Clinical Trial Protocol

SGL-TX-GFR

SGLT2i safety and efficacy on kidney allograft function in non-diabetic kidney transplant recipients: A randomized, double-blind, placebo controlled, national, multicenter trial

Sponsor
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1. General information

1.1 Title

Protocol title:
SGLT2i safety and efficacy on kidney allograft function in non-diabetic kidney transplant recipients: A randomized, double-blind, placebo controlled, national, multicenter trial

Short trial title:
SGL-TX-GFR

Danish title:
SGLT2i sikkerhed og effektivitet på nyretransplantatfunktion hos ikke-diabetiske nyretransplantationsmodtagere: Et randomiseret, dobbeltblindet, placebokontrolleret, nationalt, multicenterstudie

1.2 Sponsor

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1.5 Study Monitor

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https://open.rsyd.dk/faciliteter/open-gcp-enheden

1.6 Study setting

Nephrology department Odense University Hospital
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In cooperation with
Nephrology outpatient clinics at Odense University Hospital, Rigshospitalet, Aarhus University Hospital and The Regional Hospital Gødstrup

Region Hovedstadens Pharmacy, Rigshospitalet

Department of Clinical Biochemistry, Odense University Hospital, Rigshospitalet, Aarhus University Hospital and The Regional Hospital Gødstrup

Open Patient data Explorative Network – OPEN, Odense University Hospital

1.7 Guidelines

This study will be conducted at all times in accordance with

- The protocol
- The Helsinki Declaration (1996 version)
- The International Conference on Harmonization guidelines for GCP
- The Danish Code of Conduct for Research Integrity
- National and Danish legislation

This study complies with regulation (EU) No 536/2014 of European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guideline E6.

The project is accepted as PhD-enrollment at the Graduate School, Faculty of Health Sciences, Clinical Institute, SDU

All applications will be approved in CTIS before the start of the study.
The trial is fully funded.

1.9 Signature Page

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This is an electronically document without sponsor and principal investigator signatures.
The protocol with signed signatures is filled in the Trial Master File and available upon request.

1.10 List of specific abbreviations

ACEi: Angiotensin Converting Enzyme inhibitors
AE: Adverse Event
AJT: American Journal of Transplantation
ALAT: Alanine aminotransferase
ARB: Angiotensin receptor blocker
B: Blood
BMI: Body mass index
BMJ: British Medical Journal
BP: Blood pressure
CI 95%: 95% Confidence Interval
CKD: Chronic kidney disease
CNI: Calcineurin inhibitor
CRF: Case report form
CTCAE: Common Terminology Criteria for Adverse Events
CTIS: Clinical Trial Information System
Dept.: Department
DiaBP: Diastolic blood pressure

eCRF: electronic Case Report Form
eGFR: Estimated Glomerular Filtration Rate
EPJ: Electronic patient record
ESRD: End-stage renal disease
EudraVigilance: European Union Drug Regulatory Authorities Vigilance
FMK: Common medicine card
FPFV: First patient first visit
GCP-Unit: Good Clinical Practice Unit
GDPR: General Data Protection Regulation
GFR: Glomerular filtration rate
GMP: Good manufacturing practice
HbA1c: Hemoglobin A1c
HR: Heart rate
ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IMP: Investigational medicinal product
INR: International normalized ratio
IT: Information Technology
IQR: Interquartile range
JASN: Journal of the American Society of Nephrology
KI: Kidney International
KTR: Kidney transplant recipients
LPLV: Last patient last visit
MD: Medical Doctor
NDT: Nephrology Dialysis Transplantation
NEJM: New England Journal of Medicine
OPEN: Open Patient data Explorative Network
OUH: Odense University Hospital
Ph.D.: Doctor of Philosophy
Post Doc.: Postdoctoral researcher
PTDM: Post-transplant diabetes mellitus
P-value: Probability value
RAAS: Renin Angiotensin Aldosterone System
REDCap: Research Electronic data Capture
SAE: Serious Adverse Event
SAP: Statistical Analysis Plan
SAR: Serious Adverse Reaction
SD: Standard deviation
SE: Standard errors
SF-36: Short Form Health Survey with 36 Questions
SGLT2: Sodium-glucose co transporter type 2
SGLT2i: Sodium-glucose co-transporter type 2 inhibitor
SmPC: Summary of products characteristics
STATA: Statistical software for data science
SUSAR: Suspected Unexpected Serious Adverse Reaction
SysBP: Systolic blood pressure
TMF: Trial Master File
U: Urine
U-ACR: Urine albumin creatinin ratio
V1-11: Visit 1-11
VNA: Vendor Neutral Archive

WHO: World Health Organization

2. Summary

2.1 Background

Kidney transplantation is the best treatment of end-stage renal disease (ESRD), although median allograft survival is only 15 years. In non-transplant patients with chronic kidney disease (CKD) sodium-glucose co-transporter type 2 inhibitors (SGLT2i) protects kidney function and reduces decline in estimated glomerular filtration (eGFR).

2.1.1 Perspective

With the current kidney transplant survival of average 15 years, app. one out of ten adult[1] kidney transplant recipients (KTR) outlive their donated kidneys. This poses a significant burden to the patients and society and increases the demand for new transplantations. WHO reported a 9% increase in the number of kidney transplant recipients from 2022 to 2023[2]. Therefore, research on extending the functional lifespan of kidney transplants is necessary. The efficacy of SGLT2i is untested in KTR and safety concerns remain, primarily those concerned with the effect of SGLT2i on kidney transplant function.

The study aim to illuminate the safety and efficacy of the new class of anti-diabetic SGLT2i upon the kidney transplant function. In the long-term perspective, we hope to contribute with knowledge to preserve kidney transplant function, benefit society, and improve patients' quality of life.

2.2 Hypothesis

We hypothesize that SGLT2i will not worsen kidney transplant function (eGFR) in non-diabetic KTR as an add-on to standard-of-care.

2.3 Research Objective

In this non-inferior randomized controlled clinical trial we will determine the safety and efficacy of oral SGLT2i compared with placebo as add-on to standard-of-care on effecting kidney transplant function in non-diabetic KTR.

The secondary objectives will evaluate the effect of oral SGLT2i compared with placebo as add-on to standard-of-care on urinary tract infection, incidence of PTDM and prediabetes status, U-ACR, renal parameters, cardiovascular parameters and adverse events in non-diabetic KTR.

2.4 Design

An investigator-initiated, placebo-controlled, double-blinded, parallel-group, randomized, national, multicenter intervention study.

2.5 Methods

Non-diabetic KTR who is more than 6 month post kidney transplant, will be randomized 1:1 to either 18 month of oral SGLT2i treatment (tablet Forxiga 10 mg once daily) or placebo both as add-on to standard immunosuppressive therapy. Participants will have follow up after one week, four weeks and then every 3. month the remaining trial period. Each participant will be monitored according to blood and urine laboratory values with efficacy and safety assessed at every visit by a nephrologist. Kidney transplant function will be estimated by ΔeGFR.

Blood and urine samples are taken through the hospital laboratories entirely on an outpatient basis, as the patients are accustomed to 1-7 days prior to planned outpatient telephone or in-person follow-up appointments.

2.6 Endpoints

2.6.1 Primary endpoint

- Kidney transplant function
    - Chronic eGFR slope (ml/min/1.73m^2) measured from week 4, and then every 3 month until 18 month post randomization.

2.6.2 Secondary endpoint

- Acute eGFR slope (ml/min/1,73m^2) measured from baseline until week 4.
- Urine sample
    - albumin/creatinine ratio (U-ACR) (mg/g)
- Blood sample
    - Creatinine (umol/L)
    - Total-Cholesterol
    - Low-and high-density lipoproteins (LDL and HDL, respectively) and triglycerides
    - Clinical routine Tacrolimus concentration (ug/L)
    - ALAT (U/L)
    - Bilirubin
    - Pro-BNP, renin, angiotensin-2, aldosterone
- Urinary tract infection (positive culture)
- Incidence of PTDM and prediabetes status
    - Urine glucose stix
    - HbA1c (mmol/mol)
    - Random blood glucose (mmol/L)
    - Continuous glucose monitoring
        - Fx. Dexcom G6 pro sensor, 10 days on visit 5 (3 month post randomization)
- Change in volume status in week 1 of therapy (Weight)
- Incidence of kidney transplant rejection (biopsy verified)
- Renal composite outcome
    - Incidence of graft failure (defined as return to dialysis or retransplantation)
    - Incidence of ESRD (defined as eGFR<15 ml/min/1.73m^2)
    - Incidence of > 25% increase in creatinine
- Change in Systolic blood pressure (SysBP) (mmHg) and diastolic blood pressure (DiaBP) (mmHg)
- Relative incidence of out-of-target measures of clinical routine blood Tacrolimus levels
- Urine biomarkers indicative of podocyt and tubular function from selected sites
- Incidence of:
    - Adverse events
    - Serious adverse events
    - Serious adverse reactions
    - Death – all cause mortality
    - Major Adverse Cardiac Events (MACE)
        - Death from cardiovascular causes
        - Nonfatal myocardial infarction
            - Acute Myocardial Infarction (AMI) – ICD-10 Codes

        - These codes cover acute myocardial infarction (AMI), including both STEMI and NSTEMI:
        - I21.0 – Acute transmural myocardial infarction of the anterior wall
        - I21.1 – Acute transmural myocardial infarction of the posterior wall
        - I21.2 – Acute transmural myocardial infarction of other localization
        - I21.3 – Acute subendocardial myocardial infarction
        - I21.4 – Acute myocardial infarction without ST-elevation (NSTEMI)
        - I21.9 – Acute myocardial infarction, unspecified
        - Reinfarction and Complications of AMI
        - I22.0 - I22.9 – Reinfarction (a new AMI within 28 days after a previous AMI)
        - I23.0 - I23.9 – Complications following acute myocardial infarction (e.g., papillary muscle rupture, ventricular septal defect, pericardial effusion)
    - Therapeutic coronary procedure
        - Coronary-artery bypass graft
        - Percutaneous transluminal coronary angioplasty, or stenting
    - Heart failure
        - Reduced EF (HFrEF): Ejection fraction below 40%
    - Nonfatal ischemic stroke
        - Diagnosed by CT or MR cerebrum
    - Nonfatal haemorrhagic stroke
        - Diagnosed by CT or MR cerebrum
    - Carotid procedure (endarterectomy or stenting)
    - All vascular intervention
        - Revascularization, Percutaneous transluminal angioplasty, or stenting
    - Peripheral limb amputation.

2.6.3 Tertiary endpoint

- SF-36 (Short Form Health Survey 36)

2.7 Study population

88 non-diabetic KTR, more than 6 month post-transplant and eGFR > 25 ml/min/1.73m^2, will be recruited from Odense University Hospital (OUH)-, Aarhus University Hospital (AUH)-, Rigshospitalet (RH)- and Regions Hospitalet Gødstrup (RHG) kidney transplant outpatient clinics. The participants will be randomized to SGLT2i or placebo treatment for a minimum of 18 month after signed consent.

3. Background

Kidney transplantation is first choice treatment in ESRD, if the patients are suitable for transplantation. More than 3000 patients are living with a kidney transplant in Denmark. [3], and approximately 250 new patients are transplanted annually. App. One out of ten adult KTR outlive the transplant due to current transplant survival of average 15 years[1]. Approximately 500[1] are currently waiting for a donor kidney.
The KTR must take immunosuppressive medication to prevent rejection of the kidney transplant. The side effects of immunosuppressive medication are serious and include among other; post-transplant diabetes mellitus (PTDM)[4], increased risk of cancer[5], atherosclerosis and Calcineurin

inhibitor (CNI) induced nephropathy, leading to diabetes related illness and short lifespan of the kidney transplant, generating the need for repeat transplantation.
Any treatment that can preserve kidney graft function will benefit patient's life quality and decrease the socio-economic burden for society.

3.1 Sodium-Glucose co-transporter type 2 inhibitor (SGLT2i)

The kidney transplant continuously filters blood glucose. Sodium-Glucose co transporter type 2 reabsorbs 80-90% of the filtered glucose load in the proximal tubules[6, 7].

In patients with type 2 diabetes, SGLT2i significantly showed to protect kidney function in the DECLARE-trial[8], reduce cardiovascular morbidity and mortality in the DAPA-HF-trial[9], EMPA-REG-trial[10, 11] and CREDENCE-trial[12] and slow the progression of albuminuria in the CANVAS-trial[13].

In patients with non-diabetic CKD, SGLT2i significantly slows the annual decline in chronic eGFR slope and also the composite "hard" renal endpoint + death in the DAPA-CKD trial and in EMPA-KIDNEY[14] [15]. The trials confirms, that SGLT2i's renoprotective effects extend to the broader population with CKD, but without type 2 diabetes. Patients for whom Angiotensin Converting Enzyme inhibitors (ACEi) previously was the only pharmacologic treatment that with significantly evidence, had shown to prevent kidney failure and lowering U-ACR
[16, 17].
The initial decline in eGFR is reversible and demonstrated within the first four weeks of SGLT2i therapy. The initial drop in eGFR with SGLT2i is followed by a reduction in chronic eGFR decline compared to placebo leading to a greater overall reduction in eGFR decline in the placebo group after one year of SGLT2i therapy. The annual fall in chronic eGFR slope is reduced 50% compared to placebo. Three years follow up shows SGLT2i significantly reduces risk of ESRD compared to placebo, and this effect is also observed in non-diabetic CKD patients [15, 18]

The primary renal protective mechanism for SGLT2i seems to be decreased glucose and sodium reabsorption in the proximal tubules leads to higher level of sodium delivery to the macula densa cells. The high sodium delivery to the macula densa cells leads to high level of adenosine resulting in vasoconstriction of the afferent arteriole. Furthermore, high sodium lowers renin production from the juxtaglomerular cells that downstream leads to efferent vasodilatation.
SGLT2i therefore results in afferent arteriole vasoconstriction and efferent arteriole vasodilatation overall lowering intraglomerular pressure and decreases hyper filtration, which is positive for prolonging kidney function.[19]

SGLT2i's physiological effects include among other glycosuria, natriuresis, blood pressure reduction, ketogenesis and improved metabolic parameters (lower HbA1c and weight reduction) [20].

Other *potential* SGLT2i mechanisms, leading to renal protection, include[21]:

- Reduced;
    - intraglomerular pressure due to tubuloglomerular feedback mechanisms
    - albuminuria
    - need for loop diuretic by diminish volume overload
    - possible direct toxic effects of oxidative stress, markers of inflammation and fibrosis in experimental models on renal tubules
    - ambient proinflammatory/ profibrotic pathways (experimental evidence only)
    - endothelial dysfunction and arterial stiffness
- Increased;

  - oxygenation of tubular cells based on reduced demand for solute transport
  - oxygen delivery due to higher hematocrit
- Direct cardiovascular effects with improved cardiac function and maintenance of renal perfusion

However no study have yet described, the SGLT2i effects in non-diabetic KTR.

Safety concerns remain whether SGLT2i can affect kidney transplant function, due to lowering intraglomerular pressure and the increased risk of urinary tract infection due to increased glycosuria in the immunosuppressive transplant patient. The study aim is to investigate the efficacy of oral SGLT2i and if treatment affects kidney graft function, cardiovascular outcomes and renal endpoints. If the study proves SGLT2i to be safe and effective, this medicine could provide new treatment for preserving kidney transplant function and treatment modality for post-transplant hyper glycaemia and PTDM.

3.2 Calcineurin inhibitor

Lifelong immunosuppressive medication is vital to avoid rejection of the kidney transplant. Calcineurin inhibitor (CNI), Tacrolimus, is preferred[22]. A Tacrolimus side effect is vasoconstriction of the afferent glomerular arteriole, leading to lower intraglomerular pressure and over time ischemia/hypoxia in the kidney transplant. Histological changes within the interstitium displays striped fibrosis and tubular atrophy [23]. Vasoconstriction of the afferent glomerular arteriole and fibrosis causes declined intraglomerular pressure and reduced GFR, referred to as CNI nephropathy[24].
Short term studies in rats have demonstrated preventive effect of SGLT2i in the evolution of CNI nephropathy[25, 26].
Whether CNI in combination with SGLT2i in KTR should be standard treatment need further investigation.

3.3 Post-transplant diabetes mellitus

Hyperglycemia or prediabetes is frequent in KTR short after transplantation, due to surgical stress, immunosuppressive medication with diabetogenic effects. Hyper glycaemia induces pancreatic beta cell stress and increase risk of PTDM.

The incidence of PTDM is 10-20% during the first year post-transplant [4, 27]. PTDM has the same harmful health care consequences as type 2 diabetes, including cardiovascular diseases and transplant nephropathy[4, 28]. Prophylactic post-transplant insulin therapy decreases the risk of PTDM [29, 30]. A randomized study displayed improved glycemic control, and did not affect eGFR in KTR with PTDM after 24 weeks of SGLT2i intervention.[31]

Pooled analyses have demonstrated 33% decreased incidence of new-onset type 2 diabetes in non-transplanted CKD patients treated with SGLT2i compared with placebo [32].

We hypothesize, that SGLT2i will affect glycemic control, the incidence of PTDM and maintain eGFR in KTR.

3.4 Renal hypoxia

The SGLT2 is highly energy(oxygen) consuming and cortical hypoxia correlate with the rate of decline in kidney function in CKD and diabetic-CKD patients[33, 34]. In rats and humans with type 1 diabetes, SGLT2i increases renal oxygenation significantly[35, 36] by lowering oxygen consumption due to decreased metabolic demand for sodium transport[6]
Hypoxia is strongly associated with developing chronic diabetic kidney disease [37, 38]

If SGLT2i decreases renal hypoxia in the kidney transplant, it may slow the decline in chronic eGFR and overall prolong the allograft survival to benefit the patients and society.

3.5 SGLT2i and cardiovascular events

In patients with type 2 diabetes, SGLT2i significantly reduce cardiovascular morbidity and mortality in the DAPA-HF-trial[9], EMPA-REG-trial[10, 11] and CREDENCE-trial[12]. The reduced cardiac vascular mortality and morbidity in patients with type 2 diabetes using SGLT2i is highlighted in a systematic review with meta-analysis[39], it shows SGLT2i has significant preventive effects on cardiovascular death, myocardial infarction, heart failure and all-cause mortality. Empagliflozin, Dapagliflozin and Canagliflozin all reduced the incidence of heart failure, but only Dapagliflozin displays a favorable effect on inhibiting stroke, but this finding could be explained due to the differences in study designs, interventions, inclusion criteria, sample sizes and other factors and thus does not rule out a class effect on stroke. Furthermore, SGLT2i reduces the incidence of heart failure and cardiovascular death in patients with high-risk factors[39].

In patients with non-diabetic CKD and heart failure, SGLT2i significantly reduces morbidity and mortality and do not worsen eGFR decline from baseline compared with placebo, in the DAPA-HF-trial[9]

The DAPA-CKD trial describes significantly, that among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of death from cardiovascular causes was significantly lower with Dapagliflozin than with placebo[15].

SGLT2i is prescribed for diabetic KTR, but data regarding non diabetic KTR cardiovascular outcomes are not available due to exclusion of KTR in the major kidney and cardiovascular outcome trials, and results in a knowledge gap towards safety and efficacy in this population. A review described that Empagliflozin was the most prescribed SGLT2i followed by Dapagliflozin and the median time from transplant for initiating SGLT2i was 3 years[40]. A cohort study including 750 KTR shows SGLT2i significantly decreases the risk of cardiovascular events in KTRs with diabetes, particularly lowering the incidence of myocardial infarction and death from cardiovascular causes[41]. A meta-analysis concluded SGLT2i treatment in KTR resulted in significant improvement of hospitalizations due to heart failure, and cardiovascular and all-cause mortality[42]. Despite increasing evidence of the benefit of SGLT2i in KTR, its use currently in these patients is off-label.

We hope, that our study will contribute to increased evidence on the safety profile regarding SGLT2i in non-diabetic KTR.

4. Investigational Medical Product (IMP)

The IMP is manufactured, handled, and stored in accordance with good manufacturing practice (GMP). The IMP will only be used as described in the protocol at all times.

4.1 Description of IMP – Dapagliflozin (Forxiga 10 mg)

Dapagliflozin[43]
Oral antidiabetic drug, acts independently of endogenous insulin by increasing glucose excretion in the urine. Selective SGLT2i.
SGLT2i originally developed for treatment of type 2 diabetes, now approved for treatment of chronic heart failure and CKD, in patients with and without type 2 diabetes.

Indications
SGLT2i is used for the treatment of type 2 diabetes, heart failure and chronic kidney disease.

The purpose of this study will be to measure the safety and effect of SGLT2i on KTR

Dosage form
Each film-coated tablet contains 10 mg Dapagliflozin (as propanediol monohydrate).
Tablets will be blinded in gelatin capsules.
One capsule a day.

Precautions
We take precautions and exclude patients form the study with Type 1 diabetes. The trial medicine will be paused in case of patients hospitalized for surgery or severe, life-threatening illness.

We will take caution and observe the participant closely for the whole trial duration.

Only patients with a kidney graft function > 25 ml/min/1.73m^2, will be included, ongoing treatment continue at the same dosage due to assumed renal protective effect until dialysis or retransplantation.

Hypo- and hypertension
Treatment of hypertension with loop diuretics may increase the risk of dehydration and hypotension.
Caution should be exercised in patients with a history of hypotension.

Temporary discontinuation of treatment
In the event of hypovolemia, dehydration, or hypotension.
During major surgeries or severe acute illness, and ketone levels in the blood should be monitored.
Should be considered during treatment of pyelonephritis if the patient is unstable, defined by impaired vital parameters and requiring IV fluid substitution.

Interactions
Dapagliflozin may enhance the diuretic effect of loop diuretics or thiazides.
Dapagliflozin may increase the excretion of lithium through the kidneys, which can lower lithium levels in the blood.

Further information can be found in the Summary of products characteristics (SmPC)

4.1.1 Placebo drug
Manufacture of Placebo Capsules (Identical to Forxiga 10mg "AstraZeneca" Capsules)
One placebo tablet (8 mm) is placed into an empty, opaque gelatin capsule, size AA. The capsule is filled with Lactose Monohydrate before being sealed using a manual capsule-filling device.
Manufactured by Region Hovedstadens Pharmacy.
For further information see appendix sIMPD for placebo

4.2 IMP dosing modifications
No dosing modifications are allowed.

4.3 Declaration on approval of IMP
SGLT2i is approved for treatment of non-diabetic kidney disease for adults (≥ 18 years) with proteinuria U-ACR 200-5000 mg/g, with beneficial effect on cardioprotective and renoprotective

shown in previous conducted long term studies.[15, 44] SGLT2i is used for treatment of diabetic KTR but it is off-label use[40].

SGLT2i is not yet recommended for KTR, due to lack of randomized clinical trials (RCT) in KTR supporting the renoprotective mechanism in the renal allograft.

4.4 Safety profile for IMP

For elaborate information regarding drug, please refer to SmPC

Documented side effects for long term use of Forxiga

System organ class	Potentially serious side effects	Most often non-serious side effects
Very common (> 10%)		
Metabolism and nutrition	Hypoglycemia*	
Common (1-10%)		
Biochemistry		Elevated hematocrit
Metabolism and nutrition	Dyslipidemia, Ketoacidosis**	
Musculoskeletal and connective tissue disorders	Back pain	
Nervous system	Dizziness	
Kidneys and urinary system	Impaired renal function, Urinary tract infection	Dysuria, Polyuria
Reproductive system and breasts		Balanitis
Skin and subcutaneous tissue		Skin rash
Vascular disorders	Hypotension	
Not common (0,1-1%)		
Gastrointestinal system		Dry mouth, Constipation
Infections and parasitic diseases	Candidiasis	
Biochemistry		Elevated plasma urea and creatinine
Metabolism and nutrition		Weight loss, thirst
Kidneys and urinary system		Nocturia
Reproductive system and breasts	Vulvovaginitis****	Vaginal itching
Vascular disorders	Hypovolemia (including dehydration)	
Very rare (< 0.01%)		
Immune system	Angioedema	
Musculoskeletal and connective tissue disorders	Necrotizing fasciitis (in the perineum - Fournier's gangrene)***	
Kidneys and urinary system	Tubulointerstitial nephritis	

* Hypoglycemia has been observed with concurrent use of sulfonylureas or insulin.
** The frequency of ketoacidosis in the treatment of type 1 diabetes (indication has been removed) is common. However, it is rare in the treatment of type 2 diabetes.
*** Patients should be informed to contact a doctor if Fournier's gangrene (necrotizing fasciitis in the perineum) is suspected. Treatment should be discontinued in cases of Fournier's gangrene.
**** Cases of phimosis/acquired phimosis have been reported in conjunction with genital infections, and in some cases, circumcision was necessary.

If any of the mentioned side-effects should occur, it will be managed with standard treatment care. Complications that might occur will be managed and followed up relevantly by the investigators. As KTR have an intensive surveillance regime, we do expect to identify all complications or adverse event that might occur.

4.5 Rationale for dose selection

A daily dose of 10 mg Forxiga has been chosen, because this is the recommended dose for the treatment of CKD in non-KTR.

This dose is comparable to the large randomized studies that form the basis for the recommendation of SGLT2i as nephroprotective[15].

A single daily dose of 10 mg Forxiga are considered safe and within the recommendations in the SmPC.

4.6 Description and handling of the IMP

The IMP will be manufactured, packaged, labeled, and stored in accordance with Good Manufacturing Practice (GMP) regulations. The IMP is supplied by Region Hovedstadens Pharmacy, formalized inspection has been conducted in accordance with GMP.

4.6.1 Description

A single daily dose of SGLT2i (Tablet Forxiga 10 mg) or placebo will be consumed by the participant in the trial period, 18 month.

Recommended method of administration

- The capsule should be swallowed whole with a glass of water.
- The capsule can be taken with or without food.

The trial medication will be distributed from the outpatient clinics to ensure that the quantity dispensed adheres to the expiration date.

4.6.2 Drug supplies

IMP and placebo medicine will be provided by Region Hovedstadens Pharmacy.

4.6.3 Packing and Labelling

Tablet packing and blinding

Tablet Forxiga 10 mg is blinded by encapsulation into an empty, opaque gelatin capsule, size AA. The capsule with the tablet Forxiga 10 mg, is afterwards filled with Lactose Monohydrate before being sealed using a manual capsule-filling device.
Manufactured by Region Hovedstadens Pharmacy.
32 capsules will come in each medicine container, for further information – see appendix sIMPD.

Labelling

The medicine container is labelled with text in Danish and batch number by Region Hovedstadens Pharmacy.

4.6.4 Drug storage

The investigator will check that the received IMP corresponds to the order, and that the item is intact and shows no signs of damage. Documentation is done via signature on the shipping receipts and in the eCRF.

The IMP will be stored out of reach of unauthorized individuals. The IMP will be kept separate from other medications. Shelves or areas where used and unused IMP are stored will be clearly marked. Guidelines regarding the storage conditions of IMP will be followed.

The IMP and placebo do not need special preparation or handling, it can be stored in the medicine container at normal house conditions.

Medical records and trial medication is stored separately in a locked medicine room.

4.6.5 Drug accountability

The IMP can be traced, due to the batch code manufactured by Region Hovedstadens Pharmacy.

The investigator will keep a record of the IMP i.e., the receipt of the medicine, distribution to trial participants, and return from participants, as well as destruction, will all be documented. The eCRF will serve as documentation for the IMP that is dispensed and returned. The IMP may only be used as described in this protocol, and it is the investigator's responsibility to ensure that trial participants are instructed in the correct use of the IMP. Participants' compliance will be assessed by counting the number of capsules returned.

Drug accountability will be performed at the investigation site at V2-V10, all packing from consumed and non-consumed drug, will be destroyed, according to regulations.

4.6.6 Drug administration

A single daily dose of tablet SGLT2i (Tablet Forxiga 10 mg) or placebo will be consumed by the participant in the trial period, 18 month. The trial medication will be distributed from the outpatient clinics to ensure that the quantity dispensed adheres to the expiration date.

If a dose is missed, it should be skipped, and the next dose should be taken as scheduled the following day.

4.6.7 Management of overdose

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

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

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

4.7 Treatment and medicine allowed during the trial.

All of the participant’s regular medicine is allowed during the trial.
It will be allowed to participate in this study in case of hospitalization, the investigating drug will be paused, and can be resumed when the condition is in remission and the participant is stable.

4.7.1 Concomitant medications

All medications or vaccines that the participant is currently taking at the time of enrollment or receives during the study must be documented in the eCRF.

4.8 Safety in non-diabetic kidney transplant recipients

The data regarding SGLT2i treatment in non–diabetic KTR are yet insufficient to recommend the use of these drugs, but previously trials on KTR with PTDM are reassuring. Novel and ongoing RCT in KTR will provide outcomes regarding renal allograft function, cardiac protective outcomes and incidence of PTDM in the near future.

A dose of Dapagliflozin 10 mg has been chosen, according to European- and Danish Medical Agency recommendations of using SGLT2i in patients with non-diabetic kidney disease. The dose is similar to the dose used in other large RCT studies investigating the effect of SGLT2i[10, 11, 15].

Long term use of SGLT2i has shown side effect, and we expect in non-diabetic to see: hypotension, dyslipidemia, urinary tract infection in 1-10%. Candidiasis and hypovolemia in 0,1-1%. We do not expect to see angioedema, necrotizing fasciitis and tubulointerstitiel nephritis but is has been described as very rare side effects. Very rare incidents of ketoacidosis have been observed but only in diabetes patients.

If any of the mentioned side-effects should occur, it will be managed with standard of care.

Complications will be managed and followed up relevantly by the investigators.

The KTR have an intensive surveillance regime, we do expect to obtain every single complication or adverse event that occur.

In case of unplanned hospitalization, the IMP will be paused by the treating doctor, to be resumed when the patient is assessed stable, and the cause of hospitalization in remission.
KTR do not need to pause project medicine when admitted for routine replacement of chronic JJ catheter and the event will not be registered as an adverse event.

4.9 Overall benefit/risk conclusion

The foreseeable risks of the trial are outweighed by the expected benefits for the trial participant and society as a whole. The expected benefits justify any potential risks associated with participation.

The effect of SGLT2i has not been examined in non-diabetic KTR.
The results and knowledge obtained from this study, we believe could contribute to improved treatment of kidney allograft in the long term. This will benefit all KTR worldwide. We believe that potential discomforts and risks are compensated by the expectable advantages of conducting this study.

4.10 Patients risks and management of complications

The risk of side effects will be presented to participants before consent to participate in the trial. If side effects or complications arise, they will be treated immediately after identification, and a doctor will assess whether it is safe for the participant to continue in the study or if the patient should be excluded. The participant may choose to withdraw from the trial at any time.

4.11 Post-study care

Following the termination of the study, there are no predefined post-study care. Participants will resume their routine appointments in the kidney transplant outpatient clinic as usual.

5. Study purpose

5.1 Purpose

The study aim to illuminate the safety and efficacy of the new class of anti-diabetic SGLT2i upon the kidney transplant function.

5.2 Research Objectives

5.2.1 Primary objective

In this non-inferior randomized controlled clinical trial we determine the safety and efficacy of oral SGLT2i compared with placebo as add-on to standard-of-care on affecting kidney transplant function in non-diabetic KTR.

5.2.2 Secondary objective

The secondary objectives will evaluate the effect of oral SGLT2i compared with placebo as add-on to standard-of-care on urinary tract infection, incidence of PTDM and prediabetes status, U-ACR, renal parameters, cardiovascular parameters and adverse events in non-diabetic KTR.

5.2.3 Tertiary objective

The tertiary objective is to examine the SGLT2i effect on overall health.
The SF-36 (Short Form Health Survey with 36 Questions) will be used, it is a widely used questionnaire that measures overall health status and health-related quality of life (HRQoL) across eight key domains. It is designed to capture the patient's self-reported health status, both physical and mental. The SF-36 is valued for broad applicability and ability to offer a comprehensive view of health, making it useful for tracking outcomes in chronic disease management and evaluating treatment impacts.

5.3 What this study adds – Potential benefits

The SGLT2i have demonstrated kidney benefits which are not fully explained. Large randomized trials have shown positive effects of SGLT2i treatment on cardiovascular outcomes in type 2 diabetes, EMPA [11], CANVAS[13], DECLARE[8], CREDENCE[12], and in non-diabetic patients (DAPA-HF[9], DAPA-CKD[15], EMPEROR[45]. The DAPA-CKD and EMPA-Kidney trials are however the only trials, investigating effect on SGLT2i in non-diabetic patients regarding decline in kidney function as primary endpoint, with significantly reducing kidney failure [15, 46].
Clinical trials investigating the SGLT2i effect in the non-diabetic study population are few, and trials investigating the SGLT2i in non-diabetic KTR are lacking.
With this study, we will investigate if SGLT2i effects renal allograft survival in non-diabetic KTR compared to placebo.

Our findings will improve evidence-based treatment for KTR. Maybe it will support the already present evidence substantiating the renoprotective effects recently seen with SGLT2 inhibitors in major clinical trials with non-transplant patients and provide new horizons for therapeutic treatments for KTR.

Our findings may show a trend towards SGLT2i prolong kidney allograft survival. Further studies should investigate the long term effect of SGLT2i on KTR.

Any treatment that will prolong the survival of the kidney allograft, will have significant socio-economic advantages for the society and for the patient.

5.4 Impact and United Nations

If SGLT2i do not worsen kidney allograft function in KTR, the decline in the kidney transplant function may also be diminished, equivalent to non-transplanted non-diabetic CKD patients, over a longer follow up period, this will prolong the half-lives of transplanted kidneys, thus decreasing the need for repeat transplantation. This may result in a shorter waiting list/waiting time for kidney transplantation.

Almost no clinical trials with SGLT2i have included KTR. However, in the published studies, only KTR with PTDM has been investigated[31]. Thus, the SGLT2i impact on kidney transplant function in non-diabetics has not been investigated. Only two trials includes non-diabetic KTR, registered on www.clinicaltrials.gov or www.clinicaltrialsregister.eu (11.10.24)

This investigator initiated project does not conflict with any of the 17 United Nations sustainable development goals. There is no gender selection, and the project illustrates the lifelong need and eagerness for education. If we are successful, the health and well-being of KTR will be improved to the benefit of the burden of kidney diseases on healthcare systems worldwide[47].

5.5 Feasibility of the project

The project is a clinical study that needs coordination and administration. The dept. of Nephrology at OUH has a research unit with laboratory technicians and study nurses, who will be involved in the project. This unit has experience in running large-scale commercial and investigator-initiated studies.

The study is funded without any sponsorship from the pharmaceutical industry.

This study is a national multicenter study, involving all kidney transplantation centers in Denmark: AUH, RH, and OUH transplantation center. We do not expect any recruitment issues to occur. If recruitment does become a problem, we will involve all outpatient clinics with kidney transplant patients in the Region of Southern Denmark to participate. This change in recruitment arrangements will require approval of a substantial modification.

Furthermore, the effect of SGLT2i treatment correlates with kidney function [48]. However, we have selected the study population with a reasonable renal reserve capacity to mitigate the decline in kidney function as a reason for drop-out.

6. Study design

6.1 Hypothesis

We hypothesize that oral SGLT2i as add-on to standard-of-care compared with placebo, is non-inferior with respect to kidney graft function in non-diabetic KTR.

We hypothesize that oral SGLT2i as add-on to standard-of-care compared with placebo, is non-inferior with respect to urinary tract infection, incidence of PTDM and prediabetes status, U-ACR, renal parameters, cardiovascular parameters and adverse events.

6.2 Endpoints

6.2.1 Primary endpoints

- Kidney allograft function
    - Chronic eGFR slope (ml/min/1.73m^2) measured from week 4, and then every 3 month until 18 month post randomization.

6.2.2 Secondary endpoint

- Acute eGFR slope (ml/min/1,73m^2) measured from baseline until week 4.
- Urine sample
  - albumin/creatinine ratio (U-ACR) (mg/g)
- Blood sample
  - Creatinine (umol/L)
  - Total-Cholesterol
  - Low-and high-density lipoproteins (LDL and HDL, respectively) and triglycerides
  - Clinical routine Tacrolimus concentration (ug/L)
  - ALAT (U/L)
  - Bilirubin
  - Pro-BNP, renin, angiotensin-2, aldosterone
- Urinary tract infection (positive culture)
- Incidence of PTDM and prediabetes status
  - Urine glucose stix
  - HbA1c (mmol/mol)
  - Random blood glucose (mmol/L)
  - Continuous glucose monitoring
    - Fx. Dexcom G6 pro sensor, 10 days on visit 5 (3 month post randomization)
- Change in volume status in week 1 of therapy (Weight)
- Incidence of kidney transplant rejection (biopsy verified)
- Renal composite outcome
  - Incidence of graft failure (defined as return to dialysis or retransplantation)
  - Incidence of ESRD (defined as eGFR<15 ml/min/1.73m^2)
  - Incidence of > 25% increase in creatinine
- Change in systolic blood pressure (SysBP) (mmHg) and diastolic blood pressure (DiaBP) (mmHg)
- Relative incidence of out-of-target measures of clinical routine blood Tacrolimus levels
- Urine biomarkers indicative of podocyt and tubular function from selected sites
- Incidence of:
  - Adverse events
  - Serious adverse events
  - Serious adverse reactions
  - Death – all cause mortality
  - Major Adverse Cardiac Events (MACE)
    - Death from cardiovascular causes
    - Nonfatal myocardial infarction
      - Acute Myocardial Infarction (AMI) – ICD-10 Codes
      - These codes cover acute myocardial infarction (AMI), including both STEMI and NSTEMI:
      - I21.0 – Acute transmural myocardial infarction of the anterior wall
      - I21.1 – Acute transmural myocardial infarction of the posterior wall
      - I21.2 – Acute transmural myocardial infarction of other localization
      - I21.3 – Acute subendocardial myocardial infarction
      - I21.4 – Acute myocardial infarction without ST-elevation (NSTEMI)
      - I21.9 – Acute myocardial infarction, unspecified
      - Reinfarction and Complications of AMI
      - I22.0 - I22.9 – Reinfarction (a new AMI within 28 days after a previous AMI)

        - I23.0 - I23.9 – Complications following acute myocardial infarction (e.g., papillary muscle rupture, ventricular septal defect, pericardial effusion)
    - Therapeutic coronary procedure
        - Coronary-artery bypass graft
        - Percutaneous transluminal coronary angioplasty, or stenting
    - Heart failure
        - Reduced EF (HFrEF): Ejection fraction below 40%
    - Nonfatal ischemic stroke
        - Diagnosed by CT or MR cerebrum
    - Nonfatal haemorrhagic stroke
        - Diagnosed by CT or MR cerebrum
    - Carotid procedure (endarterectomy or stenting)
    - All vascular intervention
        - Revascularization, Percutaneous transluminal angioplasty, or stenting
    - Peripheral limb amputation.

6.2.3 Tertiary endpoint

- SF-36 (Short Form Health Survey 36)

6.3 Methods

6.3.1 Procedure for identifying the source data.

Source data will be obtained from:

- Informed consent
- The electronic patient record (EPJ)
    - Medical records and journals, biochemistry
    - Vendor Neutral Archive (VNA) containing imaging study
    - Common medicine card (FMK)
- Electronic Case Report File (eCRF) and Serious Adverse Events (SAE) reports
- eCRF containing SF-36

An electronic Case report file (eCRF) will be produced on each participant, pseudonymized, containing the randomization code and the endpoints extracted from the source data.

6.3.2 Baseline characteristics

After signed consent and enrollment in the study, baseline characteristics will be conducted form patients medical journal and by anamnesis and entered in the eCRF.

Demographics (date of birth, ethnic origin, sex, smoker), Medical history, Medicine (Immunosuppressive, Antihypertensive, Diuretics, Cholesterol lowering medication, Blood thinning medicine), Comorbidity, Symptoms, Physical examination, Anthropometric data (Weight, Height, BMI, Blood pressure, Heart rate), eGFR ml/min, Hgb mmol/L, S-Potassium mmol/L, U-ACR mg/g.

6.3.3 Blood samples

Blood samples are collected by venipuncture technique.

A total of maximum 40 ml blood will be drawn per visit.

Routine blood sample, there is part of routine check after kidney transplantation is referred to as TX-standard, and differs between location:

OUH - TX-standard:
blood (b)-Hemoglobin A1c (HbA1c), plasma(p)-bilirubin, p-carbamide, b-Mean Cell Volume (MCV), b-Erythrocyte Volume Fraction (EVF), p-glucose, b-Hemoglobin (hgb.), b-Mean Concentration of Hemoglobin in erythrocytes (MCH), b-leukocytes, p-magnesium, b-neutrophils, p-phosphate, p-potassium, p-sodium, b-platelets, p-urate, p-calcium ion, b-reticulocytes, p-Alanintransaminase (ALAT), p-gamma-glutamyl transferase (GGT), p-lactate dehydrogenase (LDH), p-albumin, p- c-reactive protein test (CRP), p-ferritin, p- Cytomegalic virus Deoxyribonucleic acid polymerase chain reaction (CMV DNA PCR), p- Epstein Bar Virus (EBV) DNA PCR, p-CO2 total, p-creatinine, p-alkaline phosphatase, p-Tacrolimus

AUH – TX-standard:
Tacrolimus/ciclosporin/sirolimus-based regimen:
eGFR (P-creatinine), P-sodium, P-potassium, P-calcium ion, P-phosphate, P-urea, P-total CO2, B-hemoglobin, B-leukocytes, P-glucose, P-albumin, B-tacrolimus (T0)/B-ciclosporin (C120min)/B-sirolimus

With MMF/azathioprine supplementation:
B-leukocytes + differential count and B-platelets

RH – TX-standard:
P-albumine, P-ionized calcium, P-urea, P-total CO2, P-creatinine, P-CRP, P-glucose, B-hemoglobin, P-potassium, P-LDH, B-leukocytes, P-sodium, P-phosphate, B-platelets.

The Regional Hospital Gødstrup – TX-standard:
Standard tx/minimum:
HbA1c, b-hemoglobin, p-sodium, p-potassium, b-leucocytes, p-creatinine (eGFR), p-carbamide, p-albumine, urine albumin/creatinine ratio, p-tacrolimus/cyclosporin

Standard minimum tx + CKD (most used), in addition:
p-bilirubin, p-ALAT, p-alkaline phosphatase, p-calcium ion, p-phosphate, p-parathyrin (PTH), p-CO2 total

At least yearly (or more frequently as needed), additionally:
p-glucose, p-c-reactive protein (CRP), p-uric acid, P-Hepatitis B virus s(Ag) [HBsAg], P-Hepatitis C virus-Ab [HCV-Ab], P-Cytomegalovirus-Ab grp [CMV], P-Epstein-Barr virus-antibody, P-HIV 1+2 (Ag+Ab), P-Koagulationsfaktor II+VII+X [INR]**,** p-cholesterol, p-cholesterol HDL/LDL, p-triglycerides

Extra blood samples are defined as:

Liver:
ALAT and bilirubin

Tac:
Clinical routine blood tacrolimus (µg/L) must be measured before first morning dose.

Extra 1:
Pro-BNP, renin, angiotensin-2, aldosterone

Cholesterol:
Total-, HDL-, and LDL cholesterol and triglycerides

The following blood samples will be taken:

- Visit 2
  - Routine blood samples will be used as baseline if taken < 4 weeks before randomization
    - TX-standard + Liver + Tac + Cholesterol + Extra 1
  - Plasma hCG (fertile women)
- Visit 3
    - TX-standard + Tac + Extra 1 + Liver
- Visit 4-10
  - TX-standard + Tac + Cholesterol(6 + 12 + 18 month control) + Liver

All material will only be used for analysis in this study and will be destroyed after the study is completed.

Blood analyses will be performed by the biochemical department at the respective hospitals involved.

6.3.4 Urine samples

A maximum of 200 ml urine will be collected at all visits.

The following urine samples will be taken:

- Visit 2 - 9
  - U-ACR, U-glucose stix
  - Urine culture and antibiotic susceptibility testing (Urine D+R)
- Visit 10
  - U-ACR, U-glucose stix
  - Urine D+R
  - Urine biomarkers indicative of podocyt and tubular status

Additional urine cultures will be conducted in the presence of the following symptoms of urine tract infection occurs: dysuria, pollakisuria, abdominal pain fewer or medical suspicion of urinary tract infection.

All biological material will only be used for analysis in this study within the study research biobank and will be destroyed after the study is completed.

Biological material will only be stored for future unspecified research if the participant have given their signed consent.

Analyses will be performed by the department of biochemistry and microbiology at the respective hospitals involved or can be sent for analysis at the OUH department of biochemistry.

6.3.5 Continuous glucose monitoring

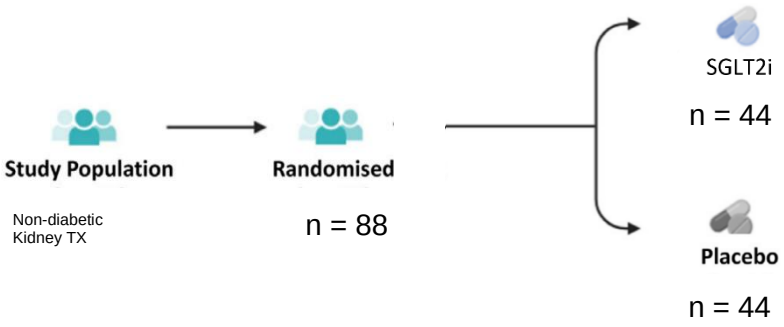
At visit 5 continuous glucose monitoring will be performed.
A professional blinded FreeStyle Libre iQ or Dexcom G6 sensor will be utilized. It will be placed on the back of the upper arm and will continuously record interstitial glucose levels every 15 minutes for a duration of 10 days. The sensor's filament, measuring less than 0.4 mm in thickness, is

inserted 5 mm beneath the skin to monitor glucose levels. Designed to be water-resistant, the sensor does not impose any restrictions on physical activity. Participants will not have access to the recorded data, and no additional components are necessary for its operation. A single reader device will be used for both activation and scanning of the sensor. The glucose monitor will be attached and later removed and read in the hospital outpatient clinic by either the principal investigator, sub-investigator, or trained outpatient clinic nurses.

6.4 Trial design

Investigator initiated, randomized, double blinded, placebo controlled, national, multicenter intervention study.

6.4.1 Figure 1 - Study design



We chose the RCT study design to achieve high level of evidence.

6.4.2 Comparative treatment regimes

The intervention will be SGLT2i compared with placebo, both as add-on to standard of care treatment.

The trial include a total of 88 non-diabetic KTR.

44 patients will be randomly assigned to treatment with SGLT2i after inclusion, follow up for 18 months.

44 patients will be randomly assigned to treatment with placebo after inclusion, follow up for 18 months.

6.4.3 Measures taken to reduce bias

6.4.3.1 Randomization

Patients who fulfills inclusion criteria and have given informed consent will be randomly assigned to receive SGLT2i or placebo as an add-on to standard of care, in a 1:1 ratio of the two regimes.

- SGLT2i treatment
- Placebo treatment

Randomization will be performed using REDCap an electronic data capture software and create a sequestered, fixed randomization schedule.
A randomization list is generated before study initiation, it will contain block identification, block size, sequence within block and allocation.

6.4.3.2 Blinding and unblinding

Randomization will be conducted through REDCap, generating a unique randomization number for each participant. Based on this number, the unblinded individual at Region Hovedstadens pharmacy will consult the randomization list to assign participants to either the SGLT2i group or the placebo group. Only the unblinded individual will have access to the allocation information. This person will also be responsible for providing the trial medication to the investigator. To maintain blinding, both SGLT2i and placebo will have identical capsules. This process ensures that the study remains double-blinded.

Randomization codes and sealed envelope with unblinding details will be stored securely at the study site, kept in a locked drawer.

The principal investigator/sub-investigator will recruit, enroll and assign all participants for sequence allocation.
The principal investigator/sub-investigator will be blinded to sequence allocation until after the last patient last visit.

All other lab-technicians, statisticians, outcome assessors, study nurses and study participants will be blinded until the end of data analysis.

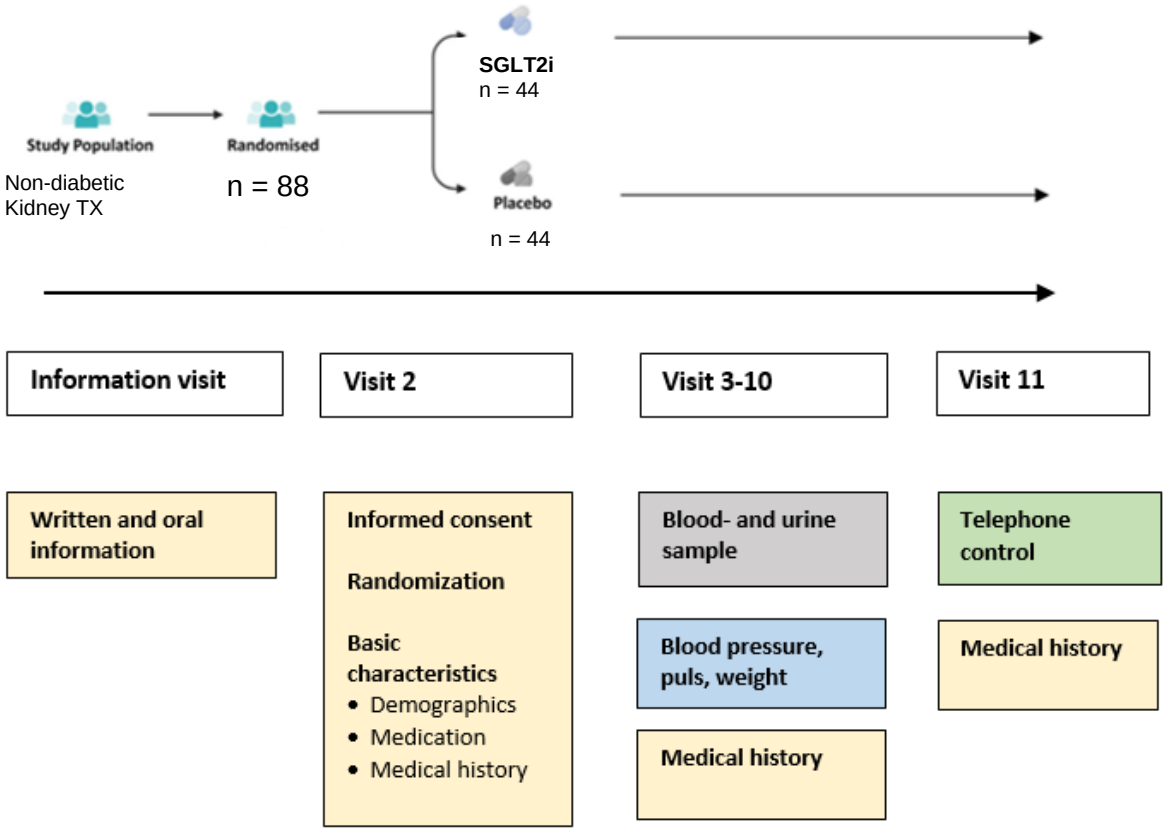
Should unblinding of a study participant be necessary because of an emergency, the investigator will be able to perform emergency unblinding as it is the sole responsibility of the investigator to decide if emergency unblinding is warranted.
If for some reason the investigator is not present a dedicated person at the nephrology dept. of OUH, not involved in the study, will perform the procedure. Alternatively, the sponsor will be able to perform unblinding.

In case of breach of randomization codes or unblinding, the patient involved will be withdrawn from the study and the GCP unit (monitor) will be immediately notified.

6.4.3.3 Arrangements for maintaining treatment randomization codes and procedures in case of breach

In case of breach, the patient involved will be withdrawn from the study.

6.4.4 Figure 2 - Study visits



6.4.5 Visit 1 – Information visit

Location: Transplant center/outpatient clinic at the respective hospitals involved in the study.

In quiet surroundings, the patient and if any, co-sitter, will be provided with written information regarding the study aim and execution and reviewed orally.

Assessment of in and exclusion criteria will be done.

The patient will have the opportunity of reflecting for at least 24 hours, before deciding to participate.

6.4.6 Visit 2

Location: Transplant center/outpatient clinic at the respective hospitals involved in the study.

After the opportunity of reflecting for at least 24 hours, the patients who approve participation, will sign the informed consent form.

After signing the informed consent, the patients will be randomized and allocated.

The following are obtained after signed consent:

- Baseline characteristics
    - Demographics

        - Date of birth, ethnic origin, sex, smoking status
    - Medical history
        - Medicine
            - Immunosuppressive
            - Antihypertensive
            - Diuretics
            - Cholesterol lowering medication
            - Blood thinning medicine
        - Comorbidity
        - Symptoms
    - Physical examination
        - Auscultation of the heart and lungs.
        - Lower extremities edema description (location: Ankle level, to knee level, above knee level and severity: mild, moderate, severe)
- Anthropometric data
    - Body weight (kg, with one decimal, without shoes)
    - Height
    - Blood pressure (home or at outpatient follow-up)
    - Bioimpedans if possible at site
- Laboratory evaluations
    - Blood samples:
        - Routine blood samples will be used as baseline if taken no more than 4 weeks before randomization, it will otherwise supplied with:
        - TX-standard
        - Clinical routine Tacrolimus
        - Extra 1
        - Cholesterol
    - Urine samples
        - U-ACR, U-glucose stix
        - Urine D+R
- Biobank samples for future research
    - Only if signed informed consent from participant.

6.4.7 Visit 3

Location: Transplant center/outpatient clinic at the respective hospitals involved in the study.

Time: 1. Week +/- 3 days from randomization

- Medical history
    - Medicine
        - Immunosuppressive
        - Antihypertensive
        - Diuretics
        - Cholesterol lowering medication
        - Blood thinning medicine
    - Comorbidity
    - Symptoms
    - Adverse events
- Physical examination:

        - Lower extremities edema description (location: Ankle level, to knee level, above knee level. and severity: mild, moderate, severe)
- Anthropometric data
    - Body weight
    - Blood pressure (home or at outpatient follow-up)
    - Bioimpedans if possible at site
- Laboratory evaluations
    - Blood samples:
        - TX-standard
        - Tac
        - Extra 1
    - Urine samples
        - U-ACR, U-glucose stix
        - Urine D+R

6.4.7 Visit 4-9

Location: Transplant center/outpatient clinic at the respective hospitals involved in the study or outpatient telephone follow-up.

Time: 1,3,6,9,12 and 15 month from randomization

- Medical history
    - Medicine
        - Immunosuppressive
        - Antihypertensive
        - Diuretics
        - Cholesterol lowering medication
        - Blood thinning medicine
    - Comorbidity
    - Symptoms
    - Adverse events
- Physical examination if physical outpatient attendance:
        - Lower extremities edema description (location: Ankle level, to knee level, above knee level. and severity: mild, moderate, severe)
- Anthropometric data
    - Body weight (home or at outpatient follow-up)
    - Blood pressure (home or at outpatient follow-up)
- Laboratory evaluations
    - Blood samples:
        - TX-standard
        - Clinical routine Tacrolimus
        - Cholesterol (6 and 12 month after from randomization)
    - Urine samples
        - U-ACR, U-glucose stix
        - Urine D+R
    - Continuous glucose monitoring at visit 5, duration 10 days

6.4.8 Visit 10

Location: Transplant center/outpatient clinic at the respective hospitals involved in the study.

Time: 18 month from randomization

- Medical history
  - Medicine
    - Immunosuppressive
    - Antihypertensive
    - Diuretics
    - Cholesterol lowering medication
    - Blood thinning medicine
  - Comorbidity
  - Symptoms
  - Adverse events
  - SF-36
- Physical examination if physical outpatient attendance:
    - Lower extremities edema description (location: Ankle level, to knee level, above knee level. and severity: mild, moderate, severe)
- Anthropometric data
  - Body weight
  - Blood pressure (home or at outpatient follow-up)
- Laboratory evaluations
  - Blood samples:
    - TX-standard
    - Cholesterol
  - Urine samples
    - U-ACR, U-glucose stix
    - Urine D+R
    - Urine biomarkers indicative of podocyt and tubular status

6.4.9 Visit 11

End of study telephone call, for detecting late adverse events.

6.4.10 Table 2 – Schedule of Activities

Visit	Recruitment	Information	V2	V3	V4-9	V10	V11
Site	Nephrology outpatient clinic	Nephrology outpatient clinic	Nephrology outpatient clinic	Nephrology outpatient clinic	Nephrology outpatient clinic	Nephrology outpatient clinic	Telephone
Estimated time from randomization	- 14 days	- 7 days	0 days	7 days	1,3,6,9,12 and 15 month	18 month	18 month + 3 days
Tolerance (+/- days)	7	7	7	3	7	7	7
General							
Informed consent			X				
Assessment of in and exclusion criteria	X	X					
Randomization			X				
Baseline characteristics							
Demographics			X				

Medical history			X	X	X	X	X
Physical examination			X	X	X	X	
Anthropometric data							
Body weight			X	X	X	X	
Height			X				
Outpatient follow-up or home blood pressure[1]			X	X	X	X	
Bioimpedans			X	X			
Laboratory evaluations							
Routine biochemistry from journal[2]			X				
P-HCG			X				
Study medication							
Intervention medicine - daily			X	X	X	X	
Drug accountability			X	X	X	X	
Endpoints							
Blood samples[3]			X	X	X	X	
Urine samples[4]			X	X	X	X	
Continuous glucose monitoring					Visit 5		
SF-36			X			X	
Safety							
Adverse events			X	X	X	X	X

1. Calibrated blood pressure monitor
2. Kidney standard biochemistry: (Hemoglobin, erythrocyte volume fraction (ery. Vol. fr.), mean cell volume (MCV), mean cell hemoglobin (MCH), leucocytes, platelets, neutrofilocytes, reticulocytes, ferritin, calcium-ion, sodium, potassium, albumine, carbamide, creatinine, eGFR, ALAT, BASP, bilirubin, LDH, phosphate, urate, GGT, magnesium, CRP, total CO) and b-Tacrolimus.
3. TX-standard + Extra 1 + Cholesterol (baseline, 6,12 and 18 month post randomization)
4. U-ACR, U-glucose stix, urine D+RU-biomarkers indicative of podocyt and tubular status

6.5 Staff training and qualifications

All personnel involved in the trial will be qualified for the specific tasks assigned. The personnel involved will have documentation of their professional specialization, research competencies, theoretical GCP experience, as well as practical GCP experience. This will be documented in a CV, which will be archived in the Trial Master File. Training in relevant protocol-specific tasks will be documented in a training log.

6.6 Delegation of trial-specific tasks.

Trial-specific tasks may be delegated. This will be documented in a delegation log. The investigator will ensure that the project staff is sufficiently informed about the trial protocol, trial medication, and the delegated tasks before performing trial-specific tasks. If trial-specific tasks are delegated to other departments, this will be reflected in a collaboration agreement and not in the delegation log. For example, blood sampling may be delegated to the clinical biochemistry department, which will be documented in a collaboration agreement. Decisions of medical nature will only be delegated to a physician.

Examples of trial-specific tasks that may be delegated include: providing information to trial participants, obtaining written informed consent, final assessment of the fulfillment of inclusion and

exclusion criteria, performing trial-specific examinations, evaluating examination results, prescribing trial medication, handling trial medication, identifying adverse events and side effects, assessing adverse events and side effects for potential causality with the trial medication, reporting SAEs to the sponsor or completing and correcting data in the CRF.

The investigator is responsible for ensuring that the trial is conducted in accordance with the protocol, written agreements with the sponsor, and applicable laws/GCP. This responsibility also includes delegated trial-specific tasks.

The investigator will ensure that their own and others' trial tasks are performed correctly and as described in the protocol, which can be done through SOPs

6.7 The criteria for discontinuing part or all of the clinical trial

- Serious Adverse Events or Suspected Unexpected Serious Adverse Reaction that will impact on the benefit-risk balance of the clinical trial.
- The study may be stopped by the investigator/sponsor if new information appears about the medicine that causes safety problems. Subjects will be informed accordingly.
- In case of breach of data security the trial will stop until data security is regained.

7. Selection and withdrawal of participants

7.1 Description of participants

All KTR without diabetes, who is 6 month or more post kidney transplantation, will be screened for identifying possible participants for inclusion to this trial.

7.2 Recruitment/Screening

Please refer to Part II document K1_Recruitment Arrangements.

7.4 Duration/Follow-up

The study duration is defined from signed consent at visit 2 to end of visit 11.
Estimated 18 months + 3 days.

The follow up period ends with visit 11, a telephone-consultation and mark the end of the study period.

7.5 End of study

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

The sponsor retains the right to discontinue the trial if safety concerns arise. In the event of early termination or suspension, the investigator must promptly notify the participants and arrange suitable follow-up care and treatment. Additionally, both the investigator and/or sponsor must ensure timely notification of the relevant ethics committee and regulatory authorities.

7.6 Discontinuation criteria

Participants may discontinue their involvement in the study under the following circumstances:

1. Withdrawal of Informed Consent:
    a. If a participant decides to withdraw their previously given informed consent, they will be discontinued from taking the study medication and will exit the trial.
2. Investigator's Security Concerns:

   a. If, at any point, the investigator deems there to be security concerns relevant to the participant, the investigator has the authority to discontinue the participant from the study.
3. Non-Compliance with the Study Protocol:
   a. If the investigator observes non-compliance with the study protocol on the part of the participant, they may decide to discontinue the participant from the study based on their judgment.
4. The participants must be discontinued from the trial under following circumstances:
   a. Alanine aminotransferase (ALAT) > 3 x upper normal limit
   b. Bilirubin > 2 x upper normal limit
   c. Pregnancy
   d. Breastfeeding
   e. Allergic or toxic reaction towards SGLT2i or the content substance
   f. New diagnose of intestinal bowel disease
   g. Dialysis initiation
   h. eGFR < 15 ml/min/1,73m^2
   i. Graft rejection

Reason for discontinuation must be recorded in the eCRF and in the participant medical records

It is essential to follow up on the subject to determine whether the cause was an adverse event (AE). If an AE is identified, it must be reported following the relevant procedures. Whenever possible, all assessments planned for the final visit should be conducted for subjects who received the investigational medicinal product (IMP) but did not complete the trial as per the protocol.

Data collected up to the point of discontinuation will be recorded in the clinical database and included in statistical analyses.

7.7 Inclusions criteria

- Obtained written informed consent
- Male or female patients, age ≥ 18 years.
- Non-diabetic KTR
- > 6 months post-transplant
- eGFR> 25 ml/min/1.73m^2 within the last 3 months pre randomization
- Immunosuppressive *must* include Tacrolimus
- Negative plasma hCG in fertile women*, and acceptance of the use of contraception during the course of the study.

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

7.8 Exclusion criteria

- Patients who is treated (diet or antidiabetics) for diabetes type 1 or 2 before randomization
- eGFR< 25 ml/min/1.73m^2 (before randomization)
- Alanine aminotransferase (ALAT) > 3 x upper normal limit
- Bilirubin > 2 x upper normal limit

- Pregnancy
- Breastfeeding
- Known allergy towards SGLT2i or the content substance
- Known intestinal bowel disease

The study aim is to look at KTR without diabetes, therefore we exclude Type 1 and 2 diabetes patients before randomization.

SGLT2i (Dapagliflozin) is approved for initiating in patients with eGFR ≥ 25 ml/min/1.73m^2, therefore patients with lower eGFR will be excluded before randomization.

SGLT2i (Dapagliflozin) can be used when ALAT and bilirubin is no more than respectively 3 times and 2 times upper normal limit, patients with higher ALAT or bilirubin will be excluded.

SGLT2i is not approved for pregnant and breastfeeding women. For avoiding pregnancy the following contraceptives are considered safe in connection with drug trials: Intra uterine device or hormonal contraception; birth control pills, implant, transdermal patches and vaginal ring or depot injection. Surgically sterilized or postmenopausal according to FSH levels do not need contraceptives during this trial.
Plasma-HCG will be performed at visit 2, in case of positive test, the participant will be excluded.

Obviously we do not want to inflict anaphylactic shock upon our patients, therefore any allergy toward SGLT2i or the content substance will lead to exclusion.

In case of gastrointestinal disease, absorption of SGLT2i may be affected therefor patients with colitis ulcerosa, Mb. Crohn or Short bowel syndrome will be excluded.

7.9 Patient withdrawal

7.9.1 Subject Withdrawal from Study

Subject withdrawal is defined as any living subject who does not complete the final follow-up visit (visit 10) as outlined in this protocol. Reasons for withdrawal include, but are not limited to:

- Subject's request (withdrawal of consent)
- Protocol violation
- Adverse events defined as:
    - Dialysis
    - eGFR< 15 ml/min/1,73m^2
    - Kidney transplant rejection
- Conditions posing unacceptable risk as determined by investigators or advisers.
- Sponsor-initiated discontinuation of the study
- Lost to follow-up.
- Pregnancy or desire for pregnancy

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

Withdrawal from IMP is defined as discontinuation of study treatment with continued follow-up until completion at visit 10. Subjects withdrawing from IMP after at least one dose will undergo safety monitoring with a follow-up visit one week after IMP withdrawal. Reasons for withdrawal from IMP may include, but are not limited to:

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

Investigators will attempt to reschedule visits for subjects who miss planned appointments. The eCRF will document the reason for withdrawal, withdrawal date, and the decision-maker (subject or investigator).

Withdrawal on participants request will be accepted at any time.

Inclusion of fertile women will need to agree upon using anticonception in case of intercourse from inclusion until 4 days after finishing visit 10, were the human teratogenicity and fetal toxicity no longer seems relevant.
In case of positive plasma-HCG at visit 2 the participant will be withdrawn.

Participants are withdrawn immediately in case of inadequate compliance to any procedure in the vigilance of the investigator.

Any disorder that might origin and compromise the safety by participating in the study will lead to immediately withdrawal.

Unacceptable adverse events determined by investigator or sponsor will lead to withdrawal.

Acquisition of data regarding trial subjects no longer participating the study can go on until the estimated last date for data collection, if the participant have given its signed consent.

Withdrawn patients will be replaced by patients recruited as before described in this protocol.

All participants will be offered to be followed up according to earlier described visit 10 to detect any late adverse events.

7.10 Patient care
This study trial does not give rise to extra care due to participation.

Normal outpatient clinic control will continue for the KTR participants disregarding this trial.

8. Assessment of efficacy
For a **detailed specification** of study endpoints refer to Section 6.2 Endpoints.

8.1 Primary endpoint
Data on the primary endpoint will be collected by the trial staff and/or investigators.

The primary efficacy analysis will be based on the intention-to-treat population, which includes all participants who have been randomized.

We will estimate response of SGLT2i in non-diabetic KTR compared to placebo on kidney allograft function by estimating the chronic eGFR slope.

8.2 Secondary endpoints
Data on the secondary endpoints will be collected by the trial staff and/or investigators.

The primary efficacy analysis will be based on the intention-to-treat population, which includes all participants who has been randomized.

8.3 Tertiary endpoints

Data on the tertiary endpoints will be collected by the trial staff and/or investigators.

The tertiary efficacy analysis will be based on the intention-to-treat population, which includes all participants who has been randomized.

9. Assessment of safety

The safety of enrolled participants will be monitored continuously based on statements of Adverse Events (AE) and Serious Adverse Events (SAE). AEs and SAEs will be monitored and recorded from the initiation of the trial until the end of the study, which is approximately 3-7 days after the final dose of the IMP. Following the occurrence of an AE or SAE, participants will receive appropriate follow-up and treatment based on standard guidelines. Adverse events will be reported by both the participant and the investigator, along with any qualified trial staff who are responsible for detecting, documenting, and recording events meeting the definition of an AE or SAE through in-person visits and telephone contacts. Annually, a safety report will be uploaded into CTIS.

9.1 Definition of safety events

9.1.1 Adverse event (AE)

An Adverse Event (AE) is an undesirable medical occurrence or condition that has arisen after treatment with a drug, regardless of whether the event is considered related to the drug or not. That is, an AE does not necessarily have to be related to the treatment with the investigational drug. AE also includes a worsening of an already existing medical condition, for example, worsening of arthritis symptoms during the trial period. AE covers symptoms, diagnoses, changes in laboratory values, etc. The collection, recording, and assessment of AE are noted in the eCRF, and the investigator evaluate whether it is likely that the event is related to the drug.
If it is suspected that there is a probable connection between the AE and the investigational drug, it is then considered an Adverse Reaction (AR)

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

Each AE must be evaluated and categorized according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). These details will be recorded on the AE form within the eCRF, providing the following information:

1. The severity grade (mild, moderate, severe)
    - Mild
        - No or transient symptoms, no interference with the subject´s daily activities
    - Moderate
        - Marked symptoms, moderate interference with the subject´s daily activities
    - Severe
        - Considerable interference with the subject´s daily activities; unacceptable
2. The following terms are used when assessing the causality between an adverse event and the IMP:
    - Probable (good reason and sufficient documentation to assume a causal relationship)
    - Possible (a causal relationship is conceivable and cannot be dismissed)
    - Unlikely (the event is most likely to ethology other than the IMP)
3. Duration (including start and end dates, or indication if the AE is ongoing at the final examination)
4. Whether it qualifies as a Serious Adverse Event (SAE)
5. Actions taken in response to the IMP

6. Outcome

9.1.2 Serious Adverse Event (SAE)

Defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment.

A serious adverse event is any that results in:

- Death
- Life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Serious important medical events

Some medical events may place the patient at risk or require intervention to prevent any of the above-mentioned consequences. Such events are referred to as "important medical events" and should also be categorized as "serious" in accordance with the definition. The decision of whether an event is "serious" is made by the investigator based on medical judgment.

The investigator must assess causality independently, considering factors such as timing and other relevant information. A planned hospitalization will not be considered an SAE.

9.1.3 Serious Adverse Reaction (SAR)

Defined as any SAE with plausible relationship to study medication that are convincible and cannot be rejected.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Defined as any SAE associated with the IMP and therefore is a serious adverse reaction, unexpected in relation to the recent product summary for Forxiga. SAR is suspected unexpected if its specificity and severity are not described in the latest product summary.

9.1.5 Pregnancies

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

9.2 Registration of events

Any side effect, AE, SAE, SAR and SUSAR will be reported and assessed in the appropriate eCRF. Registered from interviewing the participants at visit 2-10 and from examination of blood and urine samples taken at visit 2-9. Only blood samples out of reference value that requires treatment will be registered. Events may also be reported by the participants at any time it might occur to the investigator.

9.3 Reporting

When reporting any event following parameters will be recorded: study name, patient identification (subject number, sex, age), adverse event, CTCAE, IMP, reporter identification (name or initials), causality and outcome.

9.3.1 Reporting of AE and SAE by the investigator to the sponsor

1. The investigator will record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the trial period.

2. The investigator will report all SAE to the sponsor without further delay but not later than within 24 hours of obtaining knowledge of the events. Where relevant, the investigator will send a follow-up report to the sponsor to allow the sponsor to assess whether the SAE has an impact on the benefit-risk balance of the clinical trial, this will be conducted via eCRF in REDCap.

Exception from reporting SAE within 24 hours will be participant's hospitalized do to routine change of JJ catheter or other planned hospitalization.

3. The sponsor will keep detailed records of all SAE reported to him by the investigator.

4. If the investigator becomes aware of a SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical trial in a subject treated by the investigator, the investigator will, without undue delay, report the SAE to the sponsor.

9.3.2 Reporting of SUSAR by the sponsor to the Agency

1. The sponsor will report electronically and without delay to European Union Drug Regulatory Authorities Vigilance (EudraVigilance) all relevant information about the following SUSAR's.:

(a) All SUSAR's to IMP occurring in that clinical trial.

(b) All SUSAR's to IMP occurring in any of the subjects of the clinical trial, which are identified by or come to the attention of the sponsor after the end of the clinical trial.

2. The period for the reporting of SUSAR's by the sponsor to the Agency will take account of the seriousness of the reaction and shall be as follows:

(a) in the case of fatal or life-threatening SUSAR's, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction;

(b) In the case of non-fatal or non-life-threatening SUSAR's, not later than 15 days after the sponsor became aware of the reaction;

(c) In the case of a SUSAR which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor will submit an initial incomplete report followed up by a complete report.

9.3.3 Follow up

In case of AE, AR, SAE, SAR or SUSAR the patient will have follow up until the event or reaction is normalized. In case of an event that will inflict the participant lifelong, follow up in different specialties will be initiated. The participants of this study are all KTR and have lifelong follow up in respective outpatient clinic of nephrology.

9.3.4 Annual Safety Report

Regarding IMP other than placebo, the sponsor will submit an Annual Safety Report through CTIS. This safety report will adhere to the format of the Development Safety Update Report (DSUR).

It will specify the reporting timeframe and provide a concise summary of all documented SAEs and SARs.

The annual safety report will include an up-to-date benefit/risk evaluation.

The annual report will only contain aggregate and anonymized data.

10. Statistical considerations

In corporation with OPEN statistics, a statistical analysis plan (SAP) will be performed, in according to ICH E9.

We choose a non-inferiority study to show that the new treatment is not worse than an existing treatment.

10.1 Sample size

We used estimated sample size by Sealed Envelope Ltd. 2012. Power calculator for continuous outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/continuous-noninferior/ [Accessed Fri Jan 10 2025].

The calculator is designed for continuous outcome in parallel group non-inferiority trials.

The mean outcome is compared between the experimental and standard treatment groups.

The null hypothesis is that the experimental treatment is inferior to the standard treatment. We write this as the mean in the standard treatment group (μs) is better than the mean in the experimental treatment group (μe) by an amount d:

H0: $\mu s \geq \mu e + d$

which can be re-written

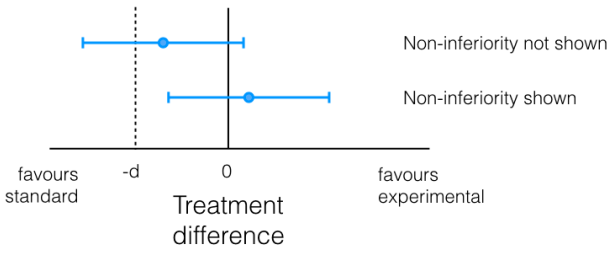
H0: $\mu e - \mu s \leq -d$

The alternative hypothesis is that the experimental treatment is non-inferior to the standard treatment:

H1: $\mu e - \mu s > -d$

We choose the non-inferiority limit, d, to be the largest difference that is clinically acceptable, so that a difference bigger than this would matter in practice. This difference should also not be greater than the smallest effect size that the standard treatment would be reliably expected to have compared with control.

Non-inferiority diagram



These calculators are based on approximations to the Normal distribution and may not be suitable for small sample sizes. These calculators have been tested for accuracy against published papers.

Calculation based on the formula:

$n = f(\alpha, \beta/2) \times 2 \times \sigma^2 / d^2$

where σ is the standard deviation, and

$f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$

Φ^{-1} is the cumulative distribution function of a standardized normal deviate.

The function of a kidney allograft decreases for numerous reasons and is highly variable. Typically the annual decrease in kidney function (ΔeGFR) is 2 ± 5 ml/min/1.73 m^2/year.
With the risk of type 1 error of 5%, power of 80%, a standard deviation of 5 ml/min/year and non-inferiority limit of 3 ml/min/year (i.e., a decline of at most 5 ml/min/1.73m^2 per year.) two groups of 35 patients will be needed to establish no difference for SGLT2i treated patients.

You could say:
If there is truly no difference between the standard and experimental treatment, then 70 patients are required to be 80% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of -3.

Assuming a drop-out rate of 20%, 88 patients will be needed for this study.

10.2 Level of significance

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

10.3 Reporting Deviations from the Statistical Plan

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

10.4 Selection of Subjects for Analyses

The selection of subjects to be included in the analyses will be all participants included and randomized by intention to treat analysis.

The main reason for discontinuation should be documented in both the eCRF and the participant's medical records. It is essential to follow up with the participant to determine whether an adverse event (AE) was the cause. If an AE is identified, it must be reported following the applicable procedures. Whenever feasible, participants who have received the investigational medicinal product (IMP) but do not complete the trial as per protocol should undergo all assessments planned for the final visit. Data collected up to the point of discontinuation will be recorded in the clinical database and included in statistical analyses.

10.5 End of study

The "End of Study" is defined as the point at which a complete dataset has been acquired for the intended study participants, which includes 88 patients.

10.6 Statistical Analysis Plan

The analysis will be performed with statistical software for data science (STATA), we will use OPEN Statistics for data analysis.

Statistical analysis will be performed blinded for IMP allocation, interim and finally after the last participant has finished the visit 11 (LPLV).

Missing data is expected to occur at random and will be handled using multiple imputation. The imputations will be performed based on other available variables in the dataset, excluding group allocation, to estimate the missing values. A comprehensive description of all data will be provided, including incomplete data and the reasons for any missing information. The principal investigator will conduct a blinded analysis of the data. Any modifications to the statistical analysis plan will be documented in future publications.

If deviations from the original statistical plan are necessary, these will be thoroughly justified, described, and approved through CTIS.

All statistical analyses will be conducted or reviewed by an independent statistician, who will be blinded to treatment allocation.

10.6.1 Effect analysis

The distribution and variations of endpoints will be presented using means ± standard error of the mean or medians with ranges or interquartile ranges for continuous variables, while categorical endpoints will be reported as frequencies and percentages. Comparisons of continuous outcomes between groups will be conducted using two-sample t-tests if the data follow a normal distribution; otherwise, the Wilcoxon rank-sum test will be applied. Categorical outcomes will be compared using the chi-squared test, or Fisher’s exact test when the number of observations for an event is less than five. Repeated measures will be analyzed using mixed regression models. A p-value of less than 5% will be considered statistically significant.

10.6.2 Baseline characteristics

Baseline characteristics will be presented as means with standard deviation (SD) or if skewed distributions, as medians with interquartile range (IQR).

Table 4 – example of presentation of baseline characteristics

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight — kg	81.5±20.1	82.0±20.9
Body-mass index‡	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure — mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean — ml/min/1.73 m^2	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m^2	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m^2	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m^2	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m^2	293 (13.6)	331 (15.4)
Hemoglobin — g/liter	128.6±18.1	127.9±18.0
Serum potassium — mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

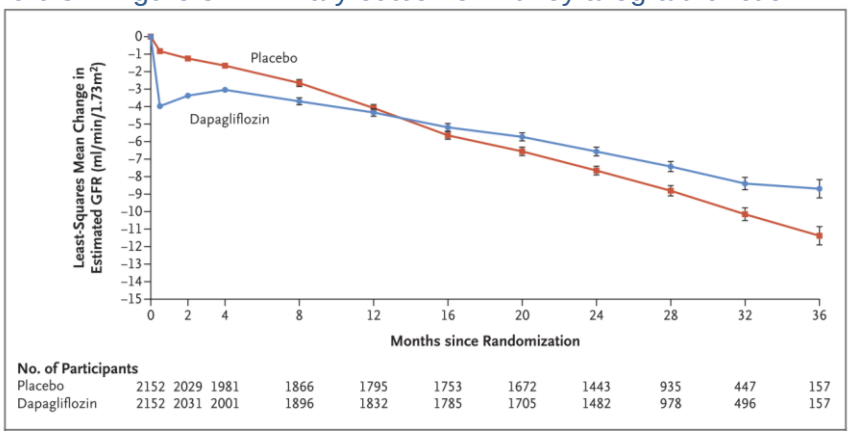
* Plus–minus values are mean ±SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and GFR glomerular filtration rate.

10.6.3 Primary outcome: Kidney allograft function

A mixed model for repeated measurements will be used to analyze changes in the chronic eGFR slope. All available on treatment measurements will be used with no distinction made for missing outcomes.
The effect of SGLT2i as compared with placebo on the rate of decline in the eGFR during the chronic phase (week 4 until end of treatment), will be analyzed with the use of a two-slope model.

Statistical significance is inferred as a two-tailed P-value < 0.05.

10.6.3.1 Figure 3 – Primary outcome: Kidney allograft function



Kidney allograft function will be presented as changes from baseline in eGFR, shown in the least-squares mean change form baseline in the eGFR, calculated with the use of a repeated-measures analysis. The I bars indicate standard errors. Linear mixed model.

10.6.4 Secondary outcomes

- Acute eGFR slope (ml/min/1,73m^2) measured from baseline until week 4.
  - A mixed model for repeated measurements will be used to analyze changes in the chronic eGFR slope. All available on treatment measurements will be used with no distinction made for missing outcomes.
- Urine albumin/creatinine ratio (U-ACR)
  - Comparisons of continuous outcomes between groups will be conducted using two-sample t-tests if the data follow a normal distribution; otherwise, the Wilcoxon rank-sum test will be applied.

- PTDM
  - Categorical outcomes will be compared using the chi-squared test

- Prediabetes status
  - We will use the American Diabetes Association criteria for prediabetes
    - Categorical outcomes will be compared using the chi-squared test
  - Urine glucose stix
  - HbA1c
  - Random blood glucose mmol/L
  - Continuously glucose monitoring
    - Comparisons of continuous outcomes between groups will be conducted using two-sample t-tests if the data follow a normal distribution; otherwise, the Wilcoxon rank-sum test will be applied

- Urinary tract infection
  - Categorical outcomes will be compared using the chi-squared test

- Change in volume status in week 1 of therapy
  - Comparisons of continuous outcomes between groups will be conducted using two-sample t-tests if the data follow a normal distribution; otherwise, the Wilcoxon rank-sum test will be applied

- Change in systolic blood pressure (SysBP) and diastolic blood pressure (DiaBP) mmHg
  - Comparisons of continuous outcomes between groups will be conducted using two-sample t-tests if the data follow a normal distribution; otherwise, the Wilcoxon rank-sum test will be applied

- Urine biomarkers indicative of podocyt and tubular status
  - Molecular laboratory investigations

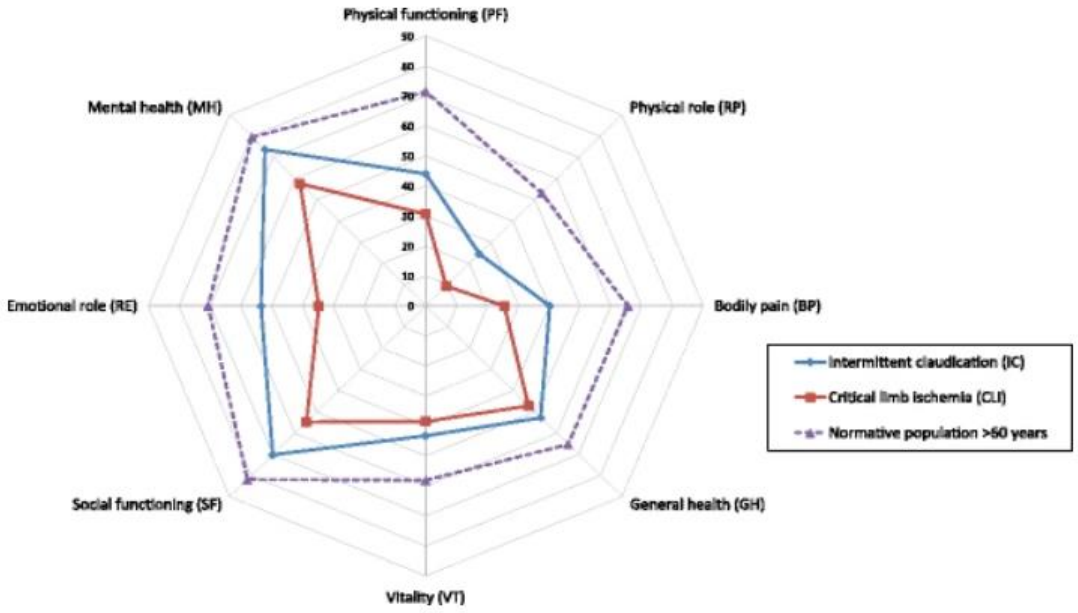
- Renal composite outcomes
  - Dialysis, ESKD (eGFR<15 ml/min/1.73m^2)
    - Categorical outcomes will be compared using the chi-squared test
  - Presented with Kaplan-Meier curve

- MACE
  - Categorical outcomes will be compared using the chi-squared test

- Death – all cause mortality
  - Categorical outcomes will be compared using the chi-squared test

10.6.5 Tertiary outcome

SF-36 will be presented as mean score for each group (example below)



10.6.6 Safety data outcomes

Safety data will be summarized according to trial group with the use of the data set for all the participants who had undergone randomization and received at least one dose of SGLT2i or placebo. Safety analyses will be performed on all adverse events occurring from randomization until end of the trial closure visit.

A numerical summary of both serious and non-serious adverse events (AEs) will be reported, while serious AEs will also be described qualitatively.

10.6.6.1 Table 3 – Adverse Events

A table presenting adverse events will be made and presented with p-value (example below)

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no./total no. (%)	*events/100 patient-yr*	*no./total no. (%)*	*events/100 patient-yr*		
Safety outcomes‡						
Discontinuation of regimen due to adverse event	118/2149 (5.5)	—	123/2149 (5.7)	—	—	0.79
Any serious adverse event	633/2149 (29.5)	—	729/2149 (33.9)	—	—	0.002
Adverse events of interest						
Amputation§	35/2149 (1.6)	—	39/2149 (1.8)	—	—	0.73
Any definite or probable diabetic ketoacidosis	0/2149	—	2/2149 (<0.1)	—	—	0.50
Fracture¶	85/2149 (4.0)	—	69/2149 (3.2)	—	—	0.22
Renal-related adverse event¶	155/2149 (7.2)	—	188/2149 (8.7)	—	—	0.07
Major hypoglycemia‖	14/2149 (0.7)	—	28/2149 (1.3)	—	—	0.04
Volume depletion¶	127/2149 (5.9)	—	90/2149 (4.2)	—	—	0.01

* NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical testing strategy.
† For the composite of long-term dialysis or kidney transplantation, there were 69 outcome events in the dapagliflozin group and 100 outcome events in the placebo group (hazard ratio, 0.66; 95% CI, 0.49 to 0.90).
‡ Safety analyses included all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo.
§ Shown are cases of surgical amputation or spontaneous or nonsurgical amputation, excluding amputation due to trauma.
¶ These outcomes are based on a predefined list of preferred terms.
‖ The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

11. Direct access to source data

Trial information containing sensitive data about the participants will be stored and handled confidentially.

Sponsor/investigator confirm that we will provide direct access to source data/documents for study related monitoring, audit, review, and inspection by regulatory authorities. This includes granting direct access to source data and study documents for review by The Danish Medicines Agency, The Ethics Committee, EMA and their collaborators.

Sponsor has made an agreement with the GCP-unit at OUH, who will be monitoring the study in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for GCP and in accordance with European regulation and legislation. The GCP-unit at OUH is qualified to monitor clinical trials and has full knowledge of all SOPs, the relevant legislation in the field, and the specific details of the trial.

The purpose of monitoring is to ensure: 1) the rights and well-being of trial participants are protected, 2) the data collected is accurate, complete, and verifiable, meaning it can be traced back to the source documents, and 3) the trial is conducted according to the approved trial protocol, applicable SOPs, GCP, and current legislation.
The GCP unit has been a partner during the trial's planning phase and will continue to be during its execution. The sponsor will use a risk-based approach to determine the extent of on-site and central monitoring, which will be outlined in a written monitoring plan. It is a requirement that an initiation visit takes place before the inclusion of the first participant.

After each monitoring visit, a monitoring report is prepared, detailing any deviations and the follow-up actions required. The sponsor holds overall responsibility for the follow-up, but the investigator

is responsible for implementing corrective and preventive actions for deviations that fall within the investigator's area of responsibility.

Participants will be informed in writing by participant information about the possibility of audits and/or inspections, performed by the hospital institutional review board or regulatory authorities.

12. Quality control and quality assurance

The execution of the clinical trial will be conducted in accordance with the ethical principles described in the Declaration of Helsinki[49], in compliance with ICH-GCP, and the applicable national legislation in the field.

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

Study approval will be obtained from CTIS.
The trial will be conducted in accordance to the study approval.
This study complies with the versions applicable at any time:

- REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use.
- ICH Harmonized Tripartite Guideline for Good Clinical Practice – Guideline for Good Clinical Practice E6 (R2)
- Clinical Facilitation Group (CTFG) - Recommendations related to contraception and pregnancy testing in clinical trials
- The Danish Ministry of the Interior and Health: Announcement no. 12 of 06/01/2022, order on clinical trials with medicinal products
- EUDRALEX, Volume 10, Recruitment and Informed consent procedure template, Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

The trial staff involved in the conduct of the trial will be qualified for the tasks they undertake, at all times.

Quality assurance systems are implemented to ensure the quality of all aspects of the trial. This is done by documenting procedures in standard operating procedures (SOPs) which can be found in the Trial Master File.

13. Ethical aspects

13.1 Ethical Conduct of the Study

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

13.2 Ethical aspect towards participants

The rights, safety, and well-being of the trial participants will always take precedence over any potential scientific and societal interests in the trial.

We believe that the clinical information already available about our investigational drug SGLT2i is sufficient to justify the conduct of this trial.

SGLT2i is approved for treatment of non-diabetic CKD for adults (≥ 18 years) with proteinuria U-ACR 200-5000 mg/g, with beneficial effect on cardioprotective and renoprotective shown in previous conducted long term studies [15, 44]

The SGLT2i and allograft protective outcome has never been examined in non-diabetic KTR. We expect to visualize the SGLT2i effect in the kidney transplant according to kidney allograft function for long term follow up, minimum 18 months.

We believe that potential discomforts and risks are compensated by the expectable advantages of conducting this study. The study will be stopped by the investigator if new information appears about the medicine that causes safety problems. Subjects will be informed accordingly.

The results and knowledge obtained from this study, we believe could contribute to a possible improved treatment of kidney allograft. This will benefit all KTR worldwide.

13.3 Patient financing and insurance

The study is initiated by the sponsor. Non-commercial funding finances the medication. There is no involvement from industry partners in the project. There will not be any remuneration during the project.

In accordance with the relevant national regulations and competent authorities, subjects enrolled in the study are under The Danish Patient Insurance that covers all study subjects as guaranteed by The Danish Act on the Right to Complain and Receive Compensation within the Health Service administered by The Patient Assurance Association.

13.4 Participant information and informed consent

Participation in this study is voluntary.

No financial compensation will be given for patients participating in the study.

Patients unable to give informed consent and minors are not invited to participate in this study.

The trial participants will be verbally informed about the trial and will receive written participant information, which has been pre-approved by the Research Ethics Committee (CTIS).

The participants will have ample time to read the written participant information and will have the opportunity to ask questions. Participants have the right to take time to consider and may bring a companion, such as a relative, to the information meeting. They will have the opportunity to reflect for at least 24 hours.

The participants must personally sign and date the consent form. Participants will be offered a copy of the signed consent form.

The participants will be informed that their consent can be withdrawn at any time without providing a reason, and choose no longer to participate in the study. This will not affect their normal treatments in the outpatient clinic.

The process regarding verbal information and obtaining written consent will be documented, and the signed consent form will be archived in the TMF. And subject to inspection as needed.

The consent must be documented in the patients EPJ medical record.

The signed consent will give the investigator access to the electronic medical record including journal entry, biochemistry, imaging, medicine until the study is completed. The participants can choose if we may contact them for study results in their interest, after the study is completed.

After signed informed consent form, study investigator and relevant authorities will access medical records, to verify and monitor the study procedures and study data.

Participants will be informed in writing about possibility of audits and/or inspections, which can be performed by the hospital institutional review board or regulatory authorities, patient records will be required and reviewed.

No study specific test are performed before obtained signed Informed Consent Form.

13.5 Access to data

To identify eligible participants, a review of the EPJ will be conducted, focusing on data related to transplantation status. These data will be used to assess the eligibility of potential participants based on patient lists within the outpatient clinic. Once signed informed consent has been obtained, the Sponsor, Investigator, the GCP unit, Ethics Committees, and regulatory authorities will be allowed access to the source data.

14. Data management

Data management follow the Responsible conduct of research and includes proper management of primary materials and data. The key purpose of data management is to guarantee credible and transparent research. Whereas primary material is defined as: any material (e.g. biological material, notes, interviews, texts and literature, digital raw data, recordings, etc.) that forms the basis of the research. Data are defined as: detailed records of the primary materials that comprise the basis for the analysis that generates the results.

The project is accepted for entrance into the Open Patient data Explorative Network (OPEN) – a research support unit that define research infrastructure for all hospitals in the region of southern Denmark, and is located on OUH. OPEN facilitates counseling regarding data collection, biobank, randomization, legislation, biostatistics and more.

14.1 Trial master file (TMF)

According to requirements from the GCP-unit, a Trial Master File (TMF) will be created before initiating the study.
The TMF refers to the collection of trial documents that GCP requires to be present before, during, and after the trial - the essential documents.

The TMF for the clinical trial will contain the documents that, individually and collectively, make it possible to assess the conduct of our trial and the quality of the data collected. Based on this information, it must be possible to reconstruct the trial. The list of documents stored will consist of the requirements described in ICH-GCP section 8. It must always be easy to retrieve all essential documents during the trial and throughout the entire archiving period.

The documents are version-controlled and archived in a way that always makes it possible to verify which versions were in effect at specific times. The previously applicable documents are retained in the TMF.

The TMF ensures that the trial information will be recorded, handled, and archived in a way that allows reporting, interpretation and verification of all information related to the collected data and the course of the trial.

TMF will contain essential documents including among others; the protocol and its amendments, participant information, curriculum vitae, signed consent forms, forms, delegation logs, approvals from authorities all correspondence with regulatory authorities including the Danish Medicines Agency, the Ethics Committee, and the Danish Data Protection Agency, source data, case report forms, source data lists, monitoring visit reports, written agreements with collaborators, and the final trial report.

14.2 Data Management Plan

The study will be registered on ClinicalTrials.gov before its initiation, and the protocol will adhere to the principles outlined in the Helsinki Declaration II. The trial will be conducted in accordance with Good Clinical Practice (GCP) guidelines. A local GCP monitor from the GCP unit at Odense University Hospital will be assigned to oversee the study. Prior to commencement, the project, including a plan for managing personal data, will receive approval from the Region of Southern Denmark, which is responsible for data protection. If required, regulatory authorities will be granted access to relevant journals, documents, and other project-related materials. Each participant will be assigned a unique subject number, which will be recorded on data sheets. Only sample collection tubes will be labeled with the subject number and trial ID, while personal details such as full name, social security number, and subject number will be securely stored in a separate location.

In corporation with OPEN a Data Management Plan will be performed.

The data management plan will secure that

A) Primary materials and data are retained, stored and managed in a clear and accurate form that allows the result to be assessed, the procedures to be retraced and – when relevant and applicable – the research to be reproduced. The primary materials and data are retained for 25 years.

B) The data records will enable identification of persons having conducted the research and persons or institutions with responsibility for the primary materials, data, and research results. The data records will contain a precise and traceable reference to the source. Any changes to the primary materials or data stored will be clearly accounted for in a way that allows clear identification of the changes made.

C) That Data retention, accessibility and ownership when researchers leave the institution are well described.

We will use OPEN Analysis, a platform within OPEN that complies with the legislation towards data protection. It will function as a terminal server solution, the investigator computer will function as the terminal, while data is stored and treated under secure conditions at a server by the Region of southern Denmark Information Technology (IT) department – fulfilling the newest legislation on the General Data Protection Regulation (GDPR).

14.3 Source data identification and source data verification

Source data are the original data, i.e., the first recording or entry of data. Source data are necessary to reconstruct and evaluate the trial. The source data are found under source

documents, and described in the TMF. Source documents are the place where data is recorded for the first time and will include medical records in EPJ, laboratory results in EPJ, X-ray images and reports in VNA. Blood pressure, pulse, and weight will be entered directly into the eCRF on the day of the trial, the eCRF will in this case be a source document. In the source documents, it will be possible to retrieve data that are recorded in the eCRF, allowing verification that the collected data are accurate and complete. This verification of data is called Source Data Verification (SDV) and is an important part of the monitor's work.

If incorrect data is mistakenly recorded in the source document, the error will be corrected. The correction will not hide the original data and will be explained. It will be possible to see who made the correction and when it was made. In our eCRF - REDCap database - an audit trail will ensure this. In accordance with the regulations, trial documents will be stored for at least 25 years after the trial's completion.

The media we use to archive the content of the TMF will guarantee that the content remains complete and readable throughout the entire archiving period.

The Investigator will prepare a source data list. The source data list must be sufficiently detailed to allow immediate location of the relevant data. It will specify exactly where the source data can be found, such as in the EPJ medication module, EPJ medical records with the date noted, EPJ laboratory results, etc. Source data that is entered directly into the eCRF, such as blood pressure, height, and weight, will be included in the source data list. The purpose of the source data list is to show where the staff first records each data point. The source data list will be version-controlled and signed by the investigator before the trial begins. Revisions to the source data list may be necessary, and all signed versions of the list will be archived in the TMF.

According to ICH-GCP, source data must follow the ALCOA+ principles, which ensure that source data are attributable, legible, contemporaneous, original, accurate, and complete. It is the investigator's responsibility to ensure that trial data adhere to these principles.

Attributable: Our eCRF ensures that the audit trail will show who entered the data and when.

Legible: All data will be archived electronically, ensuring readability for 25 years.

Contemporaneous: Data will be recorded at the time the observation is made, as later entry may be subject to errors.

Original: Refers to where data is recorded for the first time, e.g., EPJ medical records.

Accurate: Data will be entered precisely and accurately, e.g., weight will be recorded with decimals.

Complete: All data required by the protocol must be available. It must be possible to see any changes made since the initial entry

All source documentation will be securely stored under the responsibility of the Principal Investigator. The Principal Investigator will maintain complete and accurate records to ensure comprehensive documentation of the trial's execution and enable subsequent data verification.

Clinical study information, will be recorded, handled, and stored in a way that allows it accurate reporting, interpretation and verification.

14.3.1 Case Report Form and Research Electronic data Capture

Investigator will, in collaboration with OPEN, establish the Research Electronic data Capture (REDCap) database, and withhold a separate electronic Case Report Form (eCRF) for each study participant.

In the eCRF we will collect the data described in the protocol for each individual trial participant. Our eCRF is designed in the electronic online database, REDCap, where trial data are entered. The eCRF will reflect the approved protocol, ensuring that data are recorded exactly in accordance with the protocol. The eCRF, like all other trial documents, will be version-controlled. All project personnel involved in completing the eCRF will be trained, and a guide on how to correctly complete the eCRF will be prepared. All completed eCRFs must be approved by the investigator. The sponsor may not alter the data without the investigator's approval and must therefore submit a request for correction of any detected data errors for approval by the investigator (queries)

All health-related matters and sensitive personal data will be protected and handled in accordance with European legalization and be depersonalized. All participants will be given a study number referring to their personal information, which will be stored securely and separately. Adequate blinding of all personal data during data processing and publication will be ensured. Relevant patient information for study participation and safety, will transfer from the responsible clinical physician to the responsible research investigator.

The REDCap database will be protected by OPEN security, with back-up, only access for authorized personal, double entry to avoid input error, data will be locked before the data processing is started.

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

14.4 Data handling

We acknowledge that the content of the project and the handling of personal data must comply with Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 (GDPR) and the Danish Data Protection Act.

All information on study subjects is protected according to the GDPR, law on processing of personal data and the law of health, the study will be correctly reviewed and approved by CTIS.

All of the above mentioned will prevent unauthorized access, distribution, mediation, change or loss of processed information and personal data.

Sponsor shall via CTIS notify about serious breaches according to article 52 of CTR. A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

In case of breach of data security, the sponsor will notify the personal data breach to the supervisory authority, via CTIS, without undue delay and, where feasible, not later than 72 hours after having become aware of it.

OPEN will be held responsible because OPEN is the controller at OUH and are ultimately in charge of and responsible for the processing and storing of data.
The investigator will communicate to the data subject (the participants) a personal data breach, without undue delay, where that personal data breach is likely to result in a high risk to the rights and freedoms of the natural person in order to allow him or her to take the necessary precautions. It will be ascertained whether all appropriate technological protection and organizational measures have been implemented, according to the EU regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

Subject-specific documents are supplied with a unique study identification code to prevent direct subject identification. After study completion, study data will be stored in coded form for a duration of 25 years in accordance with the recommendations of CTR nr. 536/2014. After this period, the data will be securely destroyed.

14.4.1 Computer systems

Data processing will be conducted using a validated, secured and password protected computer system that complies with regulatory requirements.

14.4.2 Data entry

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

14.4.3 Data validation

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

15. Handling and archiving of biological material

The use of biological material in the biobank will comply at all times with “compliance with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects" (Regulation (EU) No 536/2014, Article 7.1 (h)).

Please refer to Part II document S1_Compliance on the collection use and storage of biological samples.

16. Administrative procedures

16.1 Study group

Principal investigator OUH:
Ph.D. student: Lotte Borg Lange, MD, Nephrologist
Overall responsible for execution of the study, recruitment of participants and daily manager of the scientific project. Principal investigator will have overall responsibility for ensuring the protection of the rights of trial participants, will be responsible for the data quality, and for ensuring sufficient resources at the trial site. Will build a database for study purposes and be first author to the scientific research paper.

Principal investigator RH:
Mads Hornum, Professor, Consultant, Ph.D. Head of research
Department of Nephrology, Rigshospitalet
Responsible for execution of the study, recruitment of participants and daily manager of the scientific project at RH. Principal investigator at RH will have overall responsibility for ensuring the protection of the rights of trial participants, will be responsible for the data quality, and for ensuring sufficient resources at the trial site. Will be second author to the scientific research paper.

Principal investigator Aarhus University Hospital
Henrik Birn, Professor, Consultant, Ph.D., Dr. Med., Head of research
Department of Nephrology, Aarhus University Hospital
Responsible for execution of the study, recruitment of participants and daily manager of the scientific project at AUH. Principal investigator at AUH will have overall responsibility for ensuring the protection of the rights of trial participants, will be responsible for the data quality, and for ensuring sufficient resources at the trial site. Will be second author to the scientific research paper.

Principal investigator at The Regional Hospital Gødstrup (RHG)
Jesper Nørgaard Bech, Ph.D., Consultant, Clinical Professor, Head of research
Department of Nephrology, The Regional Hospital Gødstrup
Responsible for execution of the study, recruitment of participants and daily manager of the scientific project at RHG. Principal investigator at RHG will have overall responsibility for ensuring the protection of the rights of trial participants, will be responsible for the data quality, and for ensuring sufficient resources at the trial site. Will be second author to the scientific research paper.

Sponsor/supervisor: Claus Bistrup, Head of research, professor, consultant, Ph.D.

Cosupervisor: Kurt Højlund, Head of research, professor, consultant, dr. med, Ph.D. Dept. of Steno Diabetes Center Odense, OUH

Cosupervisor: Per Svenningsen, professor, dr. med. Dept. of Molecular Medicine – Cardiovascular and renal research, OUH

17. Publication plan

17.1 Publication policy

This publication will be conducted in compliance with the Act on Processing of Personal Data. The principal investigator will draft manuscripts and be first author, the last author will be one of the supervisors (depending on the theme of the manuscript). At this stage, a final list of authors cannot be determined; however, all researchers who have met the Vancouver criteria for authorship will be included in the final publication.

Positive, inconclusive as well as negative data will be published in both national and international oral and written presentations as well as peer-reviewed international scientific journals: *kidney transplant journals* with the highest impact possible (American Journal of Transplantation (AJT), Transplantation, Nephrology Dialysis Transplantation (NDT)) or if, data permits, in highest-ranked *kidney journals* (Journal of the American Society of Nephrology (JASN), Kidney International (KI)) and if possible general journals of *internal medicine* (British Medical Journal (BMJ), Lancet, New England Journal of Medicine (NEJM)). Open access will be pursued.
If the data against our expectations are not published in international journals, data will be published on a public website ex. www.clinicaltrials.gov

Furthermore, the summary of the results must be submitted to the CTIS portal without undue delay and no later than one year after the trial has concluded.

The results from this trial will be published on the Danish Kidney Association's patient website as well as on public media.

18. Data security monitoring board (DSMB)

DSMB monitors the safety of study participants and the effectiveness of the study investigational therapy during the clinical trial.
DSBM will serve as an advisory committee and will consist of at least three independent individuals not directly involved in our study, who have not collaborated directly with the sponsor in the past five years. The DSBM committee will meet semi-annually to conduct a risk/benefit analysis of the available interim analyses.

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