A study to assess the anti-albuminuric effects and variability in response to dapagliflozin in subjects with type 2 diabetes

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Primary Objective: To assess the change from baseline in 24-hr albuminuria with dapagliflozin for six weeks relative to placebo treatment in patients with diabetes and albuminuria > 100 mg/day on stable ACEi or ARB treatment.Secondary Objective(s...

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

Summary

ID

NL-OMON40930

Source
ToetsingOnline

Brief title
Anti-albuminuric effects and response variability to dapagliflozin

Condition

- Diabetic complications
- Nephropathies

Synonym
Albuminuria in patients with type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMW,Bristol-Myers-Squibb (study medication); Netherlands Research Organization (NWO)

Intervention

Keyword: Albuminuria, Dapagliflozin, Response variability, Type 2 diabetes

Outcome measures

Primary outcome

Primary study goal is to assess the change from baseline in 24-hr albuminuria with dapagliflozin for six weeks relative to placebo treatment in patients with diabetes and albuminuria > 100 mg/day on stable ACEi or ARB treatment.

Secondary outcome

Secondary Objective(s):

To assess:

• To assess the within-patient variability in HbA1c, 24-hr blood pressure, body weight, and albuminuria response to dapagliflozin.

• To assess the between-patient variability in HbA1c, 24-hr blood pressure, body weight, and albuminuria response to dapagliflozin.

• The variability in HbA1c, blood pressure, body weight, and albuminuria in response to dapagliflozin during the first and second treatment period.

Study description

Background summary

Increased albuminuria is a strong risk marker for renal and cardiovascular disease. The degree of albuminuria reduction in the first months of treatment

with pharmacological or dietary intervention correlates with the degree of long-term (3 to 4 years) renal or cardiovascular protection. Despite the various available treatments to decrease urinary albumin excretion, residual albuminuria persists in many patients. Residual albuminuria predicts renal and cardiovascular function loss. Novel treatment strategies are therefore required to further decrease albuminuria. Dapagliflozin is a sodium-glucose transport inhibitor and inhibits the re-absorption of glucose in the proximale tubule. This leads to a decrease in fasting plasma glucose and HbA1c. In addition, dapagliflozin administration causes a decrease in blood pressure and body weight and increase in hematocrit suggestive of a diuretic effect. Previous studies have suggested that dapagliflozin may also decrease albuminuria. However, no study has prospectively investigated (and was designed) to assess the albuminuria lowering effects of dapagliflozin.
Previous studies have shown a large variability in response to various anti-albuminuric drugs including ACE-inhibitors, Angiotensin Receptor Blockers, Direct renin inhibitors, NSAIDs, and endothelin antagonists. Very few studies have prospectively investigated whether this response variability is a random phenomenon due to biological or measurement variability or a *true* variability in drug response. A secondary objective of this study is to address this question.

Study objective

Primary Objective:
To assess the change from baseline in 24-hr albuminuria with dapagliflozin for six weeks relative to placebo treatment in patients with diabetes and albuminuria > 100 mg/day on stable ACEi or ARB treatment.

Secondary Objective(s):
To assess:
• To assess the within-patient variability in HbA1c, 24-hr blood pressure, body weight, and albuminuria response to dapagliflozin.
• To assess the between-patient variability in HbA1c, 24-hr blood pressure, body weight, and albuminuria response to dapagliflozin.
• The variability in HbA1c, blood pressure, body weight, and albuminuria in response to dapagliflozin during the first and second treatment period.

Study design

We conduct a double blind randomized cross-over study in subjects with type 2 diabetes with albuminuria > 100 mg/day. Since each subject is his/her own control this design requires fewer patients as compared with a parallel study design. A wash-out period after each treatment period has been included in the design to avoid cross-over effects.

The study will consist of a screening visit, a run-in phase for those subjects

not on stable ACEi/ARB or glucose lowering medication, 3 consecutive 6-weeks double blind treatment periods separated by 4-weeks wash-out periods. Subjects will be assigned to one of the treatment The rationale to include two treatment periods in each arm consisting of the same treatment is to verify the consistency in response.

Each treatment period lasts 6 weeks followed by a 6 weeks wash-out period to avoid cross-over effects. Patients receive dietary counseling provided by a dietician throughout the study in order to standardize and stabilize dietary sodium intake.

Intervention

Dapagliflozin tablets and matching placebo*s are provided by Bristol-Myers-Squibb. Patients take 10 mg dapagliflozin (once daily) or matching placebo according to randomised treatment scheme. Study medication is received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location. The study medication is stored according to the instructions specified on the drug labels. Storage conditions are adequately monitored. Subjects are asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation or in every visit to the outpatient clinic. Appropriate documentation of the subject specific dispensing process is maintained. Unused drugs are destroyed by the pharmacy department at the end of the study.

Patients will have their study visit in the morning in fasted condition. Patients will be instructed to take the study medication once daily, in the morning, except on study days; on those days, the study drug will be taken after the patient visit.

Study burden and risks

The efficacy and safety of dapagliflzoine is established in multiple studies in patients with type 2 diabetes. Hypoglycemia, urinary tract infections are the most frequently reported side effects. Dapagliflozin does not cause a rise in body weight unlike sulfonylurea derivatives and insulin. Patients are asked to visit the outpatient clinical 11 times in 35 weeks. Blood will be drawn and 24-hr urine collection will be performed at 8 visits.

Advantages: we expect that dapagliflozin lowers albuminuria at a group level.

Contacts

Public

Universitair Medisch Centrum Groningen

Antonius Deusinglaan 1 FB20
Groningen 9713 AV
NL
Scientific
Universitair Medisch Centrum Groningen

Antonius Deusinglaan 1 FB20
Groningen 9713 AV
NL

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
Diagnosis of type 2 diabetes mellitus
HbA1c >= 6.6% and <11.0%
Urinary albumin excretion > 100 mg/g
On a stable dose of an ACEi or ARB for at least 4 weeks prior to randomization
On a stable dose of blood glucose lowering medication for at least 4 weeks prior to randomization
eGFR >= 45 mL/min/1.73m2
Willing to sign informed consent

Exclusion criteria

Type 1 diabetes
Urinary albumin excretion > 3500 mg/day
Active malignancy

Pregnancy or breast feeding

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-08-2014
Enrollment:	36
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	27-03-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	06-05-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-12-2016
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	EUCTR2014-000157-37-NL
CCMO	NL47928.042.14