An Open Label, Phase IV, Mechanistic, Study to Evaluate the Natriuretic Effect of 2-Week Dapagliflozin treatment in Type 2 Diabetes Mellitus Patients with Impaired Renal Function

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The central hypothesis of this study is that dapagliflozin drives a natriuretic effect independently of renal function level. The study will therefore evaluate average 24-hr sodium excretion during dapagliflozin treatment in patients with T2DM with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON52111

Source
ToetsingOnline

Brief title
DAPASALT

Condition

- Diabetic complications

Synonym
adult-onset diabetes, non-insulin-dependant diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Astra Zeneca

Intervention

Keyword: Dapagliflozin, Diabetes Mellitus, Impaired Renal Function, Kidney Function Test, type 2

Outcome measures

Primary outcome

The change in 24-hr sodium excretion during dapagliflozin treatment between Baseline (average of Days *3 to *1) and average of Days 2 to 4 in patients with type 2 diabetes mellitus (T2DM) with impaired renal function.

Secondary outcome

The secondary endpoints to be evaluated during or following dapagliflozin treatment within each study group are:

• Average change in 24-hr sodium excretion from average Baseline values to average end of treatment values (Day 12 to 14); and from average end of treatment values (Day 12 to 14) to average values during follow-up (Day 15 to 17).

• Average change in 24-hr glucose excretion from average Baseline values to average values at Day 2 to 4; from average Baseline values to average end of treatment values (Day 12 to 14); and from average end of treatment values (Day 12 to 14) to average values during follow-up (Day 15 to 17).

• Change in mean 24-hr systolic blood pressure from Baseline to Day 4; from Baseline to end of treatment (Day 13); and from end of treatment (Day

13) to end of follow-up (Day 18).

• Change in plasma volume from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18).

• Change in extracellular volume from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18).

• Dapagliflozin pharmacokinetics on Day 4 and Day 14.

• Average change in mean 24-hr UACR from average Baseline to Day 4; from average Baseline values to average end of treatment values (Day 12 to 14).

The exploratory endpoints to be evaluated during or following dapagliflozin treatment within each study group are:

•Change in day (0600 - 2200):night (2200 - 0600) ratio of systolic blood pressure from Baseline to Day 4; from Baseline to end of treatment (Day 13); and from end of treatment (Day 13) to end of follow-up (Day 18).

•Change in the following from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18).

- Hormones of the RAAS (plasma/urine renin*, urine aldosterone*, plasma AngII, uAngiotensinogen*).

- NT-proBNP and BNP.

- Urinary adenosine*.

- Plasma Co-peptin.

*: For the parameters to be assessed in urine, *end of follow-up* will be considered as Day 17.

•Average change in 24-hr urinary volume, uric acid, creatinine, cortisol, isoprostanes, and electrolytes from average Baseline values to average values at Day 2 to 4; from average Baseline values to average end of treatment values (Day 12 to 14); and from average end of treatment values (Day 12 to 14) to average values during follow-up (Day 15 to 17):

- 24-hr urine volume
- Uric acid
- Creatinine
- Cortisol*
- Isoprostanes*
- Potassium
- Bicarbonate*
- Ammonium
- Calcium
- Chloride
- Phosphate
- Magnesium

*: For cortisol, isoprostanes, and bicarbonate, the analysis will be from Baseline to Day 4; from Baseline to end of treatment (Day 14); from end of treatment (Day 14) to end of follow-up (Day 17 for cortisol and isoprostanes, Day 18 for bicarbonate). Analysis of

bicarbonate will be performed from fresh spot urine samples and not from 24-urine samples.

•Change in the plasma/ serum biomarkers of metabolism, renal function, electrolytes, uric acid, and haematocrit from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18).

- Fasting insulin
- Fasting glucagon
- Fasting beta-hydroxybutyrate
- Creatinine
- Uric acid
- Bicarbonate
- Blood urea nitrogen
- Sodium
- Potassium
- Fasting glucose
- Haematocrit
- Erythropoietin
- Fasting Fibroblast growth factor 21 (FGF21)
- Magnesium
- Calcium
- Phosphate

•Change in body weight from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment

(Day 14) to end of follow-up (Day 18).

•Change in calculated intracellular red blood cell concentrations of sodium, potassium, phosphate and magnesium from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18).

•Change in intracellular volume from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18).

•Change in total body water from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 18).

•Changes in extracellular volume and intracellular volume over a 4-hr time course after 2 weeks of dapagliflozin treatment in relation to pharmacokinetics measurements.

•Change in relative amount of specific solute transporters present in the exosomes as well as changes in their phosphorylation state from Baseline to Day 4; from Baseline to end of treatment (Day 14); and from end of treatment (Day 14) to end of follow-up (Day 17).

•To collect data on body composition analysis for later exploratory analysis.

•To collect serum/plasma samples for later exploratory analysis of metabolic, cardiovascular, and renal biomarkers.

•To collect 24-hr urine samples for later exploratory analysis of metabolic, cardiovascular, and renal biomarkers.

Study description

Background summary

Dapagliflozin is a stable, reversible, highly selective, and orally active inhibitor of human renal sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for glucose reabsorption in the kidney. Dapagliflozin*s mechanism of action results in the direct and insulin-independent elimination of glucose by the kidneys. Results from nonclinical and clinical studies have shown that dapagliflozin can be used to promote urinary excretion of glucose as a well-tolerated and effective method of reducing blood glucose levels in type 2 diabetes mellitus (T2DM) patients. The persistent loss of glucose with associated calories in the urine, results in a consistent and maintained reduction of the total body weight, in addition to the improved glycemic control. Moreover, dapagliflozin also has been shown to reduce blood pressure and albuminuria, 2 essential prognostic risk factors for progression of renal disease.

Notably, the total amount of glucose excreted in the urine by dapagliflozin, declines with decreasing kidney function. In a recent meta-analysis of placebo controlled clinical trials from the dapagliflozin programme it was confirmed that the glycosylated haemoglobin (HbA1c) lowering effect was smaller in patients with an estimated glomerular filtration rate (eGFR) between 45 and 60 mL/min/1.73m2 compared to patients with an eGFR > 90 mL/min/1.73m2 (Sjöström et al, 2016 [2]). Intriguingly however, the effects of dapagliflozin on body weight, blood pressure, albuminuria, and haematocrit were similar regardless of the eGFR level (Sjöström et al, 2016 [2]), and may therefore be independent of glycemic effects of SGLT2 inhibitors.

T2DM is associated with an elevated risk of cardiovascular morbidity and mortality as well as renal failure. The cardiovascular benefit of dapagliflozin was demonstrated in the DECLARE-TIMI 58 study by showing a lower rate of the primary co-primary composite heart failure outcome in the active dapagliflozin treatment arm (Wiviot et al, 2018 [3]). There is also a growing body of evidence indicating that SGLT2 inhibition with dapagliflozin is nephroprotective. Post-hoc analysis from the dapagliflozin phase II and phase III programme have shown in T2DM patients with moderate renal impairment on top of renin-angiotensin-aldosterone system (RAAS) blockade reduction around 40% in albuminuria and stabilization of eGFR decline for up to 1 year (Sjöström et al, 2015 [4]) and 2 years (Fioretto et al, 2015 [5]). After an initial drop in eGFR, kidney function was stable over time while a progressive decrease in eGFR was seen in the placebo group. In the DECLARE TIMI 58 trial, a 53% risk reduction was found in doubling of serum creatinine or initiation of dialysis treatment. (Mosenzon et al, 2019 [6]).

The nephroprotective effect is thought to be achieved by mechanisms independent of blood glucose reduction (Rajasekeran et al, 2016 [7]), such as by reduced intra-glomerular pressure through an enhanced tubuloglomerular feedback mechanism (De Nicola, et al 2014 [8] and Thomas, 2014 [9]), reduced glucose and sodium transport over the proximal tubule cells (Pollock, et al 1991 [10] and Komala, et al 2013 [11]), increased natriuresis (Heerspink et al, 2013 [12]) and reduced systemic blood pressure (Baker et al, 2015 [13]).

Study objective

The central hypothesis of this study is that dapagliflozin drives a natriuretic effect independently of renal function level. The study will therefore evaluate average 24-hr sodium excretion during dapagliflozin treatment in patients with T2DM with impaired renal function.
In the majority of healthy individuals blood pressure falls (dips) at night. These individuals are classified as dippers. Those who do not exhibit this nocturnal fall in blood pressure are referred to as non-dippers. In populations with CKD, non-dippers are overrepresented due to reduced natriuretic capacity (Spencer et al, 2015 and references therein [14]). Decreased natriuresis leads to sodium retention and volume expansion with clinical consequences. Patients with T2DM often have increased extracellular volume as a result of increased glucose and sodium reabsorption in the kidney (Novikov et al, 2016 [15]). We hypothesize that SGLT2 inhibition enables improved natriuresis and diuresis as both sodium and glucose excretion contribute to osmotic diuresis. The mechanisms downstream of natriuresis and diuresis have distinct impact on a number of clinically important parameters. Enhanced natriuresis enables improved systemic sodium balance, which directly impacts both volume expansion as well as systemic sodium load. The failure to maintain natriuretic and fluid balance also results in increased demand to drive natriuresis to a greater extent. Consequently, blood pressure is increased as well as maintained at raised levels during the full 24-hr period generating the non-dipping phenotype. This has clear consequence on cardiovascular fitness via demand placed on cardiac and vascular tissues. In particular sodium and fluid accumulation are associated with impaired endothelial function, vascular stiffening and consequent left ventricular hypertrophy.

As described in the background there is an apparent disconnect between HbA1c lowering and the other effects of SGLT2 inhibition by dapagliflozin (e.g., blood pressure, body weight) which may be in part consequent on volume contraction or changes in tubuloglomerular feedback. Tubuloglomerular feedback is the process whereby the macular densa which sits downstream of the proximal tubule senses the delivery of sodium and chloride and provides feedback to the glomerulus to alter afferent and efferent pressure via several mechanisms including renin activity and adenosine production. This will be addressed in the study by assessing the impact of treatment on factors of the RAAS and urine adenosine. At the same time diuresis leads to decrease arterial pressure and volume. Dapagliflozin is hypothesized to work through both these mechanisms to

reduce renal renin activity with concomitant reductions in angiotensin II and its metabolites and alter the production of adenosine. Recent studies have also suggested a cross-talk between the SGLT2 transporter and the sodium-hydrogen exchanger-3 (NHE3) (Novikov et al 2016 [15]). NHE3 is located in the proximal tubule and responsible for approximately 30% of the reabsorption of sodium in the kidney. Inhibition of SGLT2 results in down regulation of NHE3 sodium transport activity, which may also contribute to the natriuretic effects of dapagliflozin. As a result of the interaction between SGLT2 and NHE3, as well as potential effects (both direct and indirect, e.g., via altered renal RAAS activity) on other transporters, the effect of dapagliflozin on electrolyte and fluid related parameters may persist to a significant extent in patients with lower eGFR levels. By analysing urinary exosomes using mass spectrometry it will be possible to evaluate these effects on other transporter levels (Schey et al, 2015 [16]).

This study will further clarify the dapagliflozin mechanisms of action by investigating if and how the effect of dapagliflozin on natriuresis, blood pressure regulation, plasma volume, extracellular volume, hormones, biochemical variables and electrolytes are impacted by T2DM status and level of kidney function.

Study design

This study is an open label study to evaluate the changes in average 24-hr sodium excretion during dapagliflozin treatment in patients with T2DM with impaired renal function.

Optimization of Patient Population:
The study will include patients with T2DM with impaired renal function (an eGFR by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] between >=25 and <=50 mL/min/1.73m2); Details of eGFR estimation using CKD-EPI are provided in Section 3.1.
All patients will be required to be on patient specific optimal antihypertensive doses of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) (as per Investigator*s judgement) prior to being considered for the study. During the study, all patients will be provided with food in food boxes which contain in total 150 mmol sodium per day, starting in the Run-in Period prior to treatment initiation and to be continued throughout the duration of the study. This will allow a homogenous stable population to be enrolled in the study for evaluation of the study objective.
If required patients will be using a stable insulin dosing (intermediate, long* acting, premixed insulin, basal bolus insulin) for the last 12 weeks prior to start of treatment with dapagliflozin. Metformin, sulphonylurea, Di-Peptidyl Peptidase 4 inhibitors (DPP4i), or combinations of these agents with or without insulin would be accepted but is not mandatory. If used, stable dose of metformin, sulphonylurea, DPP4 inhibitors, GLP1 receptor agonists or their combination as anti-diabetic therapy for the last 12 weeks prior to start of

treatment with dapagliflozin is required. Other oral antidiabetic drugs, including pioglitazone, are not allowed (as per Investigator's judgement).

Dapagliflozin Dose and Regimen:
Patients will receive one tablet dapagliflozin 10 mg per day for a total period of 14±1 days. This dose is the recommended dose for monotherapy and for add-on combination therapy with other glucose-lowering medicinal products including insulin to improve glycaemic control in T2DM.

Study Endpoints:
The primary endpoint of the study is the average change in 24-hr sodium excretion during dapagliflozin treatment from average Baseline to average values at Day 2 to 4. This endpoint will provide information on acute changes in sodium. Additionally, urinary sodium excretion at Days 12 to 14 will provide information on the effect of 10 mg dapagliflozin on steady state natriuresis, and Days 15 to 17 will provide data on the effect of treatment withdrawal. Additionally, changes in urinary glucose excretion, urine albumin:creatinine ratio (UACR), plasma volume, extracellular volume, and
24-hr systolic blood pressure will also be evaluated. Pharmacokinetics of dapagliflozin will also be studied.

As exploratory endpoints, changes in hormones of RAAS; N-terminal pro B-type natriuretic peptide [NT-ProBNP] and B-type natriuretic peptide [BNP], urinary adenosine and plasma co-peptin; changes in 24-hr urinary volume, uric acid, creatinine, cortisol, isoprostanes, and electrolytes; changes in serum/plasma biomarkers of metabolism, renal function, electrolytes, uric acid, and haematocrit; changes in calculated intracellular red blood cell concentrations of electrolytes; change in intracellular volume; change in total body water; and changes in extracellular volume and intracellular volume over a 4-hr time course in relation to pharmacokinetics measurements will be evaluated. Additionally, changes in day:night blood pressure ratios, and changes in body weight will be assessed. These parameters will provide more insight into the potential effects of dapagliflozin (both direct and indirect, e.g., via altered renal RAAS activity). Urinary exosome analysis will be performed using mass spectrometry and will allow analysis of dapagliflozin influence on other transporters.

Intervention

The study consists of a 2-week, open label, Treatment Period. Patients will be provided with one bottle of dapagliflozin tablets on Day 1 (Visit 4) to last for the 14±1 days of the Treatment Period. The tablet is taken orally once daily in the morning and at approximately the same time of the day.

The first dose of dapagliflozin will be administered at Visit 4 (Day 1) at the study site after all baseline assessments (including laboratory tests, plasma volume assessments, and bioimpedance spectroscopy measurement) have been

performed. On days of study site visits where blood sampling is scheduled, i.e., Visit 5 and Visit 8, the patients will be required to bring the bottle of dapagliflozin tablets to site. At Visit 5 (Day 4), the patient will consume the tablet together with breakfast after fasting blood sampling is completed at the site. At Visit 8 (Day 14), the patient will consume the tablet together with breakfast after pre-dose bioimpedance spectroscopy measurements, pharmacokinetics blood sampling, and other fasting blood sampling is completed.

Study burden and risks

Dapagliflozin has global market approval and based on global cumulative sale figures up to March 2016 it is estimated that dapagliflozin has been administered during >1000000 patient years.

Potential risks
The potential risks for the treatment with dapagliflozin and other SGLT2 inhibitors are described in the Investigator*s Brochure (IB). Due to its mode of action resulting in increased urinary glucose excretion an increased risk of urinary tract infections (slightly higher compared to placebo in the phase III studies) and genital infections has been seen. Higher proportions of patients with marked laboratory abnormalities of hyperphosphataemia were reported in dapagliflozin vs placebo. The magnitude and clinical significance of this in patients with CKD is unclear.
There have been reports of ketoacidosis, including diabetic ketoacidosis (DKA), in patients with type 2 diabetes mellitus taking FORXIGA and other SGLT2 inhibitors. Patients presenting signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, irrespective of blood glucose levels. If ketoacidosis is suspected by the Investigator, discontinuation or temporary interruption of dapagliflozin should be considered and the patient should be promptly evaluated.
Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., T1DM, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in these patients.
Patients on sulphonylurea and/or insulin at the onset of the study treatment have an increased risk of experiencing hypoglycaemic events. Blood glucose is therefore monitored at Day 4. Once patients on insulin enter the study, they will be carefully followed once starting on food boxes. Additionally, insulin dosing will be adjusted, if needed, to avoid hypoglycaema/hyperglycaemia.
In this study, indocyanine green will be used to assess changes in plasma volume. Indocyanine green has been used for decades for this purpose and has a short half-life of only approximately 3 min (Jacob et al, 2007 [17]). The risk profile of indocyanine green is considered good (Jacob et al, 2007 [18]), but there are reports of allergic reactions including anaphylactic reactions (Speich et al, 1988 [18] and Garski et al, 1978 [19]). In patients with

terminal renal insufficiency, the possibility that an anaphylactic reaction occurs seems to be increased (Summary of Product Characteristics [SPC] Verdye [20]).
Assessment of body composition (including extracellular and intracellular volume) will be conducted with bioimpedance spectroscopy. This is an easy to use and non-invasive technique not considered to cause any risk to the patient if following the manufacturer*s instructions.
No other study procedure is considered putting the patients at risk beyond those ordinarily encountered during the performance of routine medical examinations or routine tests.

Protection against risks
This study has been designed with appropriate measures in place to monitor and minimise any of the potential health risks to participating patients.
Based on the mechanism of action of dapagliflozin there may be a potential risk for this compound to cause hypovolaemia or electrolyte imbalance. As a precaution, patients who, in the judgement of the Investigator, may be at risk for dehydration or volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, should have careful monitoring of their volume status. For this study, patients on a stable dose for at least 4 weeks of loop or thiazide diuretics will be allowed to participate. In hypovolaemic patients starting treatment with dapagliflozin, there is a potential risk for increased serum creatinine levels. Patients who show a greater than 50% increase in serum creatinine should therefore be discontinued on the study drug. In patients already receiving dapagliflozin who develop conditions that may cause hypovolaemia or electrolyte imbalance, decisions to interrupt or discontinue dapagliflozin therapy and management of patients should be based on clinical judgement.

Safety signal detection will include the integration of all available sources of safety information, including clinical study data, AE reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterise unrecognised safety risks or changes in those which are currently expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of dapagliflozin will be immediately communicated to relevant Health Authorities and appropriate actions will be taken regarding the clinical programme as needed. Thus real-time, active safety surveillance will be conducted during the entire duration of this study.
In addition, all dapagliflozin studies are subject to a carefully designed patient risk management plan that includes the temporary and if necessary permanent discontinuation of the investigational product in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified.
Due to a potential risk of allergic reactions, the use of indocyanine green should be performed under supervision of a physician. Symptoms related to an allergic reaction may include unrest, feeling of warmth, pruritus, urticarial, acceleration of heart rate, fall in blood pressure, shortness of breath,

bronchospasm, flush, cardiac arrest, laryngospasm, facial oedema, and nausea. Patients with a known hypersensitivity to indocyanine green, sodium iodide, or iodine, or patients who have poorly tolerated indocyanine green in the past should not use indocyanine green again (see Section 9 Exclusion Criteria). Additionally, patients with hyperthyroidism or with autonomic thyroid adenomas are excluded (see SPC [21]). Some medicinal products and substances can reduce or increase absorption of indocyanine green and should thus be avoided (see Section 9, Exclusion Criteria). Due to the risk of allergic reactions including anaphylactic reactions, emergency equipment should be available to immediately start treatment of an allergic reaction if needed. For the bioimpedance spectroscopy measurements, patients should not be pregnant, have a pacemaker or other implanted electronic devices (see Section 9, Exclusion Criteria).

Potential benefits to patients
In this study, the dose of dapagliflozin 10 mg was chosen based on previous clinical experience. This mechanistic study is non-therapeutic; therefore, it has limit or no direct clinical benefit for the subjects. In studies of longer duration, in patients randomised to active drug, dapagliflozin is expected to reduce progression of renal failure and reduce cardiovascular mortality. Dapagliflozin is known to decrease body weight (or prevent weight gain) as well as lower blood pressure. Patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The study population will consist of patients withT2DM with an eGFR (CKD-EPI) between >=25 and <=50 mL/min/1.73m2 at the Screening Visit

Inclusion Criteria at Screening Visit (Visit 1)
1. Provision of signed and dated, written informed consent prior to any study-specific procedures.
2. Female and/or male aged between 18 years and <= 80 years.
3. A diagnosis of T2DM with HbA1c >=6.5% (>=48 mmol/mol) and <=12% (<97 mmol/mol), if using insulin or sulfonylurea (for those patients not taking insulin or sulfonylurea there is no lower limit for HbA1c). T2DM patients on insulin or sulfonylurea who do not meet the HbA1c requirement can have their medication readjusted per Investigator's judgement and rescreened after 3 months on new dose; and eGFR (CKD-EPI) between >=25 and <=50 mL/min/1.73m2
4. Patient specific optimal antihypertensive dose of an ACEi or ARB (as per Investigator*s judgement) for at least 6 weeks prior to Visit 4 (Day 1).
5. A stable insulin dosing (intermediate, long*acting, premixed insulin, basal bolus insulin) for the last 12 weeks prior to Visit 4 (Day 1) as judged by the Investigator. Metformin, sulphonylurea, DPP4 inhibitors, GLP1 receptor agonists or any combinations of these agents with or without insulin would be accepted but is not mandatory. If used, stable dose of metformin, sulphonylurea, DPP4 inhibitors, GLP1 receptor agonists or their combination as anti-diabetic therapy for the last 12 weeks prior to start of treatment with dapagliflozin is required (as per Investigator's judgement).
6. Suitable veins for cannulation or repeated venepuncture
7. Female patients must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of study drug to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must

be used.

4.1.2 Inclusion Criteria at End of Run-in Period (Visit 3)
Patients must fulfil the following criteria in order to continue participation in the study.
8. Patient specific optimal antihypertensive dose of an ACEi or ARB (as per Investigator*s judgement) for at least 6 weeks prior to Visit 4 (Day 1) (as per Investigator's judgement).
9. A stable insulin dosing (intermediate, long*acting, premixed insulin, basal bolus insulin) for the last 12 weeks prior to Visit 4 (Day 1) as judged by the Investigator. Metformin, sulphonylurea, DPP4 inhibitors, GLP 1 receptor agonists or any combinations of these agents with or without insulin would be accepted but is not mandatory. If used, stable dose of metformin, sulphonylurea, or DPP4 inhibitors or GLP 1 agonists or their combination as anti-diabetic therapy for the last 12 weeks prior to start of treatment with dapagliflozin is required (as per Investigator's judgement).

Exclusion criteria

4.1.3 Exclusion Criteria at Screening Visit (Visit 1)
Patients will not be entered into this study if they meet any of the following criteria:
Study-related:
1. Previous enrolment in the present study or participation in another clinical study with an investigational product during the last 30 days prior to Screening Visit (Visit 1).
2. Involvement in the planning and conduct of the study (applies to both UMCG staff and staff at third party vendor or at the investigational sites).
3. Hypersensitivity to dapagliflozin, indocyanine green, sodium iodide, or iodine, or patients who have poorly tolerated indocyanine green in the past.
4. Pregnancy or breastfeeding.
General health-related:
5. Known clinically significant disease or disorder; or clinically relevant abnormal findings in physical examination, clinical chemistry, haematology, and urinalysis; or unstable or rapidly progressing renal disease; other dietary restrictions that would make it difficult for the subject to follow the protocol required diet plan or any other condition or minor medical complaint, which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results, or the patient*s ability to participate in the study and comply with study procedures, restrictions and requirements.
6. Diagnosis of T1DM.
7. Hyperthyroidism or autonomic thyroid adenomas.
8. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following (Visit 1):

- Systolic blood pressure above 180 mmHg.
- Diastolic blood pressure above 110 mmHg.
9. Any of the following cardiovascular/vascular diseases within 3 months prior to signing the consent at Visit 1, as assessed by the Investigator: myocardial infarction, cardiac surgery or revascularization (coronary artery bypass graft [CABG]/ percutaneous transluminal coronary angioplasty [PTCA]), unstable angina, unstable heart failure, heart failure New York Heart Association Class IV, transient ischemic attack or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia.
10. Patients with severe hepatic impairment (Child-Pugh C).
11. Ongoing weight-loss diet (hypocaloric diet) or use of weight-loss agents, unless the diet or treatment has been stopped at least 3 months before Screening Visit, ensuring patients having a stable body weight with no verified body weight variability of
>3 kg during the 3 months before Screening Visit.
Renal failure-related:
12. Symptoms/complaints suggestive of established neurogenic bladder and/or incomplete bladder emptying.
13. History of bladder cancer.
14. Non-diabetic kidney disease.
15. UACR >2200 mg/g per day at the Screening Visit based on spot urine sample (quantitative assessment).
Concomitant Medication and/or study treatment-related:
16. Current/chronic use of the following medication: glucagon-like peptide receptor agonists or thiazolidinediones, oral glucocorticoids (if dose is stable for at least 4 weeks this is allowed), non-steroidal anti-inflammatory drugs (NSAIDs), immune suppressants, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (as per Investigator's judgement).
17. Receiving immunosuppressive or other immunotherapy for primary or secondary renal disease within 6 months prior to Screening Visit (Visit 1).
18. Treatment within the last 2 weeks prior to Screening Visit (Visit 1) with mineralocorticoid antagonists (allowed if dose is stable: loop or thiazide diuretics are allowed as long as they are used in stable dose for at least 4 weeks prior to screening).
19. A metformin dose which is outside the specified dose range for renal impairment according to local guidelines and/or Investigator*s judgement.
20. Medicinal products and substances that can reduce or increase absorption of indocyanine green

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-01-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Farxiga / Forxiga
Generic name:	Dapagliflozin / Dapagliflozin propanediol
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	30-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	30-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	29-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	27-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-001247-12-NL
ClinicalTrials.gov	NCT03152084
CCMO	NL74706.029.20