The RENAL LIFECYCLE Trial

A Randomized Controlled Clinical Trial to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients with Severe Chronic Kidney Disease

AU Protocol

Version 6.0, 1 November 2023

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CONTACT DETAILS

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PROTOCOL HISTORY

Version No.	Version Date	Summary of Revisions Made
1.0	28 June 2022	Original
2.0	16 August 2022	Update Protocol as amendments made by global sponsor (UMCG – submitted 29Jul22, V6). In addition, amendments made as requested by RPA HREC from initial submission.
3.0	30 August 2022	Amendments made to section 4.8.2 as requested by RPA HREC from v2.0 submission.
4.0	22 November 2022	Update Protocol as amendments made by global sponsor (UMCG – submitted 21Nov22, V7). In addition, section 4.6.6 Biobanking samples has been added.
5.0	04 January 2023	Update Protocol as amendments made by global sponsor (UMCG – submitted 14Dec22, V7).
6.0	1 November 2023	Update Protocol as amendments made by global sponsor (UMCG – submitted 04Aug23, V8 and 19Oct23, V9).

INVESTIGATOR AGREEMENT

I have read the following protocol:

Protocol Title: The RENAL LIFECYCLE Trial – AU Protocol
Version and Date: Version 6.0, 1 November 023
I have read this protocol and associated procedure manuals and agree that it contains all the necessary details for carrying out the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention and the conduct of the study.

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8 Nov 2023
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1 CONTENTS

2 ADMINISTRATION INFORMATION

2.1 Trial/Study Registration

The study is registered with ClinicalTrials.gov (NCT05374291).

2.2 Funding

This project is funded in Australia by a National Health & Medical Research Council 2021 Medical Research Future Fund International Clinical Trial Collaborations (ICTC 21-1 Application 2015414).

2.3 Study Management & Oversight

The RENAL LIFECYCLE Trial is sponsored globally by the University Medical Center, Groningen (UMCG) in The Netherlands and locally by The George Institute for Global Health (TGI). UMCG will be responsible for convening the Steering Committee, which will be responsible for the protocol design, overall operations, management and conduct of the trial, data collection, data analysis, interpretation, and publication of results. The Steering Committee will be formed from experts in the field who will have ultimate authority over these activities and includes representatives from each of the four coordinating centres (Netherlands, Belgium, Germany, and Australia). TGI is responsible for all trial activities in Australia.

2.4 Glossary of Abbreviations & Definitions

Abbreviation	Definition
ACEI	Angiotensin Converting Enzyme Inhibitor
ADPKD	Autosomal dominant polycystic kidney disease
AESI	Adverse Event of Special Interest
ARB	Angiotensin II Receptor Blocker
AZ	AstraZeneca
BIRC5	Baculoviral IAP (Inhibitor of Apoptosis) Repeat-Containing protein 5)
BP	Blood Pressure
CKD	Chronic Kidney Disease
CKD-EPI	CKD Epidemiology Collaboration
CMR	Cardiac Magnetic Resonance Imaging
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CRF/eCRF	Case Report Form/electronic CRF
CVD	Cardiovascular Disease
DAE	AE leading to discontinuation of study medication
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DSMC	Data Safety Monitoring Committee
EC/IRB	Ethics Committee/Institutional Review Board
EET	Early End of Treatment
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
EQ-5D-5L	EuroQol 5-Dimensional Quality of Life Questionnaire – 5 Level Version
FAS	Full Analysis Set
HR	Heart Rate
ICH-GCP	International Conference on Harmonisation guidelines on Good Clinical Practice
ID	Identification
ITT	Intention to Treat
KDIGO	Kidney Disease Improving Global Outcomes
NHE1	Sodium-Hydrogen Exchange Transporter

Abbreviation	Definition
PI	Principal Investigator
PISCF	Participant Information Sheet & Consent Form
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities Test
SF-12	Short Form Questionnaire – 12
SGLT2	Sodium Glucose Co-Transporter 2
TGI	The George Institute for Global Health
UMCG	University Medical Center Groningen
XIAP	X-linked Inhibitor of Apoptosis

2.5 Protocol Synopsis

Title	A Randomized Controlled Clinical Trial to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients with Severe Chronic Kidney Disease: The RENAL LIFECYCLE trial
Objective	To establish the reno- and cardioprotective efficacy and safety of dapagliflozin in patients with severe CKD.
Rationale	SGLT2 inhibitors are a relatively new class of agents, originally developed as oral antihyperglycemic drugs. SGLT2 inhibitors are clinically available since 2012 for the treatment of patients with diabetes mellitus type 2. Later, SGLT2 inhibitors appeared to also have specific reno- and cardioprotective effects. Notably, the trials that have been performed thus far have excluded patients with an eGFR below 25 mL/min/1.73m^2 at inclusion, prevalent dialysis patients, and kidney transplant recipients. These patients are at greater risk of developing kidney failure requiring dialysis, cardiovascular complications and mortality, however currently there are only a few proven effective therapies for these conditions. There is emerging evidence from experimental studies and post hoc-analyses of randomised clinical trials that SGLT2 inhibitors may also be effective in preventing cardiovascular and mortality outcomes in patients with severe CKD, including patients receiving dialysis or living with a kidney transplant. For instance, subgroup analysis of the DAPA-CKD trial comparing 624 patients with an eGFR <30mL/min/1.73m^2 to the remainder of the trial population with better kidney function, demonstrated that the efficacy of the SGLT2 inhibitor dapagliflozin in reducing cardiovascular, heart failure and renal outcomes persisted in the population with severely impaired kidney function. Furthermore, in the DAPA-CKD trial patients continued to use dapagliflozin or placebo when dialysis was initiated. In the subgroup of patients who initiated dialysis, dapagliflozin was associated with a relative risk reduction for mortality of 21%. Finally, in kidney transplant recipients, SGLT2 inhibitors have been shown to be effective in lowering HbA1c, body weight, blood pressure and stabilising kidney function, and these agents were well tolerated and safe. These data confirm there is a sound rationale to study the long-term reno- and cardioprotective efficacy and safety of SGLT2 inhibitors in patients with severe CKD.
Study Design	Multi-centre, randomised, controlled, double blinded, pragmatic, interventional trial.
Intervention	Dapagliflozin 10 mg/day or matched placebo daily
No. Participants	1500 (750 per randomised group)
Study Duration	18-month recruitment phase, 30-month follow-up after enrolment of the last participant: Total study duration intended to last 48 months, however, the study is endpoint driven so trial duration may therefore be shorter or longer than the intended 48 months.
Primary Outcome	Combined endpoint of all-cause mortality, kidney failure,[3] and hospitalisation for heart failure in the overall study population[2]

Secondary Outcomes	<u>Incidence in the overall study population of:</u> • All-cause mortality • Kidney failure requiring kidney replacement therapy (chronic dialysis, kidney transplantation, or death due to kidney failure)[3] • Hospitalisation for heart failure <u>Incidence of the composite outcome in:</u> • Patients with eGFR ≤25mL/min/1.73m^2 (not on dialysis and not living with a kidney transplant) • Patients on dialysis with a residual diuresis ≥500 mL/24h • Patients with a kidney transplant and an eGFR ≤45mL/min/1.73m^2 <u>Safety Outcomes:</u> • SAEs, AESIs and (S)AEs leading to drug discontinuation <u>Exploratory Outcomes:</u> • These will include, among others, quality of life as measured with the EQ-5D-5L and SF-12, and cost-effectiveness of SGLT2-inhibition in the overall study population as well as in the three subpopulations.
Sample Size & Statistical Power Analysis	Endpoint driven trial – study will finish when 468 primary study outcomes have occurred. A sample size of 1500 participants provides 80% power to detect a 25% relative risk reduction assuming an annual 12.5% incidence of the primary outcome and an alpha of 0.05. Under these estimates, 468 events will be collected during a trial duration of 4 years. <u>Statistical Analysis:</u> Time to first event analysis according to the intention to treat principle. Death will be used as competing risk for the analysis of the kidney endpoint and heart failure endpoint.
Study Visits	Screening, baseline, week 2, month 3, month 6 and every 6 months thereafter. Information needed for the trial will be obtained as much as possible from visits taking place as part of routine clinical care.

[1] Dialysis includes haemodialysis as well as peritoneal dialysis

[2] For dialysis participants the primary outcome is restricted to the combined endpoint of all-cause mortality and hospitalisation for heart failure

[3] Kidney failure defined as start of chronic dialysis or kidney transplantation, or death due to kidney failure. Death due to kidney failure is defined as death due to kidney failure because dialysis treatment/a kidney transplant was deliberately withheld, not started or discontinued for any reason. Death due to kidney failure will be adjudicated by the Clinical Endpoint Adjudication Committee

3 INTRODUCTION

3.1 Background & Rationale

Disease Burden – Chronic kidney disease (CKD) affects approximately 10% of the adult population worldwide. The most common causes of CKD are diabetes, hypertension, and chronic glomerulonephritis. People with CKD are at high risk for various complications, including cardiovascular morbidity and mortality, heart failure, and end-stage kidney disease requiring kidney replacement therapy.[1,2] Treatment for CKD encompasses tight blood pressure (BP) control, preferably with angiotensin converting enzyme inhibitor (ACE-I) or angiotensin II receptor blockers (ARBs), as well as a tight glucose control in diabetic patients to prevent or delay progression of CKD and cardiovascular disease (CVD). These interventions have been proven efficacious, but still the residual risk of developing cardiovascular complications and progressing to kidney failure remains high.[3] There is therefore a need for additional interventions.[4]

Mechanism of Action of SGLT2 Inhibitors – The sodium glucose co-transporter 2 (SGLT2) is located in the first segment of the proximal tubule and is the major transporter responsible for glucose reabsorption in the kidney.[5,6] SGLT2 inhibitors are highly selective and reversible inhibitors of this transporter. Various SGLT2 inhibitors such as dapagliflozin, empagliflozin, and canagliflozin are now available for clinical use. The mechanism of action of SGLT2 inhibitors is that these drugs cause direct and insulin independent elimination of glucose by the kidneys, which results in reduced blood glucose levels in type 2 diabetes patients. In addition, dapagliflozin has a mild diuretic and natriuretic effect which results in a reduction in body weight and BP, and increase in haematocrit.[7] Phase 2 and 3 clinical trials have also shown that dapagliflozin reduces albuminuria, an important risk marker of renal and CVD progression.[8,9]

Effects of SGLT2 Inhibition on Cardiovascular Outcomes – The cardiovascular efficacy and safety of SGLT2 inhibitors has been established in two dedicated kidney outcome trials recruiting more than 4000 patients in each trial. The first trial, CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) demonstrated that in adult patients with type 2 diabetes and CKD (estimated glomerular filtration rate [eGFR] 30-90mL/min/1.73m^2), the SGLT2 inhibitor canagliflozin reduced the risk of renal and cardiovascular outcomes.[10] The second trial, DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease), was designed to assess the efficacy and safety of dapagliflozin in patients with CKD with and *without* type 2 diabetes.[11] The trial enrolled adult patients with an eGFR between 25 and 75mL/min/1.73m^2 and a urinary albumin:creatinine ratio between 200 and 5000mg/g. After a median of 2.4 years follow-up, the trial was terminated early by the independent data monitoring committee for overwhelming efficacy. Dapagliflozin, compared to placebo treatment, reduced the primary outcome (50% eGFR decline, end-stage kidney disease, renal or cardiovascular death) by 39%. In addition, dapagliflozin reduced the risk of the composite endpoint of heart failure hospitalisation or cardiovascular death by 29% and reduced the risk of all-cause mortality by 31%. These effects were present both in patients with and without type 2 diabetes. Interestingly, dapagliflozin, although developed as a glucose-lowering agent, only reduced HbA1c compared to placebo by 0.1% in patients with type 2 diabetes, whereas it did not reduce HbA1c in patients without type 2 diabetes. These data highlight that other mechanisms account for the beneficial effects of dapagliflozin on clinical outcomes. Other proposed mechanisms include reduced intra-glomerular pressure through an enhanced tubuloglomerular feedback mechanism,[12] reduced glucose and sodium transport by proximal tubular cells,[13,14] increased natriuresis,[7] and reduced systemic BP. Interestingly, there is also a theoretical rationale for an improved oxygen availability in the impaired kidney during dapagliflozin treatment. This could potentially be achieved via two mechanisms. Firstly, an improved oxygen delivery due to a small but consistently observed haemo-concentration and secondly through a reduced renal oxygen consumption due to a reduced energy requirement from the potassium sodium pump situated on the basolateral membrane striving to retain the sodium gradient over the tubular cells.[15,16] Finally, there are emerging theories around metabolic benefits connected to a mild ketosis induced by SGLT2 inhibition.[17]

Based on the CREDENCE trial and DAPA-CKD trial, canagliflozin (in patients with type 2 diabetes) and dapagliflozin have been approved for the treatment of CKD by regulatory agencies. The recent international Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines recommend the use of SGLT2 inhibitors for the treatment of CKD due to type 2 diabetes in patients with eGFR ≥30 mL/min/1.73m^2. Commencement of SGLT2 inhibitors is, however, not indicated in patients with lower kidney function, patients receiving dialysis, or kidney transplant patients since these patients were not included in most trials and the long-term efficacy and safety of SGLT2 inhibitors including dapagliflozin, are not established in these patients.

Effects on Cardiovascular Outcomes in People with Severe CKD – There is emerging evidence that SGLT2 inhibitors may be effective in preventing cardiovascular and mortality outcomes in patients with severe CKD including patients receiving dialysis and kidney transplantation. In these patients with a reduced number of functioning nephrons, it may be expected that SGLT2 inhibitors have less efficacy, because the number of proximal tubules containing SGLT2 transporters is reduced. There is, however, evidence that SGLT2 inhibitors may exert other extra-renal benefits. An experimental study using serum of patients with severe CKD showed that the uremic milieu impairs endothelial cell biology and alters cardiomyocyte function. This deleterious effect was blunted by the SGLT2 inhibitor empagliflozin.[18] Subsequently this study was performed in an in-vitro system, with results suggesting that empagliflozin exerts direct effects on endothelial-cardiac tissues which are unlikely mediated by the SGLT2 transporter in the proximal tubule of the kidney. Of note, cardiomyocytes express SGLT1 but not SGLT2. Direct effects on cardiac tissue should then be mediated via non-SGLT2 mechanisms. Interestingly, in vitro data have suggested that SGLT2 inhibitors inhibit the sodium-hydrogen exchange transporter (NHE1) in cardiac tissues through binding to the extracellular Na^+ binding site of NHE1 resulting in a reduction in cytosolic Na^+ levels and decreased Ca^{2+} concentration. Reduced cytosolic Ca^{2+} can lead to improved cardiac function. Moreover, in constant infused Langendorff-perfused mouse hearts, empagliflozin and canagliflozin were reported to induce coronary vasodilation, an effect independent of SGLT2 transporter inhibition.[19] These SGLT2 transporter independent benefits are supported by an artificial intelligence study to evaluate cellular mechanisms of SGLT2 inhibition.[20] The conclusion of this study was that inhibition of NHE1, potentially through restoration of the antiapoptotic activity of XIAP (X-linked inhibitor of apoptosis) and BIRC5 (baculoviral IAP repeat-containing protein 5) may explain the heart failure protective effects of SGLT2 inhibitors. Finally, in a porcine model of heart failure SGLT2 inhibitors have been shown to improve cardiac energetics, possibly through extra-renal direct mechanisms on the heart.[21] These studies collectively suggest that even in the setting of minimal diuresis (and thus little disposition of SGLT2 inhibitors to the transporter as expected in dialysis patients) SGLT2 inhibitors may still exert favourable effects on cardiac function.

There is also clinical evidence that supports the hypothesis that SGLT2 inhibitors reduce dialysis, heart failure and mortality in patients with eGFR <30mL/min/1.73m^2. A subgroup analysis of the DAPA-CKD trial among 624 patients with eGFR <30 (the majority having an eGFR between 25 and 30 mL/min/1.73m^2) demonstrated that the efficacy of the SGLT2 inhibitor dapagliflozin in reducing clinical outcomes persisted in this population.[22] Furthermore, in the DAPA-CKD trial patients continued to use dapagliflozin or placebo when dialysis was initiated. In the subgroup of patients who initiated dialysis, dapagliflozin was associated with a relative risk reduction for mortality of 21% *[data on file]*. In addition, in kidney transplant recipients, SGLT2 inhibitors have been shown to be effective in lowering HbA1c, body weight, BP and stabilising kidney function. SGLT2 inhibitors are also well tolerated as shown in a meta-analysis involving 8 clinical studies and 132 patients. However, the eGFR was >60mL/min/1.73m^2 in the majority of kidney transplant recipients and the efficacy and safety of SGLT2 inhibitors has yet to be established in kidney transplant recipients with more severe CKD.[23]

Rationale for Study Population – This is a randomised, double-blind, parallel-group study. Randomisation and double blinding will minimise potential bias. A parallel group design was chosen because a crossover study cannot assess major clinical outcomes. The study will be multicentre across Netherlands, Belgium, Germany, and Australia, to provide a wide applicability of results.

The study population chosen for this study is a broad population of patients with severe CKD. Three strata of patients will be included:

- Patients with an eGFR ≤25 mL/min/1.73m^2 (not on dialysis or living with a kidney transplant)
- Prevalent dialysis patients with residual diuresis ≥500 mL/24-hour (including haemo- and peritoneal dialysis), and
- Kidney transplant recipients.

These populations are nearly always excluded from clinical trials while they are at very high risk of adverse outcomes and few effective therapies are available for these patients. However, patients with type 1 diabetes or patients with a life-expectancy less than 6 months in the opinion of the treating clinician or a scheduled start of dialysis within 3 months or kidney transplantation within 6 months will be excluded.

All-Cause Mortality, Kidney Failure, And Heart Failure Hospitalisations a Clinical Trial Outcome – The primary outcome measure is the incidence of a composite of all-cause mortality, kidney failure, and heart failure hospitalisation. This is a clinically relevant outcome measure and previous trials with dapagliflozin in patients with earlier stages of CKD than enrolled in the current trial have shown that dapagliflozin reduces the incidence of each of these outcomes.

Rationale For Dose Selection – The marketed dose, 10 mg of dapagliflozin, has been demonstrated to be well tolerated and effective for the treatment of CKD in patients with and without type 2 diabetes. In a trial of participants with heart failure and reduced ejection fraction, dapagliflozin 10 mg was also effective and safe. Dapagliflozin is metabolised by the liver to inactive 3-O-glucuronide, and this inactive metabolite is eliminated by the kidneys into urine, with a small part via faeces. From a pharmacokinetics (PK) and pharmacodynamics perspective, dapagliflozin 10 mg is therefore appropriate for use in patients with kidney function impairment and dose adjustment in case of (severely) impaired kidney function is therefore not needed.

3.2 Objectives

3.2.1 Primary Objective

To determine whether dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of kidney failure, hospitalisation for heart failure, and all-cause mortality in the overall patient group, consisting of patients with eGFR ≤25 mL/min/1.73m^2, dialysis patients with residual diuresis ≥500 mL/24hr, and kidney transplant recipients with eGFR ≤45 mL/min/1.73m^2.

Of note:

- Kidney failure is defined in the pre-dialysis and in the kidney transplant subgroups as start of chronic dialysis or receiving a kidney (re)transplant. In the dialysis subgroup there will be no kidney failure endpoint. Death due to kidney failure events will be adjudicated by an independent clinical endpoint adjudication committee that is blinded to treatment assignment. Endpoint definition and details about the adjudication process will be provided in the endpoint charter.
- Hospitalisation for heart failure is defined as admission to hospital for a diagnosis of, or a diagnosis compatible with heart failure. Potential hospitalisation for heart failure events will be adjudicated by an independent clinical endpoint adjudication committee that is blinded to treatment assignment. Endpoint definition and details about the adjudication process are provided in the endpoint charter.

3.2.2 Secondary Objectives

1. To determine if dapagliflozin is superior to placebo in reducing the incidence of each of the components of the primary composite endpoint in the overall patient group:
   - All-cause mortality
   - Kidney failure (chronic dialysis, kidney transplantation or mortality due to kidney failure)

  - Kidney failure defined as chronic dialysis, kidney transplantation, or death due to kidney failure
  - Death due to kidney failure is defined as death due to kidney failure but dialysis treatment was deliberately withheld; dialysis was not started or discontinued for any reason
- Hospitalisation for heart failure

2. To determine whether dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of all-cause mortality, kidney failure, or heart failure hospitalisation in each of the three subgroups of participants:
   - Patients with advanced CKD i.e. an eGFR ≤25 mL/min/1.73m^2
   - Dialysis patients with residual diuresis ≥500 mL/24h
   - Transplant patients with an eGFR ≤45 mL/min/1.73m^2

3.2.3 Exploratory Objectives

1. To determine whether dapagliflozin is superior to placebo in reducing the incidence of
   - all-cause mortality in pre-dialysis patients, dialysis patients, kidney transplant recipients separately
   - kidney failure in pre-dialysis and kidney transplant recipients
   - hospitalisation for heart failure in pre-dialysis patients, dialysis patients, kidney transplant recipients
   - new onset type 2 diabetes mellitus in patients without diabetes mellitus
     - De novo diabetes mellitus type 2 is defined as repeating (twice) HbA1C >6.5% and/or start of glucose lowering drugs
   - Diuresis <200 ml/24hr in the dialysis subgroup (for this purpose 24hr urine samples will be collected ≥2 times per year)
   - eGFR slope (for the dialysis subgroup slope residual kidney function will be calculated using the average of 24hr urinary creatinine and urea clearance values over time)
     - Assessed using 24hr urine samples. For haemodialysis participants, urine will be collected prior to the first dialysis session in a week (and may be a 44 hrs urine collection when local custom).
   - The primary outcome in participants with and without type 2 diabetes separately

2. To determine quality of life as measured with the EuroQol 5-Dimension Quality of Life Questionnaire 5L version (EQ-5D-5L) and Short Form Survey 12 (SF-12), and cost-effectiveness of SGLT2-inhibition in the overall study population as well as in the three subpopulations.

3.2.4 Safety Objectives

To evaluate the safety of dapagliflozin by recording:

- Serious adverse events (SAEs)
- Adverse events leading to investigational medicinal product (IMP) discontinuation (DAEs)
- Adverse events of special interest (AESIs)
  - clinically significant hypoglycaemia (as defined as glucose concentration <3.0 mmol/L, i.e. 54 mg/dL)
  - diabetic ketoacidosis
  - urinary tract infections
  - genital infections

4 METHODS

4.1 Study Design

The RENAL LIFECYCLE trial consists of a screening period and a double-blind treatment period. The study is endpoint driven and will continue until the required number of endpoints is achieved. This multicentre study will recruit from academic and non-academic hospitals in The Netherlands, Belgium, Germany, and Australia.

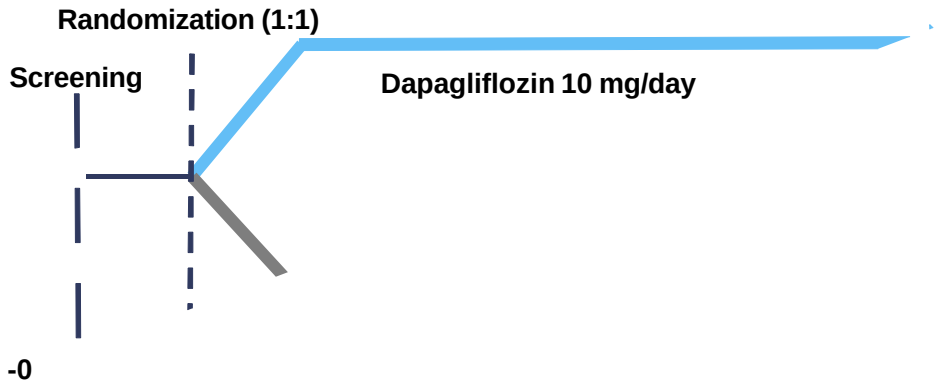

Figure 1: The RENAL LIFECYCLE Study Design

4.2 Study Population

Adult participants with severe CKD are eligible to participate defined as an eGFR ≤25 ml/min/1.73m^2, on dialysis (haemo- as well as peritoneal dialysis) or living with a kidney transplant). Recruitment will be monitored to ensure that in each stratum of participants (pre-dialysis, dialysis, kidney transplant recipients) at least 400 and no more than 600 participants will be enrolled.

4.3 Eligibility Criteria

4.3.1 Inclusion Criteria

To be eligible to participate in the trial, potential participants must meet the criteria for one of the three strata:

- Patients with advanced CKD i.e. an eGFR ≤25 mL/min/1.73m^2,
- Haemo- or peritoneal dialysis patients with a residual diuresis ≥500 mL/24h (at least 3 months after start of dialysis), or
- Transplant patients with an eGFR ≤45 mL/min/1.73m^2 (at least 6 months after transplantation)

In addition, to be eligible the following criteria must be met:

- Age ≥18 years;
- Pre-dialysis participants with eGFR ≤25 mL/min/1.73m^2 must be on a stable dose (no changes in dose or type of drug) of ACEI or ARB for at least 4 weeks prior to the screening visit to be eligible to proceed to the randomisation visit unless there is documented evidence that the participant does not tolerate an ACEI or ARB. These participants will maintain their stable doses of ACEI/ARB throughout the trial (when possible and tolerated by the participant). ACEIs or ARBs are not required for participants on maintenance dialysis or kidney transplant recipients; and
- Willing to sign informed consent.

4.3.2 Exclusion Criteria

To be eligible, potential participants must not meet any of the following criteria:

- Mentally incapacitated subjects (i.e. not able to sign informed consent)
- Diagnosis of type 1 diabetes mellitus
- Concurrent treatment with SGLT2 inhibitor

- History of ≥2 urinary tract/genital infections during the last six months
- Life expectancy <6 months in the opinion of the treating physician.
- Scheduled start of dialysis within 3 months or scheduled kidney transplantation within 6 months
- Patients treated for a renal indication during the last 6 months with a course of systemic immunosuppressive agents or intensification of treatment with systemtic immunosuppressive agents, such as patients with a kidney transplant and acute rejection or patients with GPA (Morbus Wegener) and a recent flare. *Of note, this implies that patients receiving non-systemic immunosuppression (eg. topical, ophthalmic, rectal, intra-articular or inhaled corticosteroids) are allowed to participate, as well as patients having received a short course of oral/IV steroids within 6 months prior to screening for non-renal indications (e.g. for gout or an asthma flare) as well as patients receiving during the last 6 months stable low-dose immunosuppression for whatever reason (e.g. kidney transplant recipients, patients with GPA, patients with gout).*
- Active malignancy aside from treated squamous cell or basal cell carcinoma of the skin.
- History of severe hypersensitivity or known severe hepatic impairment (Child-Pugh class C)
- History of severe noncompliance to medical regimens or unwillingness to comply with the study protocol.
- People of child-bearing potential who are pregnant, breastfeeding, have the intention of becoming pregnant or are not using adequate contraceptive measures until 4 weeks after last intake of the study medication
- Presence of other transplanted organ besides a kidney transplant
- Severe lactose intolerance
    - The study medication contains small traces of lactose, most people with lactose intolerance will not have a severe reaction – see current Investigator's Brochure for more information
- People with autosomal dominant polycystic kidney disease (ADPKD) and treated with tolvaptan

4.4 Visit Outline

4.4.1 Informed Consent

Written informed consent must be conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP) and obtained from all participants before conducting any study procedures including screening assessments. The participant information sheet and informed consent form (PISCF) signed by the participant and the authorised person conducting the informed consent process must be the current ethics committee/institutional review board (EC/IRB)-approved version. If new information becomes available that may influence participants' decisions to continue in the trial, re-consent must be obtained.

The process of obtaining informed consent should be documented in the participant's study records. The complete, original, signed PISCF must be filed in the participant's study file. A copy must be provided to the participant.

Prospective participants will be informed as part of the consent discussion that the screening phase will determine eligibility for the trial, and that signing the informed consent form does not guarantee enrolment into the trial.

Informed consent may be obtained remotely via the mailing of consent forms or verbal consent, in cases where it is difficult for the patient to attend the study site. The following options can be used for remote informed consent;

Option 1 - Mailing consent: The Investigator (or authorised delegate) will complete the consent discussion during a telephone/telehealth/video conference consultation. A hardcopy of the PISCF will be mailed to the participant with an enclosed prepaid return envelope. The participant can sign the PISCF at home and return the original signed consent form to site via post or at the next face-to-face visit. The Investigator can then

sign the consent form upon receipt. The person obtaining informed consent should document (e.g. note to file) the date of consent discussion and explain why there is a discrepancy in the dates of signature for the participant and the person who obtained informed consent.

Option 2 - Verbal consent: The Investigator (or authorised delegate) will complete the consent discussion during a telephone/telehealth/video conference consultation. A hardcopy of the PISCF can be mailed to the participant prior to the discussion. The consent form must be read to the participant and completed by the person obtaining informed consent. Participant responses, including any provision of verbal informed consent, must be recorded on the form. The person obtaining informed consent must sign and date the consent form at the time of verbal consent. The participant can sign the PISCF at the next face-to-face visit. Local regulatory requirements may require an impartial witness to listen to the consent process. The person obtaining informed consent should document (e.g. note to file) the date of consent discussion and explain why there is a discrepancy in the dates of signature for the participant and the person who obtained informed consent.

Regardless of the method of remote consent, a copy of the signed consent form or record of verbal consent will be provided to the participant.

4.4.2 Visit 1 – Screening & Study Eligibility

The procedures to be performed at the initial screening visit are outlined in Table 1: Schedule of Assessments. The investigator will register the participant through the Interactive Web Response System (IWRS) and obtain a participant identification number (ID). Potentially eligible pre-dialysis participants with eGFR≤25 mL/min/1.73m^2 must be on a stable dose (no changes in dose or type of drug) of ACEI or ARB for at least 4 weeks prior to the screening visit to be eligible to proceed to the randomisation visit unless there is documented evidence that the participant does not tolerate an ACEI or ARB. These participants will maintain their stable doses of ACEI/ARB throughout the trial (when possible and tolerated by the participant). ACEIs or ARBs are not required for participants on maintenance dialysis or kidney transplant recipients. Dietary advice will be provided according national or local clinical practice guidelines.

While the participant is in screening, tests for eligibility may be repeated twice if there is historical clinical evidence that the participant qualifies for the trial. Participants who fail the screening test will be allowed to be rescreened per investigator's judgment after one month. These participants must sign a new PISCF and will receive a new participant ID. Participants who meet all entry criteria can proceed to the randomisation visit. Visit 1 (Screening) and Visit 2 (Baseline/Randomisation) can be combined on the same day if no historic tests are used, i.e. if tests are specifically performed for the study.

4.4.3 Visit 2 – Baseline & Randomisation Visit

The randomisation visit will occur approximately 2 weeks after the participant's screening visit (with a window of ±2 weeks). Procedures to be performed at this visit are outlined in Table 1. Randomisation will be performed via web-based system, ALEA. Participants will be randomly assigned in a 1:1 ratio to either dapagliflozin 10 mg daily or matched placebo. At the randomisation visit, one early morning void urine sample will be collected in pre-dialysis and kidney transplant recipients to assess sodium, albumin, protein, and creatinine concentrations. In dialysis participants, 24-hour diuresis, residual renal kidney function (average of 24-hour urinary urea and creatinine clearances) and Kt/V will be recorded (most recent Kt/V will be recorded with a time window of ± 6 months). Blood samples will also be taken for clinical chemistry measurements, vital signs will be recorded, and a physical examination performed. For haemodialysis participants, blood samples will be taken at the start of dialysis during any dialysis session, but preferably the first dialysis session in a week. Participants will be instructed to take their study medication in the morning and adhere to treatment. Randomised participants will receive a sufficient drug supply until the month 3 visit, including the maximal time window (±0.5 months).

4.4.4 Visit 3 Onwards – Follow-up Visits

Per protocol in-patient follow-up visits are scheduled after two weeks, three months, six months, and every six months thereafter. The 3-month and 6-monthly visits can be scheduled such that they coincide with the visits taking place as part of routine clinical care. At each visit vital signs (heart rate [HR], BP and body weight) and eGFR should be recorded at a minimum as part of routine clinical care. At the 3-month visit and all following visits until End of Study (EoS)/Early End of Treatment (EET), one early morning void urine sample should be collected for assessment of sodium, protein, albumin, and creatinine concentration. In dialysis participants, 24-hour diuresis, residual renal function (average of 24-hour urinary urea and creatinine clearances) and Kt/V (most recent Kt/V will be recorded with a time window of ± 6 months) will be recorded every 6 months. In addition, AEs will be recorded at each visit. Participants will receive a sufficient drug supply until the next visit, including the maximal time window (±1 month).

4.4.5 End of Study/Early End of Treatment Visit

At the end of the study, when the estimated 468 events have occurred, an EoS visit will be scheduled. When participants opt to withdraw consent from the study prior to the study ending, an EET visit will be scheduled 14 days (±3 days) after discontinuation of study medication. Procedures at these visits include physical examination (only on indication), blood sampling, endpoint, and AE recording. Pre-dialysis participants and kidney transplant recipients are also asked to collect one early morning void urine sample for sodium, urinary albumin, protein, and creatinine assessment.

4.5 Schedule of Assessments

Table 1: RLC Schedule of Assessments

Visit No.		1[l]	2[l]	3	4	5	6	7-12+	EOS/EET[m]
Visit Name		Screening	Baseline/ Randomisation	Follow-Up	Follow-Up	Follow-Up	Follow-Up	Follow-Up	Study Close-Out Visit
Visit Month (M)		-0.5M	0M	0.5M	3M	6M	12M	Every 6M	
Time Window		-48 days	N/A	±14 days	±14 days	±28 days	±28 days	±28 days	
Informed Consent[a]		X							
Randomisation			X						
Significant Medical History		X							
Physical Examination		X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Serum or Urine Pregnancy Test[b]		X							
Blood Sampling	Sodium, potassium, creatinine, urea	X		X	X	X	X	X	
	Sodium, potassium, creatinine, urea, Hb, HbA1c, total cholesterol, HDL, LDL, calcium, phosphate, PTH		X						X
Early Morning Void Urine Sample – sodium, albumin or protein, creatinine		X	X		X	X	X	X	X
24-hour Urine Collection[c] – sodium, albumin or protein, creatinine			X[e]		X	X	X	X	X
Residual Renal Function[c]			X			X	X	X	X
Kt/V[c]			X			X	X	X	X
Vital Signs – HR, BP, weight		X	X	X	X	X	X	X	X
EQ-5D-5L & SF12 Questionnaires			X			X	X	X[f]	X
Endpoint Assessment				X	X	X	X	X	X
Dispense Study Medication			X		X	X	X	X	
Study Medication Accountability – pill count				X	X	X	X	X	X
SAEs, DAEs & AESIs			X	X	X	X	X	X	X
Review Medications		X	X	X	X	X	X	X	X
Biobanking (plasma and urine) – Optional			X		X				X
Cardiac MRI sub-study – Optional			X[i]				X[i]		
Echocardiogram sub-study – Optional	Echocardiogram & KCCQ-12		X			X	X[j]		
	Dialysis modality, average ultrafiltration[g] & PET-data[h]		X			X	X[j]	X[j]	X[j]
Cognitive sub-study (SDMT) - Optional			X			X	X	X[k]	X

a. Informed consent is obtained before any study specific procedure is done.
b. People of child-bearing potential must have a negative serum or urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening visit or if pregnancy is suspected at baseline/randomisation and follow-up visits
c. 24-hour diuresis, residual renal function and Kt/V only recorded in dialysis patients. The most recent Kt/V values for each visit will be recorded with a time window of ± 6 months
d. Only on indication
e. Results of the 24-hours urine collection at the baseline visit should be taken within 3 months
f. EQ-5D-5L and SF 12 questionnaires to be completed once every year after visit 6 until EoS/EET
g. Average ultrafiltration the 4 weeks prior to the study visit
h. Collection of the most recent PET-data if performed during routine medical care
i. Cardiac MRI will be scheduled and recorded with a time window of + 28 days from Visit 2 (baseline) and Visit 6 (12-month)
j. Only participants who are still receiving PD-treatment
k. SDMT to be completed once every year after visit 6 until EoS/EET
l. Visit 1 (Screening) and Visit 2 (Baseline/Randomisation) can be combined on the same day if no historic tests are used, i.e. if tests are specifically performed for the study
m. EET follow-up visit to be scheduled 14 days (±3 days) after discontinuation of study medication

AESI Adverse Event of Special Interest
BP Blood Pressure
DAE Discontinuation Adverse Event
EET Early End of Treatment
EOS End of Study
EQ-5D-5L EuroQol Questionnaire 5-Level
HbA1c Glycated haemoglobin
HDL High Density Lipoprotein
HR Heart Rate
KCCQ-12 Kansas City Cardiomyopathy Questionnaire-12
LDL Low Density Lipoprotein
MRI Magnetic Resonance Imaging
PET Peritoneal equilibration test
PTH Parathyroid Hormone
SAE Serious Adverse Event
SDMT Symbol Digit Modalities Test
SF-12 Short-Form Survey 12

4.6 Study Procedures

All screening, randomisation and follow-up visits will be performed at participating sites.

4.6.1 Physical Examination

Participants will undergo a physical examination at the screening visit. This examination entails a routine investigation of at least heart, lungs, and abdomen (and other body parts when indicated). At the study visits thereafter, a physical examination will only be performed on indication. At each examination it will be noted whether a participant has a functioning arteriovenous shunt (upper or lower arm).

4.6.2 Blood Pressure & Body Weight Measurements

BP will be measured as office BP by an automated device during the study visits. Participants will be in a semi-supine position during the BP measurement. The average of three readings will be used. Body weight will be recorded at each clinic visit. Participants will be asked to take off their shoes and jacket. Participant's height will be recorded at the randomisation visit to calculate body mass index (BMI).

4.6.3 Venepuncture

At each of the study visits a venepuncture will be performed for routine blood tests in accordance with local practice (for haemodialysis participant, blood can be drawn from the inlet blood line or the access cannulation line during a dialysis session). More details on blood and sample collection can be found in the Lab Manual.

4.6.4 Urine Collection

At baseline and during the study pre-dialysis participants and kidney transplant recipients are asked to collect an early morning void urine sample. The urine sample will be collected in the morning of the study visit. Sodium, albumin, protein, and creatinine will be determined in urine samples. In participants on dialysis a 24-hour urine sample instead of an early morning sample will be collected for assessment of protein, albumin, creatinine, sodium, and urea.

4.6.5 Laboratory Measurements

The laboratory measurements assessed in this study will be part of standard care. All routine laboratory measurements will be assessed in local laboratories of participating centres.

Table 2: Laboratory blood & urine assessments.

Laboratory Assessments	Parameters	
	Screening[4] and all other visits	Baseline[4] & EOS/EET Visit
Plasma[1]	Sodium Potassium Creatinine Urea	Sodium Potassium Creatinine Urea Hb HbA1c Cholesterol HDL-cholesterol LDL-cholesterol Calcium Phosphate PTH
Urine	Sodium[2] Albumin or protein[2] Creatinine[2] Pregnancy Test[3]	Sodium Albumin or protein Creatinine

[1] For blood sampling of haemodialysis participants, samples are to be taken from inlet blood line or the access cannulation line at the start of the first dialysis session in a week
[2] Except for visit 3
[3] Pregnancy test only conducted at the screening visit for people of child-bearing potential or if pregnancy is suspected at baseline/randomisation and follow-up visits
[4] **Visit 1 (Screening) and Visit 2 (Baseline/Randomisation) can be combined on the same day if no historic tests are used, i.e. if tests are specifically performed for the study**

4.6.6 Biobank samples

Study sites will have the option to participate in the collection and storage of blood and urine samples at baseline, 3 month and EOS. Blood and urine will be collected and stored for potential future analysis for exploratory biomarkers to assess correlations with disease activity, effects of dapagliflozin, clinical outcomes, and toxicity. Biomarker samples will be collected, handled and shipped as detailed in the laboratory manual. It is mandatory to obtain the patient's consent to the donation and use of biological samples. The consent date will be recorded in the eCRF. Patient not consenting to donate biological samples for future biomarker analysis are still able to participate in the study, but without providing samples for biomarker analysis.

Samples will be collected by the hospital pathology services, spun/prepared using standard operating procedures and stored in the freezer facility of the local pathology department at the study site in Australia before transfer to the University Medical Center Groningen, Netherlands for a maximum of 25 years from the date of the last patient's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the clinical study report or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with dapagliflozin to generate hypotheses to be tested in future research. The site Principal Investigator (PI) ensures that samples are labeled and shipped in accordance with the Laboratory Manual.

A full chain of custody is maintained for all samples throughout their lifecycle. The PI at each site keeps full traceability of collected biological samples from the patients while in storage at the study site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival. The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

4.6.7 Cardiac Magnetic Resonance Imaging

All participants will undergo two optional non-contrast cardiac magnetic resonance imaging (CMR) scans at baseline and 12 months. This will take place at the participating site or at a central scanning centre. More details can be found in Appendix A and in the CMR Manual of Operations.

4.6.8 Echocardiogram & Questionnaire

Participants receiving peritoneal dialysis will undergo optional echocardiograms as well as completing the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) at baseline, 6 months and 12 months (if participants are still undergoing peritoneal dialysis). This will take place at the participating site or at a central scanning centre. More details can be found in Appendix A and in the Echocardiogram Manual of Operations.

4.6.9 Symbol Digit Modalities Test

All participants will complete optional symbol digit modalities tests (SDMT) at baseline, 6 month, 12 month and once every 12 months thereafter until EoT/EET. This will take place at the participating site. More details can be found in Appendix B and in the Cognitive Function Manual of Operations.

4.7 Participant Withdrawal of Consent

Participants are free to withdraw from the study at any time – either from taking study medication or from the study entirely – without consequences for further treatment. Reasons for withdrawal of individual participants can be at the request of the participant, occurrence of adverse events (such as allergic reactions to study medication, pregnancy, laboratory abnormalities) leading to substantial changes in the participant's risk-benefit considerations that suggest a discontinuation of study medication or new medical conditions not allowing for continuation of the protocol and/or conform to the study treatment. If a participant withdraws consent to participate, they will be asked to complete an EET visit within 14 days (±3 days) after discontinuation of the study medication.

Withdrawal of consent must be ascertained and documented in writing by the investigator who must inform TGI and document the withdrawal of consent in the eCRF and medical records. A participant who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up AEs reported outside of the clinical study. If a participant withdraws from participation in the study, then their enrolment and randomisation codes cannot be reused. Withdrawn participants will not be replaced. Data generated to the time of complete withdrawal from the study will not be destroyed.

4.7.1 Vital Status of Withdrawn Participants

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at study closure. When participants withdraw consent to participate, they will have the option to allow study staff to contact the participant, their treating physician, or another party (including publicly available sources) to discern vital status (dead or alive). Participants can freely opt out of all data collection.

4.8 Guidance for Stopping Study Treatment

Study medication can be stopped temporarily for medical reasons for a period of 28 days. Temporary stops in IMP for a longer period may be permitted following discussion with TGI team. All temporary and permanent stops to IMP must be recorded in source and in the eCRF.

If a participant permanently stops taking study medication, they may continue with follow-up visits. Discontinuation of study medication is not considered withdrawal of consent.

4.8.1 Guidance for IMP Discontinuation Due to AE

In case of pregnancy, hypersensitivity to study medication or known severe hepatic impairment (Child Pugh C), study medication will be immediately discontinued upon the PI receiving first knowledge of the event. Any reason for study medication discontinuation will be noted in the eCRF, and the participant involved will be asked to continue in follow-up.

When participants reach a renal endpoint, e.g. start or chronic dialysis or receiving a kidney transplantation, study medication will not be stopped as customary in many other trials in nephrology but continued in the new phase of their "renal lifecycle", hence the name of the trial.

4.8.2 Guidance for treatment of participants undergoing surgery

To minimise the risk of diabetic ketoacidosis, if the participant requires a scheduled surgery, the study medication should be withheld temporarily for at least 3 days prior to the surgery.[24] Specialist endocrinology advice is strongly recommended for participants requiring an unscheduled or emergency surgery. In this situation, the Australian Diabetic Society advises measuring both blood glucose and blood ketone levels. If the ketones are <1.0 mmol/L, proceed with the surgery with hourly blood glucose and blood ketone testing during procedure.[25] These participants should be admitted postoperatively for regular monitoring of blood glucose and ketone levels until eating and drinking normally. Restart the study medication post-operatively only when the patient is eating and drinking normally or close to discharge from hospital.

If surgery is urgent or needed in an emergency, study drug should be withheld at the time of the surgery. Unblinding of study allocation is usually not indicated. However, unblinding may be considered but should only be performed if knowledge of randomized treatment allocation will influence clinical management. If study drug is permanently ceased, the date and reason of permanent study drug discontinuation should be documented in the database.

4.8.3 Guidance for treatment of participants with gastrointestinal symptoms and/or fever

In case of threating dehydration, for instance due to vomiting (>3 times), diarrhoea (>3 times a day during at least 2 days) or fever (>38.5 C during at least 2 days), study medication can be ceased as is routinely often done with diuretics and RAAS inhibition. If study medication is ceased, it should be re-started if clinically appropriate, as soon as deemed feasible. If study medication is permanently ceased, the date and reason of permanent study medication discontinuation should be documented in the eCRF.

4.8.4 Guidance for treatment of participants with symptomatic hypotension

If the participant experiences symptomatic hypotension, consider down-titration of anti-hypertensives and/or diuretics, at the discretion of the treating physician, prior to consideration of discontinuation of study medication. If study medication is ceased, it should be re-started if clinically appropriate, as soon as deemed feasible. If study medication is permanently ceased, the date and reason of permanent study medication discontinuation should be documented in the eCRF.

4.9 Study Duration

The study will have an 30-month recruitment phase and a 18-month follow-up after enrolment of the last participant. Total study duration is therefore intended to last 48 months. It should be noted that for individual participants the duration of the trial can differ. In principle, the first participant will be in the trial for 48 months, and the last participant, for 30 months. In addition, the trial is powered to be event driven and will be terminated when 468 primary composite outcomes have occurred (see paragraph 4.4 Power Analysis). The exact trial duration may therefore be shorter or longer than the intended 48 months.

4.10 End of Study

When the study is stopped (either as planned or when discontinued prematurely) all participants will be invited to perform an EoS visit (see Table 1).

4.10.1 Premature Termination of The Study

There are no predefined criteria for premature termination of the study. If, however, during the conductance of the study information becomes available showing that continuation of the study would result in a significant safety risk for the participants, the Steering Committee will decide to terminate the study.

4.11 Sample Size Calculation

Assuming 25% risk reduction in the 12.5% annual incidence rate of the primary outcome in a trial of 4-year duration (1.5-year inclusion and 2.5-year follow-up after last participant in) with a power of 80% and an alpha of 0.05, it follows that 1442 participants must be included, which is rounded to 1500 (calculations made with PASS Power Analysis and Sample Size Software).

Table 3: Sample size calculations.

Event Rate	Risk Reduction				
	20%	22.5%	25%	30%	33%
7.5%	3716	3186	2305	1549	1254
10%	2849	2441	1765	1184	958
12.5%	2330	1996	1442	966	781
15%	1985	1700	1227	822	664

Previous studies with SGLT2 inhibitors in patients with CKD have shown that SGLT2 inhibitors reduce the risk of renal failure, heart failure and all-cause mortality by 30 to 40%. These effects were consistent regardless of whether participants had/did not have type 2 diabetes, and regardless of renal function or degree of albuminuria.[10,22,26,27] Based on these studies, we expect that in The RENAL LIFECYCLE Trial dapagliflozin will reduce the risk of the composite endpoint of renal failure, heart failure and death by at least 25%. The study is powered for an effect measure that is lower than observed in previous studies with patients with chronic kidney damage. It is important to note that the trial will reach statistical significance if the observed effect shows a risk reduction of 22%.

The overall 12.5% annual event rate for the primary composite outcome of incident kidney failure, hospitalisation for heart failure and all-cause mortality is based on data from previous trials and observational studies (details are provided in Appendix B). Given that the incidence rates of the composite endpoint in each of the three subgroups, we assumed a 12.5% annual event rate for the overall study population. Because the incidence rates in these subgroups differ slightly, inclusion will be weighed to allow a better estimate of the treatment effect within each subgroup.

We will therefore include 450 to 525 participants with CKD stages G4/5, 400 to 475 participants on dialysis, and 550 to 650 participants with a kidney transplant. In case the maximum participant number of a subgroup is reached, inclusion of participants will be stopped for this subgroup, with a total number of participants to be included being 1500. An annual lost to follow-up rate of 1% is accounted for in the power analysis (a conservative estimate and higher than those observed in other randomised clinical trials with SGLT2 inhibitors in CKD). Of note, when pre-dialysis participants start dialysis or are transplanted, they will continue in the trial, and this will not be a reason for study discontinuation. Likewise, when dialysis participants are transplanted, they will also continue in the trial. A 5% annual IMP discontinuation is also incorporated.

With the above assumptions (25% risk reduction/12.5% annual event rate/1500 participants) we expect to accrue 468 events which provide 82% power. It should be noted that the trial is event driven and will be terminated when 468 primary composite outcomes have occurred. The exact trial duration may therefore be shorter or longer than the intended 48 months. A sample size of 1500 participants leads to a minimal detectable effect size at alpha 0.05 of 18% (hazard ratio: 0.82) assuming a primary outcome event rate of 12.5%.

An interim analysis of the sample size will determine if the sample size should be adjusted based on the actual event rate observed during the trial. Moreover, when financial resources allow it, it may be considered to increase sample size to allow more solid conclusions on the efficacy of the SGLT2 inhibitor versus placebo on the primary endpoint in each of the three subgroups separately. In case it will be deemed appropriate to increase the sample size ethics approval will be sought before doing so.

5 STUDY MEDICATION

5.1 Investigational Medicinal Product

Dapagliflozin tablets and matched placebos will be provided in-kind by AstraZeneca (AZ). Labelling of dapagliflozin and placebo will be performed by Apotheek A15, Buys Ballotstraat 2, GORINCHEM, 4207HT, Netherlands (GMP certificate number: NL/H 20/2024128). Tablets are supplied in HDPE bottles and each bottle contains 35 tablets. Tablets will be kept in their original primary packaging and Apotheek A15 will label the container with a study label. The IMP will be labelled according to the requirements set in Annex 13 of the GMP.

Participants take 10 mg dapagliflozin or matched placebo once daily in the morning according to a randomised treatment scheme. At the randomisation visit, study medication will be dispensed based on the randomisation number generated in the central web-based system. The pharmacy of each study site will store the randomisation code. Study medication is received at the study site by a designated and qualified person, handled and stored safely and properly according to the instructions specified on the drug labels. Study medication is kept in a secured location. Storage conditions are adequately monitored. Participants are asked to return all unused study medication and packaging at each visit (including at the EoS or EET visits). Unused IMP will be destroyed by the local pharmacy department at the end of the study.

5.2 Concomitant Medications

Open label SGLT2 inhibitors are not allowed to be used during the trial. No other medication is disallowed. Of note, the glucose-lowering efficacy of dapagliflozin is dependent on kidney function and is reduced in patients with an eGFR <45 mL/min/1.73m^2. Therefore, additional glucose-lowering treatment should be considered in participants with diabetes mellitus when deemed necessary.

6 ENDPOINTS & RANDOMISATION

6.1 Primary Endpoint

Time to the composite endpoint of all-cause mortality, kidney failure (chronic dialysis, kidney transplantation or death due to kidney failure), and hospitalisation for heart failure

Potential endpoints will be identified when questioning the participant about their overall health and through information received through standard medical practice. Investigators will be encouraged to inquire about events that might represent an endpoint.
Heart failure hospitalisation and death due to kidney failure endpoints will be recorded in the eCRF and submitted for central adjudication. The source documents and relevant eCRF data will be sent for adjudication. Detailed instructions regarding endpoint reporting will be provided to the study sites. Additional details about the evaluation of heart failure hospitalisations and death due to kidney failure will be described in the Clinical Endpoint Adjudication Committee charter.

Participants will continue taking the study medication after reaching a primary endpoint (except all-cause mortality).

6.2 Secondary Endpoints

- Time to kidney failure (in advanced CKD and transplant participants only)
- Time to the first occurrence of heart failure hospitalisation
- Time to all-cause death

Each of these study endpoints will be investigated in the overall study population.

In addition, it will be investigated whether dapagliflozin is superior to placebo in reducing the incidence of the composite outcome of all-cause mortality, kidney failure, or heart failure hospitalisation in each of the three subpopulations.

6.3 Exploratory Endpoints

- Time to new onset type 2 diabetes in participants without diabetes
- Time to diuresis <200ml/24h in the dialysis subgroup
    - Two consecutive values must both be <200 ml/24hr with the date of the first value counting as the time of occurrence of the event. In the CRF it should be noted what the exact volume of diuresis was and whether it was collected over 24hr. If collection time deviates, the collection time (i.e. number of hours) should be recorded.
- Rate of change in eGFR over time
- Quality of life
- Cognitive function

6.4 Cost-effectiveness of Intervention

New onset of type 2 diabetes, post randomisation, is defined according to the following criteria:

- Reporting of new onset of type 2 diabetes necessitating initiation of anti-diabetic medication OR
- HbA1c ≥6.5% (48 mmol/mol) measured by local laboratory at two consecutive study visits

eGFR will be calculated with the CKD Epidemiology Collaboration (CKD-EPI) equation. For the dialysis subgroup eGFR will be calculated using the average of 24hr urinary creatinine and urea clearance values.

Quality of life will be assessed by the validated EQ-5D-5L questionnaire and SF-12 questionnaire.

6.5 Safety Endpoints

- SAEs
- DAEs
- AESIs:
    - clinically significant hypoglycaemia (i.e. glucose concentration <3.0 mmol/L or 54 mg/dL)
    - diabetic ketoacidosis
    - urinary tract infections
    - genital infections

The diagnosis of diabetic ketoacidosis must be based on robust biochemical data and can be classified as either 'definite diabetic ketoacidosis' or 'probable diabetic ketoacidosis' based on the following criteria:

- **Definite diabetic ketoacidosis**: In a clinical setting, consistent with diabetic ketoacidosis (history, symptoms, and physical exam) and the absence of more likely alternative diagnoses thought to be the primary cause of presentation, with the following biochemical data:
    - Ketonemia ≥3.0 mmol/L and/or significant ketonuria (more than 2+ on standard urine sticks) and

- At least one of the following criteria suggesting high anion gap metabolic acidosis:
    a. Arterial or venous pH ≤7.3
    b. Serum bicarbonate ≤18 mmol/L
    c. Anion gap [Na – (Cl + HCO3)] >10

- **Probable diabetic ketoacidosis**: Does not meet strict criteria for definite diabetic ketoacidosis due to incomplete biochemical workup, but clinical setting consistent with diabetic ketoacidosis (history, symptoms, and physical exam) and the absence of alternative diagnoses thought to be the primary cause of presentation. Probably will be indicated when it is the most likely clinical diagnosis taking into account available data – for example:
    - Evidence of elevated total body ketones (blood or urine) with suspected acidosis, but without documented metrics for metabolic acidosis,
    - Evidence of anion-gap metabolic acidosis with a lactate <2mmol/L and with suspected, but without documented metrics for elevated total body ketones.

6.6 Randomisation, Blinding & Treatment Allocation

Treatment assignment of dapagliflozin or placebo will be randomised. A minimisation randomisation method will be used. The randomisation procedure including the drug supply management tool will be designed and implemented by IM Onderzoek UMCG (IM-O) using a web-based system called ALEA. Randomisation will be done with stratification for four subgroups (pre-dialysis, peritoneal dialysis, haemodialysis, kidney transplant recipient), centre and type 2 diabetes mellitus status (yes/no). The randomisation system will register if a participant participates in either the Cardiac MRI Sub-study and/or Echocardiogram Sub-study. Every user will receive an individual login code with which they can randomise participants.

7 SAFETY REPORTING

7.1 Data Safety Monitoring Committee

An independent data safety monitoring committee (DSMC) will be appointed and will report to the Steering Committee. The DSMC will be responsible for safeguarding the interests of the patients in the study by assessing the safety of the IMP during the study, and for reviewing the overall conduct of the study. The DSMC will receive from IM-O the collected study data merged with the coded individual treatment codes before the DSMC meeting. On request IM-O can provide a code list of the randomisation outcome. A DSMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Steering Committee.

7.2 Temporary Halt of Study

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise participant health or safety. Data derived during this trial or from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study. This might include the occurrence of adverse events which character, severity or frequency is new in comparison to the existing risk profile. The sponsor will notify the accredited ethics committee, without undue delay, of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited ethics committee. The investigator will take care that all participants are kept informed about the communication between the accredited ethics committee and sponsor.

7.3 Adverse Event Definitions

7.3.1 Adverse Events

AEs are defined as any undesirable experience occurring to a participant during the study (from randomisation to last visit), whether or not considered related to dapagliflozin. In this study AEs will not be collected, unless they meet the criteria for potential endpoints – SAEs, DAEs, or AESIs. The term AE in this document refers only to these categories.

An AE reported by the participant should be recorded in the eCRF only if it qualifies as:

- An SAE (as defined in Section 7.3.2)
- A DAE
- An AESI:
    - significant hypoglycaemia (i.e., glucose concentration <3.0 mmol/L or 54 mg/dL)
    - diabetic ketoacidosis – as defined in Section 6.5
    - urinary tract infections
    - genital infections

The causal relationship between IMP and each AE (for those collected above) will be assessed, and investigators are asked to answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

Given the reversible renal haemodynamic effect of SGLT2-inhibitors, a decline in eGFR of 20-25% from baseline could be acceptable and will not considered an AE. A decline of ≥25% for each subgroup will be considered an AE. A sudden decline in eGFR may result in a temporary stop of the study medication, but first a stop or down-titration of concomitant diuretics (if used) should be considered. It is up to the investigator whether the study medication should be stopped. If so, study medication may be stopped for a maximum of 2 weeks. The eGFR should then be checked for reversibility, and study medication should preferably be restarted within 2 weeks.

7.3.2 Serious Adverse Events

An SAE is any untoward medical occurrence or effect that:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect; or
- any important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator.

An elective hospital admission will not be considered as an SAE.

7.3.3 Suspected Unexpected Serious Adverse Reactions

Adverse reactions are all untoward and unintended responses to an IMP related to any dose administered. Unexpected adverse reactions are Suspected Unexpected Serious Adverse Reactions (SUSARs) if the following three conditions are met:

1. the event must meet the definition of an SAE (see Section 7.3.2)
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the IMP, regardless of the administered dose
3. the adverse reaction must be unexpected, i.e., the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

- Summary of Product Characteristics for an authorised medicinal product
- Investigator's Brochure for an unauthorised medicinal product.

7.4 Safety Reporting

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. SAEs that result in death or are life-threatening must be entered into the database within 24 hours of the investigator becoming aware of the event.

All SUSAR reporting and other additional SAE requirements will be performed by the local monitoring parties according to the national reporting obligations. The sponsor will inform participating centres about SAEs and SUSARs and will take care of the periodic safety reports for the ethics committee and authorities.

TGI will report the SAEs to the appropriate competent authority quarterly. In case there are additional requirements to report SAEs to local authorities for sites in other countries, these will be followed. This process will be delegated by the PI to local contracted monitoring parties.

The sponsor will report to the applicable ethics committees any SUSARs that have arisen in other clinical trials of the same sponsor and with the same IMP, and that could have consequences for the safety of the participants involved in the study.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half-year to the competent authorities and ethics committees that approved the study. This line-listing provides an overview of all SUSARs from the IMP, accompanied by a brief report highlighting the main points of concern.

The reporting of SUSARs will occur no later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

7.5 Annual Safety Report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to applicable ethics committees and competent authorities. This safety report consists of a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system.

7.6 Follow-up of Adverse Events

All SAEs and AESIs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs and AESIs need to be reported until the end of study, as defined in the protocol.

7.7 Safety Reporting to AstraZeneca

The global sponsor (UMCG) is responsible for reporting to AZ. SAEs (both SUSAR and suspected serious adverse reactions) related to the IMP must be reported to AZ on an ongoing basis (initial and follow-up information) as well as individual case reports. SUSARs must be provided unblinded and at the same time these events are notified to the Regulatory Authority. More information can be found in Appendix C.

7.8 Emergency Unblinding

In case of an emergency code break, the online ALEA system has an emergency procedure in place to unblind participants after approval by the PI. In case ALEA is down the UMCG Pharmacy has a paper backup list to follow the procedure described above. Even though the code is broken for an individual participant, any blood samples for safety or pharmacodynamic assessments will continue to be drawn, for at least 24hr following the last dose as long as doing so will not compromise participant welfare.

It is the responsibility of the PI to ensure that there is a procedure in place to allow access to the code break procedures in case of emergency. IMP must be discontinued after unblinding, but the participant will be followed until resolution of the AE. At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports.

8 STATISTICAL ANALYSIS

8.1 Efficacy Analysis Set

All participants who have been randomised to study treatment will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised IMP assignment, irrespective of the treatment received. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

8.2 Safety Analysis Set

All participants who receive at least one dose of IMP will be included in the safety population. Participants will be analysed according to the treatment received. The safety analysis set will be considered the primary analysis set for all safety variables.

8.3 Primary Study Parameter

The primary variable is the time to first event included in the primary composite endpoint. The primary analysis will be based on the intention to treat (ITT) principle using the FAS.

In the analysis of the primary composite endpoint, treatments (dapagliflozin versus placebo) will be compared using a Cox proportional hazards model with a factor for treatment group, stratified by randomisation stratification factors (subgroup, centre, and type 2 diabetes mellitus status). In general, the analysis will use each participant's last contact as the censoring date for participants without any primary events. The p-value, hazard ratio, and 95% confidence interval will be reported.

Kaplan-Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoint will be calculated and plotted, for overall analysis and for the individual components. Methods similar to those described for the primary analysis will be used to separately analyse the time from randomisation to the first occurrence of each component of the primary composite endpoint.

8.4 Secondary Study Parameter

The secondary variables will be analysed in the similar manner as the primary variable.

Subgroup variables for the primary efficacy endpoint and secondary efficacy endpoints include demography, baseline disease characteristics, baseline concomitant medications and others. Cox proportional hazards models will be performed to examine treatment effects within relevant subgroups separately. The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. Event rates by treatment and hazard ratios with 95% confidence intervals will be reported for each subgroup. Hazard ratios and confidence intervals for overall analysis and subgroups will be presented with forest plots. Subgroup analysis by baseline age, sex, treatment modality, diabetes status, and other relevant subgroups will be performed by testing for interaction.

The Fine-Gray model will be used to estimate the cumulative incidence to account for competing risks. Further details of the subgroup analysis, including the list of subgroup variables, will be provided in the Statistical Analysis Plan (SAP).

8.5 Safety Analysis

The number and percent of participants with SAEs, DAEs and AESIs, will be summarised by treatment group. Changes in relevant clinical chemistry/haematology parameters will be summarised over time by treatment group. In addition, the number and percent of participants with a marked abnormality in clinical laboratory tests will be summarised over time by treatment group. For safety analyses, summaries will be provided using both on treatment observations and using all observations regardless of whether participants are on or off study treatment.

8.6 Interim Analysis

No efficacy interim analysis is planned in the study. Safety will be monitored on an ongoing basis by the DSMC.

9 ETHICAL CONSIDERATIONS

9.1 Regulation Statement

The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. In Australia, a Human Research Ethics Committee (HREC) must approve the study before any study specific procedure commences.

9.2 Recruitment & Consent

Participants will be screened and recruited from academic and non-academic hospitals and renal centres in Europe and Australia. Prior to their visit to the outpatient clinic, potential participants will be invited to participate in the study verbally or by sending a letter of invitation via the treating renal physician who provides their clinical care. The invitation letter, will include a brief explanation of the study, advantages and disadvantages of participating, and contact information of the research team members working on this study. Potential participants will be given ample time to consider their decision and discuss this study with others, including their GP/medical specialist prior to consent and throughout the duration of the study. Thereafter, potential participants will be asked to sign their written informed consent before they take part in the study. Informed consent may be obtained remotely via the mailing of consent forms or verbal consent, in cases where it is difficult for the patient to attend the study site.

10 COMPENSATION

If a participant suffers any injuries or complications as a result of the research project, they will be advised to contact the study team and will be assisted with arranging appropriate medical treatment. If participants are eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, patients may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if their injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). Patients do not give up any legal rights to compensation by participating in this study.

11 ADMINISTRATIVE ASPECTS, MONITORING & PUBLICATION

11.1 Handling & Storage of Data & Documents

A participant ID list will be made to link data to participants in order to be able to trace data to an individual participant. This code will not be based on the participant initials or birthdate. The key to the code will be safeguarded by the PI since the data will be kept for a period of 25 years. The handling of personal data will comply for respective local and national regulations.

11.2 Monitoring & Quality Assurance

Independent clinical site monitoring and quality assurance is conducted at all hospitals to ensure that the rights and well-being of participants are projected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, with ICH-GCP, and with applicable regulatory requirement(s). Monitoring will be conducted according to the Monitoring Plan.

11.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the original ethics application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the participants of the trial
- the scientific value of the trial
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the HREC and to the competent authority in Australia. Non-substantial amendments will not be notified but will be recorded and filed by the sponsor.

11.4 Annual Progress Report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited HREC once a year. Information will be provided on the date of inclusion of the first participant, numbers of participants included and numbers of participants that have completed the trial, SAEs/serious adverse reactions, other problems, and amendments.

11.5 Temporary Halt & End of Study Report

The sponsor will notify the accredited HREC and the competent authorities of the end of the study within a period of 90 days. The end of the study is defined as the last participant's last visit.

The sponsor will notify the HREC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited HREC and the competent authorities within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited HREC and the competent authorities.

11.6 Public Disclosure & Publication Policy

Publication policy is in agreement with the Dutch Central Committee on Research Involving Human Subjects' publication statement. Neither the sponsors, nor the PI has a right of veto regarding the way of publishing the results.

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13 APPENDICES

13.1 Appendix A – The RENAL LIFECYCLE Trial: Cardiac Sub-studies

Background

Left ventricular (LV) hypertrophy is highly prevalent in chronic kidney disease (CKD), affecting 30-45% of patients with non-dialysis CKD, 75% of patients with dialysis-dependent kidney failure, and 50% of kidney transplant recipients.[1,2] Further, left ventricular hypertrophy is associated with an increased risk of cardiovascular events and death in this patient population.[3]

As a result, LV dysfunction is highly prevalent in patients with advanced CKD and end-stage kidney disease (ESKD). Global LV systolic longitudinal strain (GLS) is a non-invasive echocardiographic measure of LV-systolic and diastolic function[4] and a stronger prognostic predictor of mortality and adverse CV-events, as compared to ejection fraction, in both the general population[5] and in ESKD.[6 7]

The mechanisms underpinning the cardiovascular and renal benefits of SGLT2 inhibitors are still under investigation. Their primary action is through the inhibition of the coupled reabsorption of sodium and glucose from the proximal tubules in the kidney, leading to natriuresis, glucosuria and diuresis; and thereby lowering systemic blood pressure or intraglomerular pressure. Since SGLT2 transporters are expressed nearly exclusively in the kidney (in the first segment of the proximal tubule), it was believed that SGLT2 inhibitors' action would be attenuated at reduced eGFR levels. Emerging experimental data, however, show that SGLT2 inhibitors exert direct cardioprotective and nephroprotective effects that are independent of their action in the proximal tubules. Pre-clinical studies show that SGLT2 inhibitors improve myocardial bioenergetics, reduce cardiac fibrosis, and alter adipokines and cytokine production.[8] Indeed, trials have shown that, compared to placebo, SGLT2 inhibitors significantly reduced left ventricular mass and improved GLS[9] in patients with type 2 diabetes, thus providing a novel mechanism underlying the direct cardioprotective effects of SGLT2 inhibitors.[10,11]

There are two cardiac sub-studies proposed. The RENAL LIFECYCLE Trial cardiac MRI sub-study will evaluate the effect of dapagliflozin, as compared to placebo, on left ventricular mass, an intermediate cardiovascular outcome, in 250 participants with advanced CKD. This will provide robust evidence on the mechanisms underpinning the cardioprotective effects of SGLT2 inhibitors in this high-risk patient population.

The RENAL LIFECYCLE Trial cardiac echocardiography sub-study will evaluate the effect of dapagliflozin, as compared to placebo, on LV-GLS, in 100 participants with ESKD treated with peritoneal dialysis. This will provide additional evidence on the mechanisms underlying the cardio-protective effects of SGLT2i in patients with ESKD. Furthermore, the GLS-data will be related to measured CKD- and PD-associated mediators of heart failure (measured in serum, urine and peritoneal effluent. This will aid to determine their relevance in patients with ESKD, as well as to define if and to what extent SGLT2i affect these mediators in patients with ESKD. Finally, this sub-study allows prospective evaluation of LV-GLS as a predictor of adverse cardiovascular events in patients treated with PD.

Cardiac MRI Sub-study

Hypothesis

The cardiac MRI sub-study of The RENAL LIFECYCLE Trial will test the effects of dapagliflozin compared to placebo on indexed left ventricular mass at 12 months in a subset of 250 participants included in the trial.

Recruitment & Follow-up

250 participants will be recruited from about 10 sites (approx. 25 per site) that have access to an MRI scanner with capabilities to perform a cardiac MRI, and a cardiac MRI physician able to supervise the scans. Participants will follow the same enrolment, randomisation and follow-up schedule as the main trial with the addition of a non-contrast cardiac MRI done at baseline and 12 months using a standardised protocol outlined in the *'Cardiac MRI Technical Manual.'* In brief, this will include cine imaging of the heart in different views, to assess atrial and ventricular geometry and function.

Primary & Secondary Outcomes

The primary outcome of the cardiac MRI sub-study will be indexed left ventricular mass in g/m^2. Secondary outcomes will be:

- non-indexed left ventricular mass,
- indexed left atrial volume,
- non-indexed left atrial volume,
- indexed left ventricular end diastolic volume,
- indexed left ventricular end systolic volume; and
- left ventricular ejection fraction.

All outcomes will be evaluated as the change from baseline to 12 months with comparison made between randomised groups. Outcomes will be determined from de-identified MRI images assessed in duplicate by independent reviewers masked to treatment allocation.

Sample Size & Analysis

The sample size will provide 90% power (p=0.05) to detect a difference in indexed left ventricular mass of $6.5g/m^2$ between treatment groups assuming a standard deviation of $15g/m^2$ and allowing for up to 10% missing follow-up data. The mean difference between groups will be determined using analysis of covariance adjusting for baseline values.

The statistical power is based on the below assumptions:

- Baseline indexed left ventricular mass of $105g/m^2$ (as was seen in the ACTIVE Dialysis trial).[12]
- Dapagliflozin treatment effect size of 6% reduction in indexed left ventricular mass (as was observed in 2 prior SGLT2 inhibitor trials).[10,11]
- 10% missing data (due to death or other reasons).

Data Analysis

The mean change in left ventricular mass indexed to body surface area (and other cardiac MRI measures) will be presented as mean (95% CI), and the adjusted difference between groups for the intention-to-treat population. The data will be analysed using analysis of covariance adjusting for baseline values.

Additional Participant Burden

The cardiac MRI sub-study involves two additional participant visits of approximately 30-45 minutes duration. The MRI is non-contrast and does not involve venous access, however, participants will be required to lie still in an MRI scanner for 15 minutes attached to ECG gating. Exclusion of those with a contra-indication to MRI will ensure there is no risk to the individual, however, some may feel claustrophobia or distress from the confined space. Any chance findings identified will be communicated by the site team to the participants primary care physician within one week of the scan.

Specific Exclusion Criteria

For the cardiac MRI sub-study there is an additional exclusion criteria:

- Severe claustrophobia or absolute contra-indication to MRI.

Cardiac Echocardiography Sub-study

Hypothesis

SGLT2-inhibition improves cardiac function (as measured by LV-GLS) in patients with ESKD, since SGLT2i-induced cardio-protection is independent of substantial kidney function.

Recruitment & Follow-up

We aim to include 100 peritoneal dialysis (PD)-treated participants of the RENAL LIFECYCLE Trial (approximately 50 from the Dutch participating centres and ~50 from the site(s) in Australia). Participants will follow the same enrolment, randomisation and follow up schedule as the main trial with the addition of: an echocardiogram combined with a body composition measurement (BCM) (not applicable for Australia) to account for changes in volume status, as well as blood, urine- and peritoneal effluent sampling at baseline and the 6-month study visit (biobanking) (not applicable for Australia). Furthermore, according to availability at the specific sites, functionality and symptoms will be assessed by a six-minute walking-test (6MWT) (not applicable for Australia) and a Kansas City Cardiomyopathy Questionnaire (KCCQ-12). If participants are still PD-treated at the 12-month study visit, the measurements will also be performed at that time-point. During routine clinical care, information about PD modality, average ultrafiltration and PET-data is collected in the medical chart. From visit 2 until end of PD-treatment, EET or EOS information about PD modality, average ultrafiltration the 4 weeks prior to the study visit and PET-data will be retrieved from the medical chart. PET-data is only retrieved if a PET-test is performed during routine clinical care the 6 months prior to the study visit and at visit 2 the most recent PET-data available is retrieved from the medical chart.

Primary & Secondary Outcomes

Primary outcome: change in LV-GLS from baseline to 6 months with comparison made between randomised groups.

Secondary outcomes:

Differences between randomised groups:

- Echocardiography parameters: E/e', LV-end diastolic volume index
- Change in LV-GLS from baseline to 12 months
- Volume status: BCM (not applicable to Australia)
- Functionality/symptoms: 6MWT (not applicable to Australia); KCCQ-12
- Dialysis modality, average ultrafiltration and PET-data

Sample Size

Difference in GLS is the primary outcome of this proof-of-concept study. A GLS of -20% is considered normal with standard deviations (SD) ranging 2.0-3.5% across populations including ESKD.[4,6,7] GLS-data in stable PD-treated patients are limited. A GLS of -16.5%±2.8% was found in an unselected population of 110 stable PD-patients.[7] We found a GLS of -12.8%±3.4% in 60 prevalent PD-patients, who met the eligibility criteria of the proposed study (unpublished data).

There are no data on SGLT2i-induced changes in GLS from randomized placebo-controlled trials. Data are limited to a study in 53 patients with T2DM, stable HF and a comparable baseline GLS as in our population (Tanaka, 2020). In that study, a 6-month treatment with dapagliflozin induced an absolute 1.7% reduction in GLS, as compared to baseline.

Hence, using a two-sample paired-means test as reference in a placebo-controlled study with a one-sided alpha of 0.05 and a 15% withdrawal rate, a sample size of N=100 has 80% power to detect a significant 1.7% reduction in GLS in a population with a baseline SD of 3.4%.

Data Analysis

The mean change in LV-GLS will be presented as mean (95% CI) and the adjusted difference between groups for the intention-to-treat population. The data will be analysed using analysis of covariance adjusting for baseline values.

Additional Patient Burden

The cardiac echography sub-study in Australia involves the following additional study procedures at the baseline- and 6-month study visit. This also applies to the 12-month visit for participants who still receive PD-treatment at that time-point:

- Echocardiography
- KCCQ-12

This will result in an approximately 60 min longer study visit at baseline and at 6 months (and at 12 months for participants who remain on PD-treatment at that time-point).

Specific Inclusion Criteria

For the Echocardiography Sub-study there is additional inclusion criteria:

- PD patients

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13.2 Appendix B – The RENAL LIFECYCLE Trial: Cognitive Sub-study

Background

Patients with chronic kidney disease (CKD) are at a much higher risk for developing cognitive impairment compared with the general population and both lower glomerular filtration rate and the presence of albuminuria are associated with its development [1]. Given the excess of vascular disease seen in patients with CKD, cerebrovascular disease is likely the dominant pathology, but impaired clearance of uremic metabolites, depression, sleep disturbance, anemia, and polypharmacy may also contribute [1]. In keeping with an important role for vascular disease is the high prevalence of structural cerebral damage in patients with CKD with more severe damage in patients with higher stages of CKD. A recent study showed that lower eGFR and higher urinary albumin to creatinine ratio were associated with reduced brain cortex volume, greater white matter hyperintensity volume and more brain infarcts and microhemorrhages [2].

Initiation of hemodialysis can improve the severe cognitive impairment associated with uremia but cannot prevent the progression of cognitive impairment in the first year after starting hemodialysis [3,4]. A longitudinal study in incident hemodialysis patients even showed a marked increase in white matter hyperintensities during the first year after starting hemodialysis [5]. The adverse hemodynamic effect of hemodialysis are probably a key factor in the acceleration of cerebral damage but oxidative stress, inflammation and endothelial dysfunction probably also play a role. We have previously shown that global cerebral perfusion of elderly patients falls on average 10% during a single hemodialysis session [6]. Following this observation, the group of McIntyre has recently shown that a single hemodialysis session induces cerebral ischemia by showing disruption of the integrity of matter tracts using diffusion tensor imaging MRI and the appearance of ischemia markers like choline and N-acetyl aspartate by proton magnetic resonance spectroscopy in the last hour of the hemodialysis session [7].

In contrast, kidney transplantation appears to lead to improved cognitive function in many transplant recipients with some studies even showing some reversibility of the cerebral damage [8-10]. However, the prevalence of cognitive impairment after kidney transplantation is still much higher compared to age and sex matched individuals with normal renal function [11].

At present, options to prevent the development or progression of cognitive dysfunction and structural cerebral damage are limited. Modification of vascular disease risk factors may be helpful in limiting decline, though definite data are lacking. Specific to CKD, targeting a low blood pressure and reduction in albuminuria with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may slow cognitive decline but again large studies in patients with CKD including those on hemodialysis and after kidney transplantation are lacking. Some small studies suggest that intervention in lifestyle factors like more physical activity and cognitive training may protect against the progression of cognitive dysfunction.

In a recent meta-analysis, the use of SGLT-2 inhibitor was associated with a reduced risk of stroke [12] and SGLT inhibitors may yield a protective effect after acute ischemic stroke [13]. A recent longitudinal study in patients with type 2 diabetes revealed an association between ≥3 years SGLT2 inhibitor use and improved cognitive scores globally and in the language domain and executive function [14]. Another study reported significant beneficial effects of the SGLT2 inhibitor empagliflozin on cognitive and physical impairment in frail older adults with diabetes and heart failure with preserved ejection fraction [15].

Hypothesis

SGLT-2 inhibitor use is associated with better preservation of cognitive function in patients with CKD including those on hemodialysis and after kidney transplantation compared to placebo.

Recruitment and follow-up

Participants will follow the same enrolment, randomisation and follow-up schedule as the main trial with the addition of the symbol digit modalities test (SDMT) at visit 2 (baseline), visit 5 (6 months), visit 6 (12 months) and once every 12 months thereafter until EoT/EET using standardised administration instructions outlined in the *'SDMT Technical Manual'*. The SDMT is easy to use, takes only 90 seconds to perform and has a very limited learning effect. The test is universal and as such is language independent. The test is validated for use on a mobile phone and tablet and has good sensitivity to monitor changes in cognition over time [16-18]. Participants will complete the SDMT during their study visit on a mobile phone or tablet.

Primary outcome

The primary outcome of the cognitive sub-study is the change over time in the number of correct answers in the SDMT within 90 seconds.

Data analysis

The change in the number of correct answers over time for the active treatment arm and the placebo arm will be presented as mean (95% CI) on an intention-to-treat basis. The data will be analysed using analysis of covariance adjusting for baseline values.

Additional patient burden

The SDMT has limited patient burden since performing the test takes 90 seconds to perform.

Specific exclusion criteria

Since the performance can be influenced by literacy and hand function, patients with certain characteristics will not be invited to perform the SDMT:

- Reduced function of the dominant hand according to the investigator
- Insufficient comprehension of the instruction to perform the test according to the investigator
- Patient preference not to participate in a cognition test

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13.3 Appendix C – Details of the Power Analysis

Based on data of previous trials and observational studies, a 12.5% annual event rate was assumed for the primary composite outcome of incident kidney failure, hospitalisation for heart failure and all-cause mortality:

Subgroup eGFR <30 mL/min/1.73m2

A. Incidence all-cause mortality
- 4.6%/year (DAPA-CKD, eGFR 25-30, ACR>200, avg ACR 1000)
- 3%/year (Beacon, CKD G4, avg eGFR 22, avg ACR 350)

B. Incidence of kidney failure
- 6.3%/year (DAPA-CKD)
- 8%/year (Beacon)

C. Incidence of heart failure hospitalisation
- 1.8%/year (DAPA-CKD)

Incidence composite outcome kidney failure, hospitalisation for heart failure or death
- 12.5%/year (DAPA-CKD)
- Of note, in Beacon incidence of hospitalisation for heart failure is not available. The incidence of the composite of kidney failure or all-cause mortality is 10.5%/year, and hospitalisation for heart failure will add ±1.5%/year.

Subgroup on dialysis

A. Incidence all-cause mortality
- 13.4%/year (DAPA-CKD, placebo group that started HD in SGLT2i trial)
- 14%/year (Aurora, placebo group statin trial)
- 12%/year (4D, placebo group statin trial)
- 15%/year (ACHIEVE, placebo group MRA trial, personal communication M. Walsh)

B. Incidence of kidney failure
- Not applicable

C. Incidence of heart failure hospitalisation
- 3.5%/year (ACHIEVE)

Incidence composite endpoint hospitalisation for heart failure or death
- 17.3%/year (ACHIEVE)

Subgroup of kidney transplant recipients

A. Incidence all-cause mortality
- 4%/year (Else cohort, eGFR 15-45, personal communication S. Berger)
- 5%/year (NITRA database, eGFR 15-45, personal communication S. Berger)

B. Incidence kidney failure endpoint
- 3.5%/year (Else cohort)
- 4%/year (NITRA database)

C. Incidence of hospitalisation for heart failure is not available in both cohorts of kidney transplant recipients but based on the above data is expected to add 1.5% per year.

Incidence composite outcome kidney failure, hospitalisation for heart failure or death
- 9%/year (Else cohort)
- 10.5%/year (NITRA database)

Given the incidence rates of the composite endpoint in each of the three subgroups, we assumed a 12.5% annual event rate for the overall study population. Because the incidence rates in these subgroups differ slightly, inclusion will be weighed to allow a better estimate of the treatment effect within each subgroup. We will therefore include 450 to 550 patients with CKD stages G4/5, 400 to 500 patients on dialysis, and 550 to 650 patients with a kidney transplant. In case the maximum patient number of a subgroup is reached, inclusion of patients will be stopped for this subgroup.

13.4 Appendix D – Safety Reporting to AstraZeneca

During the study, the Sponsor shall:

- Send SAE reports (individual case reports and quarterly line listings) including accompanying cover page via secure mail to AEmailboxclinicaltrialTCS@astrazeneca.com
- Provide the Company with a copy of their DSUR (Development Safety Update Report) in those cases the safety reference information used by the Sponsor, is inconsistent with the AZ IB and Local Label.
- Emerging Safety Events: provide AZ with any emerging safety issues, unanticipated problems or actions as a result of a safety signal with the IMP within 24 hours of knowledge.
- Provide the Company yearly with a line listing of all SAEs notified to regulatory authority and Company during the study, for reconciliation purpose. Send via secure mail to AEmailboxclinicaltrialTCS@astrazeneca.com.

At end of Study, provide the Company with a final unblinded summary line listing of all Safety events notified to the regulatory authority and/or IRB/EC and Company during the Study, for reconciliation purposes. Send via secure mail to AEmailboxclinicaltrialTCS@astrazeneca.com.

13.5 Appendix E – Information for Participants

Benefits and risk assessment, group relatedness

There are no direct benefits for the patients to be included. Participation in the study is on a free-will base. Patients will receive restitution of all costs of transportation that is necessary beyond transportation normally made for patient care. Patients will not receive priority for treatment of other diseases in the clinic during this study. Participation in the proposed study is accompanied with only minor risks. The blood samples will be drawn by means of venepuncture that will be performed during the visit to the outpatient clinic as much as possible as part of routine clinical care. All further performed measurements are non-invasive and therefore only minor risks are associated with participation.

Compensation for injury

The sponsor University Medical Center Groningen (UMCG) has a liability and subject insurance which is in accordance with the legal requirements in the Netherlands (Article 7, subsection 6 of the WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study that becomes apparent during the study or within 4 years after the end of the study.
Participating centres within the Netherlands fall into the scope of the subject insurance. All patients will receive written information about this insurance. For participating sites outside the Netherlands, liability and/or subject insurance should be organized by these sites according to prevailing local and national regulations.

Incentives

Participation of patients in the study is a free-will decision. Patients will receive restitution of costs for transportation which fall outside the standard care visits. Patients do not receive priority for treatment of other diseases in the clinic during this trial.

Consumer input

The Dutch Kidney Patient Society (Nierpatienten Vereniging Nederland, NVN) is involved in the organisation and execution of the trial. This society has appointed a Patient Advisory Board. This Board will help the Steering Committee with the design of the trial (among others safeguarding patient friendliness and incorporation of relevant patient centred outcomes), optimizing patient inclusion (among others by advertising it on the national kidney patient website, and by raising attention for it during their annual national and regional meetings) and implementation of the results (by presentations during their annual national and regional meetings, and by editorials on relevant websites). To ensure optimal patient involvement, a member of the Patient Advisory Board will be member of the Steering Committee, and during the trial the Patient Advisory Board may provide the Steering Committee with solicited and unsolicited advice. For other participating countries similar cooperation with national and/or regional patient societies will be sought.

Within Australia, the Kidney Health Consumer Panel from The George Institute for Global Health has provided local consumer advice, feedback and input to all participant facing documents. Involvement of Australian consumers has ensured all documents are transparent and appropriate for the Australian setting.

13.6 Appendix F – Structured Risk Analysis

Potential Issues of Concern

a. Level of knowledge about mechanism of action

The sodium glucose co-transporter 2 (SGLT2), located in the proximal tubule of the kidney, is an effective transporter system which is responsible for the nearly complete reabsorption of glucose in order to maintain appropriate glucose levels. Each glucose molecule that is reabsorbed is accompanied by reabsorption of a sodium molecule in a 1:1 ratio. SGLT2 inhibitors reversely inhibit the SGLT2 transporter which leads to enhanced glucose and sodium excretion and a reduction in plasma glucose and HbA1c. The effects of dapagliflozin on the SGLT2 transporter are well characterized and sufficient knowledge is available about the mechanisms of action.

b. Previous exposure of human being with the test product(s) and/or products with a similar biological mechanism

Previously, twelve phase 3 randomized controlled clinical trials were conducted involving more than 6000 patients with type 2 diabetes mellitus of whom ~4000 were treated with dapagliflozin. Eleven studies were 24-weeks in duration with extension in 6 studies up to 78 weeks. One study was 52 weeks in duration with extension of another 52 weeks.

More recently, the DAPA-CKD trial reported the efficacy and safety of dapagliflozin in 4,304 patients with chronic kidney disease with or without type 2 diabetes. The trial demonstrated that dapagliflozin significantly reduced the risk of kidney and cardiovascular endpoints and prolonged survival. Dapagliflozin was well tolerated in keeping with the established safety profile. Specifically, in this population there was no diabetic ketoacidosis with dapagliflozin. In patients with CKD without type 2 diabetes no major hypoglycaemic events were reported.

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

Various animal models and cell lines are available to study the effect of SFGLT2 inhibitors in more detail at a tissue/cell level.

d. Selectivity of the mechanisms to target tissue in animals and/or human beings

SGLT2 is highly localized to the kidney and major effects are expected to be related to glycosuria and natriuresis.

e. Analysis of potential effect

In placebo controlled clinical trials the following adverse reactions have been identified:

- Infections and infestations: vulvovaginitis, balanitis and related genital infections, urinary tract infections (common); fungal infection (uncommon)
- Metabolism and nutrition disorders: hypoglycaemia (when used with SU or insulin) (very common); volume depletion (uncommon)
- Nervous system disorders: dizziness (common)
- Gastrointestinal disorders: constipation, dry mouth (uncommon)
- Skin and subcutaneous tissue disorders: rash (common)
- Musculoskeletal and connective tissue disorders: back pain (common)
- Renal and urinary disorders: dysuria, polyuria (common); nocturia (uncommon)
- Reproductive system and breast disorders: vulvovaginal pruritis, pruritus genital (uncommon)
- Investigations: haematocrit increased, creatinine renal function decreased during initial treatment, dyslipidaemia (common); blood creatinine increased during initial treatment, blood urea increased, weight decreased (uncommon).

Definitions are: common (>1/100 to <1/10) and uncommon (>1/1000 to <1/100)

Few adverse events led to discontinuation of treatment and adverse events were balanced across study groups. The most commonly reported events leading to discontinuation in patients treated with dapagliflozin 10 mg/day were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), and rash (0.2%). It should be noted that the transient rise in serum creatinine may reflect a reduction in intra-glomerular pressure which may be associated with long-term structural renal protection.

A pooled analysis of 3152 patients who received dapagliflozin in doses between 2.5 and 10 mg/day showed that the incidence of urinary tract infection was increased with dapagliflozin dosage. Most diagnosed infections were mild to moderate and responded to standard antimicrobial treatment.[17]

Overdose:

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the dose aimed to be used in the present study). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose) with no reports of dehydration, hypotension, or electrolyte imbalance and with no clinically meaningful effect on QT_c interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg dapagliflozin were administered for 2 weeks in healthy subjects and type 2 diabetes mellitus subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

f. Pharmacokinetic considerations

Dapagliflozin is filtered in glomeruli and reabsorbed via the SGLT2 transporter. Dapagliflozin is metabolized in the liver and excreted with faeces. Only a very small part (0.2%) is renal excreted. Dose adjustment in patients with impaired kidney function is therefore not needed.

In in-vitro studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 nor induced CYP1A2, CYP2B6, CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolized by these enzymes.

Interaction studies conducted in healthy subjects, using mainly a single dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

g. Study population

The enrolled population is in a stable condition and no unexpected serious adverse events are foreseen.

h. Interactions with other products

See F.

i. Predictability of effect

Efficacy is monitored by measuring the urine albumin-to-creatinine ratio / blood pressure / body weight / eGFR / plasma glucose, which are accepted and accurate surrogates to evaluate efficacy.

j. Can effects be managed?

Patients are regularly monitored and asked about adverse effects of urinary tract infections or infestations. As reported above, dapagliflozin administration is associated with an increased risk of urinary tract and genital infections which can be managed with standard antimicrobial treatment.[16]

Synthesis

The available data show that dapagliflozin decreases glucose, blood pressure and body weight in patients with type 2 diabetes. The drug received marketing approval from the European Medicines Agency (EMA) and is registered in various countries in the European Union (EU). Dapagliflozin increases incidence of urinary tract infections. This adverse effect led in rare instances to treatment discontinuation and is manageable with standard antimicrobial treatment.

13.7 Appendix G – Further IMP Information

Name and description of investigational product(s)

Drug name: dapagliflozin (Forxiga, AstraZeneca, EU/1/12/795/009); Chemical structure: (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol;

Summary of finding from non-clinical studies

This is not applicable as dapagliflozin is already registered for the treatment of cardiovascular disease in patients with and without type 2 diabetes, including subjects with CKD.

Summary of findings from clinical studies

Dapagliflozin

SGLT2, located in the proximal tubule of the kidney, is an effective transporter system that is responsible for reabsorption of glucose and sodium. Dapagliflozin is an SGLT2 inhibitor that reversely inhibits the SGLT2 transporter. This leads to enhanced glucose and sodium excretion and reductions in HbA1c, plasma volume, body weight and blood pressure. When given as mono-therapy or as add on to other glucose lowering agents dapagliflozin reduces HbA1c by 0.5 to 0.9% and reduced body weight and systolic blood pressure by approximately 2 kg and 3 mmHg (Dapagliflozin Investigator Brochure).

A cardiovascular outcomes study (DECLARE) was conducted to determine the effect of 10 mg dapagliflozin compared with placebo in 17,160 patients with type 2 diabetes mellitus with or without established cardiovascular disease on cardiovascular and renal events.[11] 8,582 patients were randomized to dapagliflozin 10 mg and 8,578 to placebo and were followed for a median of 4.2 years. The co-primary outcome was CV death or heart failure hospitalisation and 2) nonfatal myocardial infarction, nonfatal stroke, or CV death. Dapagliflozin was superior to placebo in preventing the primary composite endpoint of heart failure hospitalisation and CV death (hazard ratio 0.83 (95%CI 0.73, 0.95); p=0.005). There were also numerically fewer MACE events in the dapagliflozin group compared with the placebo group, but the treatment effect did not show superiority (hazard ratio 0,93 (95%CI 0.84, 1.03); p=0.172).

The DAPA-CKD trial was conducted in 4,304 patients with CKD, with or without type 2 diabetes.[8] Participants were randomly assigned to receive dapagliflozin (10 mg once daily) or placebo. The trial was recommended to stop by the independent data monitoring committee because of efficacy of dapagliflozin in patients with CKD. The primary outcome was a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (HR 0.61, 95% CI 0.51 – 0.72; p <0.001). The number needed to treat to prevent one primary outcome event was 19 (95% CI 15 – 27). The hazard ratio for the composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI 0.45 – 0.68; p <0.001). Dapagliflozin also reduced mortality. Both cardiovascular and non-cardiovascular deaths occurred less frequently with dapagliflozin compared to placebo.[40] No major hypoglycaemic events were reported in patients without type 2 diabetes and in these patients the difference in Hba1c between dapagliflozin and placebo was 0.0%. The effects of dapagliflozin on efficacy and safety were similar in participants with type 2 diabetes and in those without type 2 diabetes.[27] The known safety profile of dapagliflozin in patients with CKD, regardless of the presence or absence of diabetes, was confirmed.

In the DAPA-CKD trial patients with eGFR between 25 and 75 mL/min/1.73m^2 and substantial albuminuria (proteinuric range) were recruited. Whether the results of the DAPA-CKD trial can be extrapolated to a broad population of patients with an eGFR ≤25 mL/min/1.73m^2, dialysis patients, or kidney transplant recipients is unknown, and it is the objective of the present study to answer this question.

Summary of known and potential risks and benefits

Type 2 diabetes mellitus

The primary assessment of safety and tolerability of dapagliflozin was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects with diabetes mellitus type 2 treated with dapagliflozin 10 mg and 2,295 with placebo.

In the 13 short-term placebo-controlled studies, the overall incidence of adverse events (short-term treatment) in subjects treated with dapagliflozin 10 mg was similar to placebo. Few adverse events led to discontinuation of treatment and were balanced across study groups. The most commonly reported events leading to discontinuation in patients treated with dapagliflozin 10 mg or placebo were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%).

The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add-on sulphonylurea and add-on insulin therapies. Combination therapies with sulphonylurea and add-on insulin had higher rates of hypoglycaemia.

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection. In the dapagliflozin cardiovascular outcomes study (DECLARE), the number of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

In the large-scale clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin. The most frequently reported adverse reactions across the clinical studies were urinary tract and genital infections. No additional safety signals were found.

Heart failure

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 30 mL/min/1.73 m2. The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

Chronic kidney disease

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m2, and albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5000 mg/g). Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m2.

In the DAPA-CKD trial, the proportion of patients with serious adverse events was similar in the dapagliflozin and placebo group. This was consistent for patients with and without type 2 diabetes. Adverse events of interest in the DAPA-CKD trial, including diabetic keto-acidosis, severe hypoglycaemia, fractures, amputations, AKI were similar between the dapagliflozin and placebo groups. Notably, there were no hypoglycaemia events reported in patients without diabetes. In addition, diabetic ketoacidosis did not occur in patients receiving dapagliflozin.

According to the label no dose adjustment is needed for dapagliflozin with mild, moderate, or severe hepatic impairment. In subjects with severe hepatic impairment (Child-Pugh class C), however, it was reported that mean Cmax and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively. In this study, known severe hepatic impairment will therefore be an exclusion criterion.

Description and justification of route of administration and dosage

Dapagliflozin is absorbed from the digestive tract and can therefore be orally administered.

Dosages, dosage modifications and method of administration

Dapagliflozin will be administered in a dose of 10 mg/day. Dapagliflozin is excreted by the kidney. Dose adjustment in case if impaired kidney function is therefore not needed.

Preparation and labelling of Investigational Medicinal Product

AZ supply chain provides the Investigational Medicinal Product Dapagliflozin 10 mg and matching placebo in unlabelled bottles. Design of labels, labelling, QP release and distribution of finished packs is the responsibility of the Pharmacy of the University Medical Center Groningen.

Drug accountability

All study medications will be stored at room temperature at the pharmacy department of participating centres. Study medication will be collected from the pharmacy department by the local principal investigator. Non-used medication will be returned to the pharmacy where it will be destroyed. Adherence to study medication will be monitored by pill count.

Handling and dispensing

The investigational product should be stored in a secure area according to local regulations. The local principal investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.

The local principal investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity).

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

Drug ordering

Initial Orders

Contact the protocol manager at the University Medical Center Groningen for information.

Re-Supply

Contact the protocol manager at the University Medical Center Groningen (trials@apoth.umcg.nl) for information.