A study to assess the renoprotective effects of the SGLT2 inhibitor Dapagliflozin in non-diabetic patients with proteinuria: a randomized double blind 6-week cross-over trial

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Primary: * To assess the change baseline in 24-hr proteinuria with dapagliflozin for six weeks relative to placebo treatment in patients with non-diabetic kidney disease and proteinuria > 500 mg/day on stable ACEi or ARB treatment. Secondary: *...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON47662

Source
ToetsingOnline

Brief title
The effects of dapagliflozin in non-diabetic patients with proteinuria

Condition

- Nephropathies

Synonym
Chronic kidney disease, Kidney function loss

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Astra Zeneca

Intervention

Keyword: Chronic, Dapagliflozin, Diabetes Mellitus, Renal insufficiency, Sodium-glucose transporter 2, Type 2

Outcome measures

Primary outcome

Main study parameters/endpoints: Change in 24-hr proteinuria

Secondary outcome

Secondary study parameters/endpoints (if applicable)

* Glomerular Filtration Rate measured with iohexol

* Systolic/diastolic blood pressure

* Neurohormones/biomarkers

o Hormones of the RAAS (renin, aldosterone in plasma and urine)

o Natriuretic Peptides

o Urinary adenosine

o Co-peptin

o Immunoglobulin G

Other study parameters (if applicable)

* Number of hypoglycaemic episodes

* Serious Adverse Events

* Drug related adverse events (causality to investigational product assessed by

research physician).

Study description

Background summary

Despite optimal treatment with renin-angiotensin-aldosterone-system (RAAS) inhibitors, many patients with non-diabetic kidney disease show progressive kidney function loss, which is associated with high residual albuminuria. Novel treatment strategies are therefore required to further decrease albuminuria and to slow kidney function decline.
Dapagliflozin is a sodium-glucose transport (SGLT2) inhibitor and inhibits the reabsorption of glucose and sodium in the proximal tubule. The increased natriuresis following dapagliflozin administration normalizes tubuloglomerular feedback resulting in a reduction in intra-glomerular hypertension, which is in turn manifested by acute reductions in glomerular filtration rate and albuminuria. Since many etiologies of non-diabetic nephropathy are characterized by intraglomerular hypertension, we hypothesize that dapagliflozin acutely decreases GFR and albuminuria in patients without diabetes at risk of progressive kidney function loss via a glucose independent hemodynamic mechanism.

Study objective

Primary:
* To assess the change baseline in 24-hr proteinuria with dapagliflozin for six weeks relative to placebo treatment in patients with non-diabetic kidney disease and proteinuria > 500 mg/day on stable ACEi or ARB treatment.

Secondary:
* To assess the effect of dapagliflozin 10 mg/d compared to placebo on Glomerular Filtration Rate (GFR) using iohexol clearance.
* To assess the effect of dapagliflozin 10 mg/d compared to placebo on systolic/diastolic blood pressure
* To assess the effect of dapagliflozin 10 mg/d compared to placebo on body weight
* To assess the effect of dapagliflozin 10 mg/d on selected neurohormones/biomarkers:
o Hormones of the RAAS (plasma and urine)
o Natriuretic peptides
o Urinary adenosine
o Co-peptin
o Immunoglobulin G (plasma and urine)
* To characterize the safety of dapagliflozin vs. placebo by determining the

number of hypoglycemic episodes between groups, and serious adverse events.

Study design

Randomized placebo controlled double blind cross-over trial
Eligible participants will be randomly assigned to one of the two treatment orders: placebo-dapagliflozin or dapagliflozin-placebo. Each treatment period lasts 6 weeks followed by a 6 week wash-out period to avoid cross-over effects.

Intervention

Dapagliflozin 10 mg/day, once a day in the morning OR matched placebo once a day in the morning.

Study burden and risks

Patients visit the outpatient clinic on a more regular base than standard patient care - i.e. at study inclusion and at start and end of each treatment period (8 hospital visits in a total study duration of 25 or up to 29 weeks) - for clinical assessment. A fasting blood sample is collected with venipuncture. Non-radioactive iohexol GFR measurements are performed at start and end of each treatment period as well as at the end of the wash-out period. 24hr urine will be collected one the day prior to the hospital visit. No other invasive measurements will be executed. Patients receive restitution of all travel costs. Patients receive no priority in treatment of other diseases in the clinic during this study. There are no direct benefits for the patients to be included and participation is on a voluntary basis.

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. 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 venipuncture that will be performed during the visit to the outpatient clinic. All further performed measurements are non-invasive and therefore only minor risks are associated with participation.

At each of the visits, approximately 20 ml will be taken for routine blood tests (approximately 20 ml/ 9 visits = 180 ml). At each of the 5 visits to assess kidney function, approximately 24 ml will be taken (total 96 ml), plus another 20 ml at each kidney function visit for measurement of hormones and other factors associated with kidney disease (approximately 20 ml for each of the 4 kidney visits = 80 ml). At the end of the treatment period, 9 blood samples of 1ml will be taken for dapagliflozin PK analysis. A total of

approximately 374 ml of blood will be collected over a 6 month (24 week) period

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

- Age *18 and *75 years
- Urinary protein excretion > 500 mg/g and * 3500 mg/g in a 24-hr urine collection
- eGFR * 25 mL/min/1.73m2
- On a stable dose of an ACEi or ARB for at least 4 weeks prior to randomization
- Willing to sign informed consent
- Women of Child-Bearing Potential (WOCBP) must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.
- WOCBP must have a negative serum or urine pregnancy test result (minimum sensitivity 25

IU/L or equivalent units of HCG) within 0 to 72 hours before the first dose of study drug.
- Women must not be breast-feeding

Exclusion criteria

- Diagnosis of type 1 or type 2 diabetes mellitus
- Urinary protein excretion > 3500 mg/day
- Peripheral Vascular Disease
- Autosomal dominant polycystic kidney disease or autosomal recessive polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis
- Indication for immunosuppressants as per the treating physician*s judgment.
- Receiving cytotoxic therapy, immunosuppressive therapy, or other immunotherapy for primary or secondary renal disease within 6 months prior to enrolment.
- Active malignancy aside from treated squamous cell or basal cell carcinoma of the skin.
- Any medication, surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of medications including, but not limited to any of the following:
o History of active inflammatory bowel disease within the last six months;
o Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
o Gastro-intestinal ulcers and/or gastrointestinal or rectal bleeding within last six months;
o Pancreatic injury or pancreatitis within the last six months;
o Evidence of hepatic disease as determined by any one of the following: ALT or AST values exceeding 3x ULN at the screening visit, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt;
o Evidence of urinary obstruction of difficulty in voiding at screening
- History of severe hypersensitivity or contraindications to dapagliflozin
- History of hypersensitivity or contraindications to iodinated contrast media
- Subject who may be at risk for dehydration or volume depletion that may affect the interpretation of efficacy or safety data
- Participation in any clinical investigation within 3 months prior to initial dosing.
- Donation or loss of 400 ml or more of blood within 8 weeks prior to initial dosing.
- History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during the screening.
- History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
- Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
- Pregnancy or breastfeeding
- WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and up to 4 weeks after the last dose of study drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-11-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Farxiga
Generic name:	Dapagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-07-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-09-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2017-001090-16-NL
ClinicalTrials.gov	NCT03190694
CCMO	NL61865.042.17