnormalities at the toes, either with or without an abnormal sensation of the foot and leg.

9.11 Ancle and Patella reflexes (Reflex hammer)

Ancle and Patella reflexes will be perform using a reflex hammer on both sides.

9.12 Intraepidermal nerve fiber density (IENFD)

Two skin punch biopsy will be obtained at week 0, 36 and 78 in accordance with published guidelines. Skin biopsies will be taken on the left leg on all participants and a less than ½ centimeter apart. Skin biopsies can be taken on the right side if there is a contra indication of performing a biopsy on the right side e.g. a skin condition.

After intradermal injection of 1% lidocaine 10 cm proximal to the lateral malleolus, two skin biopsy will be obtained using sterile technique with a disposable 3-mm punch. Samples will be fixed with Zamboni fixative

overnight and then cryoprotected in 20% sucrose 0.1 M phosphate buffer. The biopsies will be stored at -80°C until further processing. Sections will be stained using the free-floating protocol, and intraepidermal nerve fiber density (IENFD quantified following international guidelines (41). The biopsies will be immunostained for fibrosis markers including but not limited to PRO-C6 and C3M (Nordic Bioscience A/S Herlev, Denmark). Analyses will be performed at Danish Pain Research Center, Aarhus University, Aarhus, Denmark

9.13 Questionnaires for painful and painless peripheral neuropathy

The following neuropathy questionnaires will be used to assess peripheral neuropathy:

- The Douleur Neuropathique 4 (DN4) to assess painful peripheral neuropathy with a cut-off ≥ 4 (42).
- Michigan Neuropathy Screening Instrument (MNSI) with ≥ 4 a cut-off (43)

The Toronto Consensus Criteria will be applied to categorize DPN into four groups: possible, probable, definite and subclinical (46).

9.14 Sudomotor function of the hands/feet

Peripheral small-fibre autonomic function will be assessed by electrochemical skin conduction (ESC) test on the hands and feet by the Sudoscan™ device (Impeto Medical, Paris, France. Age and gender stratified ESC thresholds for hands and feet were used (47).

9.15 Questionnaires for autonomic neuropathy

Autonomic dysfunction will be evaluated using the Composite Autonomic Symptom Scale 31 (Compass 31), where a cut-off ≥ 16(48) will be applied. Gastrointestinal symptoms were evaluated using the gastrointestinal symptom rating scale (GSRS) (cut-off ≥ 1.53(49)) and the presence of symptoms of gastroparesis with the gastroparesis cardinal symptom index (GCSI) (cut-off ≥ 2.6(50).

9.16 Orthostatic blood pressure testing

Supine blood pressure will be measured three times after 10 minutes of rest and the average of the last two was calculated. Standing blood pressure will be measured one, two, three, four and five minutes after rising from supine position. Orthostatic hypotension will be defined as decline in systolic blood pressure from lying position ≥ 20 mmHg or diastolic blood pressure ≥ 10 mmHg or a decrease in systolic blood pressure to < 90 mmHg within five minutes of standing in accordance with guidelines of the European society of Cardiology (51). Blood pressure will be measured by automated oscillometric blood pressure (AND UA-787plus, A&D medical, California, USA).

10 Biobanks

Research biobank

A study related research biobank will be established to store samples for analyzing blood, and urine markers at all physical study visits obtained during the study. Theses samples are only to be used to assess predefined study biomarkers that are not analyzed immediately after drawing of blood. Participants will fill out the informed consent form regarding this biobank. The biobank will be established at the to study sites at SDCC and at SDCN for storage at -80 degrees Celsius until analysis. 30 ml blood and 6 ml urine will be collected from each visit. One 3-mm punch skin biopsy will be collected the research biobank at study visits week 0, 36, 78.

This material will be stored for analysis as described above in connection to the study. Safety potassium samples will be analysed immediately and will not be stored in any biobank. The final biochemical analysis will be carried out at SDCC. The samples will be destroyed when the last biochemical analysis has been performed no later than one year after last patient last visit.

Biobank for future research

All participants will be asked if they are willing to donate extra biological material to a biobank for future research. Guidelines from Danish data protection guidelines will be followed throughout the process. Participants will sign a separate informed consent form if they agree to have their biological material stored in the biobank for future use. If the participant wishes the material can be destroyed at any time.

A total blood volume of approximately 20 ml blood will be draw for the biobank for future research at each physical visit and divided into samples of 3 x 1.8 ml plasma, 5 x 1.8 ml serum, 2 x 1 ml buffy-coat. In addition, 1 x 5 ml urine. At visits 0+36+78 one 3-mm punch skin biopsy will be collected and stored. The material in the biobank for future use will be stored at SDCC or SDCN during the study in a freezer at -80 degrees Celsius. Study material will be shipped frozen (on dry ice) from SDCN to SDCC when appropriate and no later than 2 months after last patient last visit.

The material in the biobank for future use will be stored at SDCC, Borgmester Ib Juuls Vej 83, 2730 Herlev, in a freezer at -80 degrees Celsius. The material will be stored for 50 years.

Adverse effects and risks

10.1 Adverse effects of finerenone

Finerenone is currently under 'supplerende monitorering" meaning all potential adverse reactions will be reported to the Danish Medicines Agency. The table below gives an overview of the known adverse reactions.

Adverse reactions to finereone by System Organ Class (SOC) and frequency

System Organ Class	**Potentially serious adeverse reactions**	**Usually, non-serious adverse reactions**
Very common (>10%)		
Metabolism	Hyperkalemia	
Common (1-10%)		
Test	Elevated serum urate	
Metabolism	Hyponatremia	
Renal system	Reduced renal function	
Skin		Pruritus
Vascular	Hypotension	
Non common (0.1-1%)		
Test		Reduced hemoglobin

10.2 Risk related to procedures

The table below provides an overview of the risk related to the study procedures.

Assessment	Potential risks
CARTs	Dizziness
HRV indices	No risks
Cardiac vagal tone	Allergy (gel)
Blood sampling	Risk of bruises and/or infection
Urine sampling	No risks
Corneal neuropathy	Moderate discomfort on eye during examination
Retinopathy	Moderate discomfort on eye during examination
Sural nerve assessment	Transient discreet electrical pain
Vibration sensation threshold	No risk
Light touch and pain sensation	Transient discreet pain
Cold/warm sensation	Transient pain and/or unpleasantness
Skin biopsy	Bleeding, bruising and/or infection
Questionnaires: peripheral neuropathy	No risks
Sudomotor function	No risks
Questionnaires: autonomic neuropathy	No risks
Orthostatic blood pressure	Dizziness

10.3 Risk/Benefit assessment

Finerenone may present a valuable therapeutic option for cardiovascular autonomic neuropathy (CAN), a severe complication affecting over 100 million people with diabetes globally and linked to increased morbidity and mortality. CAN independently predicts adverse cardiovascular outcomes such as arrhythmia, silent ischemia, and diabetic kidney disease. Hyperkalemia is a recognized risk of finerenone, reported in 14% of treated patients versus 6.9% with placebo; however, most cases are mild and manageable, with serious events being rare (1.1%) (Investigator Brochure). In the FINEART-HF study, involving 3,000 patients receiving finerenone (up to 40 mg), hyperkalemia-related hospitalizations were low (0.5% in the active group vs. 0.2% placebo) with no fatalities, supporting finerenone's potential favorable risk-benefit profile in CAN management for people with diabetes (31).

11. Assessment of safety and reporting

11.1 Unblinding

The code for randomization numbers will be stored at The Hospital Pharmacy of The Capital Region of Denmark (Marielundvej 25, 2730 Herlev) until the study is completed, so that the investigators are not familiar with the contents behind the treatment. In addition, all sites receive for each randomization number a sealed envelope with information on the treatment given. The sealed envelopes will be kept in a secured place but authorized personnel (including investigator) will have access to the sealed envelopes at all times during the study period in case of emergency unblinding.If necessary, the investigator shall unblind the treatment code of the study medication immediately and as a result may occur without prior contact with the monitor/sponsor. However, the sponsor shall be contacted shortly (within 24 hours) after unblinding of the treatment code. If the envelope with the treatment code is broken, the date, time, the reason for unblinding and name of the person who broke the treatment code is recorded.

11.2 Safety endpoints

All adverse events will be reported from week 0 to the end of safety follow-up visit four weeks after the participant has received the last dose of the investigational medication. An adverse event related to finerenone treatment is hyperkalemia therefore safety serum potassium tests will be performed at week 4, 8, 24, 36, 52, 64, 78 and additionally after 4 and 20 weeks if study drug dosage is changed.

11.3 Adverse events and reactions

Definitions of serious adverse events (SAE), serious adverse reactions (SAR) and suspected unexpected serious adverse rations (SUSAR)

- Serious adverse event (SAE) or serious adverse reaction (SAR) an untoward medical occurrence or affect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, or is a congenital anomaly or birth defect.
- Suspected unexpected serious adverse reaction (SUSAR) an untoward and unintended response to a study drug, which is not listed is the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Definition of adverse event (AE), adverse reactions (AR), unexpected adverse reactions (UAR)

- Adverse event (AE) any untoward medical occurrence in the patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment, as assessed by the investigator, as this is a medical decision.
- Adverse reaction (AR) any untoward and unintended response to an investigational medicinal product related to any dose administered.
- adverse reaction (AR) any untoward and unintended response to an investigational medicinal product related to any dose administered.

Guideline for assessing the relationship between adverse events and treatment

- Unrelated - no temporal relationship or other etiologies are very likely the cause.
- Unlikely related – unlikely temporal relationship or other etiologies are more likely the cause.
- Possibly related - less clear temporal relationship, other etiologies are also possible.
- Probably related - clear temporal relationship with improvement after discontinuation of medicament and not reasonably explained by the patient's clinical condition known.
- Related - clear temporal relationship with laboratory confirmation or a positive new additional treatment trial.

Severity grading

- Mild: Usual transient and generally not interfering with normal activities
- Moderate: discomforting enough to interfere with normal activities
- Severe: Prevents normal activities

Reporting of adverse events

The investigator will assess causality of AEs/SAEs and the investigator shall report all SAEs to the sponsor within 24 hours. This is for the sponsor in time to enter the event(s) to the Eudravigilance database if it is

considered a SUSAR. The information to the sponsor should include patient number, name of investigator, detailed description of the SAE, investigator's assessment of the relationship between the adverse events and the study drug, a statement that the event is serious and that it is unexpected, and the consequence for the study and the serious adverse event form.

The sponsors shall ensure that information about all unexpected and serious adverse reactions, which are fatal or life-threatening, are registered and reported through the Eudravigilance database as soon as possible and not later than 7 days after the sponsor has been made aware of such a suspected adverse reaction. Not later than 8 days after the reporting, the sponsor shall notify the relevant authorities (e.g., the Danish Medicines Agency and the Ethics Committee) with all relevant information on sponsor's and investigator's follow-up on the report. All other unexpected and serious suspected adverse reactions shall be reported to DMA and EC not later than 15 days after the sponsor has been made aware of these. SUSAR reporting will be done electronically using the Eudravigilance database.

Once a year during the entire trial period, the sponsor will prepare a list of all suspected serious adverse reactions, which have occurred during the trial period, and a report on the trial subjects' safety. List and report will be submitted to the Clinical Trials Information System (CTIS).

Follow-up after reporting of an adverse reaction

Following the adverse effect reported by the patient, this will be followed up at the next visit. If the patient drops out of the trial, the adverse event will be followed up with a telephone call after one month.

Reference Document

The SmPC from the Danish Health and Medicine Authority is used as a reference document for assessing SUSARs.

Patient dropout because of events

Any patient can because of an event, regardless of the time, be excluded from the trial according to the investigator's discretion.

12 Data management

All personal information will be protected under the General Data Protection Regulation (GDPR), and in accordance with GDPR article 30. The project will be registered in both Capital Region of Denmark (SDCC) and North Denmark Region (SDCN).

Essential study documents will be stored in REDCap, secure computer drives or at the study site in the trial master file. The investigator is responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the study. Data will be stored for 25 years. The principal investigator must maintain complete and accurate records to ensure that the execution of the study is fully documented, and the study data subsequently can be verified. These documents should be classified into two separate categories: (1) the researcher's Trial Master File and (2) the participant's clinical source documents (eCRF). The trial master file must contain the protocol/amendments, correspondence with the Medical Research Ethics Committee and Danish Data Protection Agency, informed consent, staff curriculum vitae, forms, and other appropriate documents/correspondence. Investigator allows direct access to all source data and documents, auditing, and inspection.

Electronic Case Report Forms (eCRFs) will be completed for each subject enrolled in this study, to the extent possible directly in Research Electronic Data Capture (REDCap) without the use of a paper CRF. The site investigator will document subject data in his/her own subject files or in REDCap. These subject files will serve as source data for the study. Errors and corrections are logged as provided by the REDCap interface, and information from the original version will still be available. When data have been entered, reviewed, and verified, the data will be locked to prevent editing.

13 Quality control and quality assurance

The study will be conducted in accordance with Good Clinical Practice (GCP).

13.1 Monitoring

This trial will be monitored by the GCP Unit at Aalborg University Hospital and Copenhagen University. The monitor (the person who is responsible for monitoring) will advise the investigator on the experimental implementation and assist him/her in working in accordance with the protocol, GCP and the regulatory requirements.

The investigator will allow the sponsor or its representatives to conduct periodic monitoring during the trial and after the trial has been completed, control/monitoring of all CRFs and the corresponding source documents. The monitor must therefore have direct access to these records. Monitoring visits will give the sponsor or his representatives the opportunity to evaluate the progress of the trial to verify the accuracy and completeness of CRFs, to ensure that all protocol requirements, applicable local authority regulations and investigator obligations are met and to resolve any inconsistencies in the trial records.

13.2 Direct access to source data / documents

Investigators will permit trial-related monitoring by or on behalf of the sponsor, Medical Research Ethics Committee, the GCP unit and regulatory controller(s) by providing direct access to source data / documents. Source documents are original registrations in which raw data is first recorded. These include CRFs, eCRFs, diaries and patient records; definitive clarification of source data will be detailed in the trial master file. All source documents must be accurate, clear, unambiguous, lasting, and able to undergo audits. They are made using a permanent form of registration (ink, typing or optical disk).

14 Ethical considerations

This clinical study will be conducted in compliance with Good Clinical Practice (CPMP/ICH/135/95) Regulation 536/2014)), the protocol, designated Standard Operating Procedures, the Danish Medicines Agency, the Medical Research Ethics Committee, and within the principles of the Declaration of Helsinki (amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).

The trial will only be initiated once the approval from the Danish Medicines Agency and the Medical Research Ethics Committee is granted. Any significant modifications to the protocol will be submitted as protocol amendments and subsequently approved by the regulatory authorities. Information about the participants is protected by The General Data Protection Regulation and The Danish Health Care Act.

15 Budget

The project is initiated by principal investigator Peter Rossing. This study has received funding from several entities, Svend Andersen Fonden has granted 700,000 DKK, Vissing Fonden has granted 442,400 DKK and Novo Nordisk fonden has granted 10,8 mio. DKK. Expenses covered by the various funding bodies are described in the table below.

Study medication and matching placebo has been provided from Bayer A/S.

The budget is sufficient to cover all material and study related human resources. The amount is administered from SDCC.

None of the researchers have financial interest in the study.

Foundation		DKK
Svend Andersen Fonden	Operational expenses	700.000
Vissing Fonden	Equipment and operational expenses	442.400
Novo Nordisk Fonden	Salary for Ph.d. students, post docs, senior researchers, operational expenses, dissemnination activities, travel costs, participation in international congresses and symposiums, administration costs and publication fees	10.800.000

Participants will receive travel reimbursement according to current legislation. The amount is not liable to tax.

16 Insurance

Participants are covered by the Danish Patient Compensation Association (Patienterstatningen).

17 Dissemination of results

The results of the study will be published regardless of the outcome. A summary of the results will be submitted to the CTIS portal as soon as possible and no later than one year after the study has ended.

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Appendix A

The following list comes from the Clinical Trials Coordination Group. This study will follow their recommendation (link: https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2024_HMA_CTCG_Contraception_guidance_Version_1.2__March_2024.pdf).

Short summary:

Definition of women of childbearing potential:

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

List of highly effective contraceptions that can be used in the trial:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
    a. Oral
    b. Intravaginal
    c. Transdermal

2. progestogen-only hormonal contraception associated with inhibition of ovulation1:
    a. oral
    b. injectable
    c. implantable[2]
3. intrauterine device (IUD)[2]
4. intrauterine hormone-releasing system (IUS)[2]
5. bilateral tubal occlusion[2]
6. vasectomised partner[2,3]
7. sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3)

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Appendix B

List of medication that is prohibited during the trial:

1. CYP3A4 inducers
    a. Rifampicin
    b. Carbamazepine
    c. Phenytoin
    d. Phenobarbital
    e. St John's Wort / Perikon
    f. Efavirenz
2. CYP3A inhibitors:
    a. Itraconazol
    b. Ketoconazol
    c. Ritonavir
    d. Cobicistat
    e. Clarithromycin
    f. Grapefruit
3. MRA or potassium-sparing diuretics
    a. Amilorid
    b. Eplerenone
    c. Spironolactone
4. Other
    a. Beta-blocker use
    b. Chemotherapeutic treatment within last 12 months