# Individual albuminuria lowering response to dapagliflozin in a decentralized clinical trial in patients with type 2 diabetes mellitus and elevated albuminuria

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Primary: To determine the individual response to the SGTL2 inhibitor dapagliflozin in urine albumin-to-creatinine ratio (UACR) Secondary:- To determine the individual response to the SGLT2 inhibitor dapagliflozin in: - Systolic blood pressure - Body…

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Glucose metabolism disorders (incl diabetes mellitus) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON50915

**Source**
ToetsingOnline

**Brief title**
@Home study

### Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Diabetic complications
- Nephropathies

**Synonym**
Albuminuria in patients with type 2 diabetes mellitus.

**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,AstraZeneca,Universitair Medisch Centrum Groningen

## Intervention

**Keyword:** Albuminuria, Decentralized, SGLT2 inhibitor, Type 2 diabetes mellitus

## Outcome measures

### Primary outcome

Primary study goal is to assess the change in first morning urinary

albumin-to-creatinine ratio from start to end of treatment.

### Secondary outcome

Secondary study goal is to assess changes from baseline in systolic blood

pressure, body weight, eGFR and fasting plasma glucose.

# Study description

### Background summary

Persistent increased albuminuria is a strong risk marker for progressive kidney disease and cardiovascular disease in patients with or without diabetes. 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. The high residual albuminuria in a proportion of patients is at least in part explained by suboptimal response to the current treatments (i.e., ACE inhibitor or Angiotensin Receptor Blockers). Dapagliflozin is a sodium-glucose transport inhibitor and inhibits the reabsorption of glucose in the proximal tubule. This leads to a decrease in fasting plasma glucose and HbA1c in patients with type 2 diabetes. In addition, dapagliflozin administration causes a decrease in blood pressure and body weight and an increase in hematocrit suggestive of a diuretic effect. Previous

studies have also demonstrated the albuminuria lowering effects of dapagliflozin in patients with type 2 diabetes mellitus.
Although dapagliflozin markedly slows progression of kidney function decline (and reduces cardiovascular outcomes) on a population level, randomized parallel group trials have suggested a marked variation in the response to dapagliflozin between individual patients. By design, randomized parallel group placebo-controlled clinical trials test the efficacy of new interventions on a population level but do not assess the efficacy of a drug for the individual. Although there is variation in response between patients, parallel group trial does not allow conclusions whether this variation is a true variation in drug response, or measurement or temporal random variation. We therefore propose a cross-over trial with repeated administration (i.e., a series of N=1 trials) to ascertain the individual drug response. This design specifically allows for assessment of drug efficacy and safety at an individual level.

**Study objective**

Primary: To determine the individual response to the SGTL2 inhibitor dapagliflozin in urine albumin-to-creatinine ratio (UACR)

Secondary:
- To determine the individual response to the SGLT2 inhibitor dapagliflozin in:
- Systolic blood pressure
- Body weight and
- eGFR
- Fasting plasma glucose

**Study design**

Randomized placebo-controlled double-blind cross-over N=1 trial. Eligible participants will be invited for screening. After a screening visit, eligible patients will be randomly assigned to a cross-over study consisting of two periods of 1-week treatment with dapagliflozin and two periods of 1-week treatment with placebo in random order with a 1-week wash-out period between every treatment period to avoid cross-over effects. Based on a prior study where patients were exposed to dapagliflozin 10 mg, effects of dapagliflozin on UACR, blood pressure, body weight, eGFR and plasma glucose were fully present after 1 week and returned to baseline 4 days after drug discontinuation. Hence, a 1-week treatment followed by 1 week wash-out is considered sufficient to detect treatment effects.

**Intervention**

Dapagliflozin tablets and matching placebos will be purchased and provided by AstraZeneca. Patients take 10 mg dapagliflozin or matching placebo once daily in the morning according to a randomized treatment scheme. At the randomization

visit, study medication will be dispensed in standard medicine bottles with a cap that allows real-time monitoring of adherence. Patients receive four numbered bottles with seven tablets in each bottle, according to their randomized treatment schema.

**Study burden and risks**

The efficacy and safety of dapagliflozin is established in multiple parallel randomized controlled trials involving more than 25,000 patients with type 2 diabetes. Urinary tract infections and genital infections are the most frequently reported side effects. Dapagliflozin reduces body weight unlike sulfonylurea derivatives and insulin.

Participants visit the outpatient clinic at three occasions (i.e., a screening visit, a randomization visit and end of study visit) and have to record body weight and blood pressure at home and collect blood and urine at home.

Blood pressure and body weight are measured at home by the participants using ambulant devices (Withings BPM Connect and Withings Body+, respectively). Patients measure their blood pressure and body weight once daily on 28 and 40 days in total, respectively. Capillary blood will be sampled at home by participants using a BD Microtainer® Contact-Activated Lancet (once daily on 22 days in total). Blood is collected with the Hem-Col® device, which is designed to collect capillary blood drawn with a finger prick. In order to make patients comfortable with the blood collection procedures, they first collect a capillary blood sample at the study site during the randomization visit under supervision of trained lab technicians. A venous blood sample will also be taken during the randomization visit in order to compare the clinical chemistry assessments in capillary blood with those measured in venous blood samples (NL70447.100.19). Participants will be asked to draw blood samples at home by a finger prick and send the samples to the laboratory. Participants will collect first morning void urine samples through the PeeSpot® device (once daily on 40 days in total) which allows for decentralized urine collection in a small tube. The urine tubes and blood samples will be sent by regular mail to the laboratory. No other invasive measurements will be executed.

The advantage of an N=1 study is that efficacy of the intervention is vetted for the actual participant. Dapagliflozin is currently marketed in the Netherlands and recommended in patients with type 2 diabetes mellitus and eGFR>45 mL/min/1.73m2. Patients who show a satisfactory response to dapagliflozin and whose characteristics fulfull the criteria according to which dapagliflozin can be prescribed in clinical practice are offered to receive dapagliflozin after the study. It is expected that the indication for dapagliflozin will be broadened to patients with eGFR 25-45 mL/min/1.73m2 in the near future. If this occurs, these patients can also be treated on-label in practice.

The expected time investment for patients is 20 hours, including measurements at home. Patients receive restitution of travel costs to visit the outpatient clinic for the screening, randomization and end of study visit. Patients receive no priority in treatment of other diseases in the clinic during this study. Participation in this study is on a free-will base. Patients can keep the blood pressure device and body weight scale at the end of the study.

## 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 years
- Diagnosis of type 2 diabetes mellitus
- Urinary albumin-to-creatinine ratio >20 mg/g (2.26 mg/mmol)
- eGFR >30 ml/min/1.73m2

- Willing to sign informed consent

## Exclusion criteria

- Diagnosis of type 1 diabetes
- Prior treatment with SGLT2 inhibitor in the four weeks prior to randomization
- History of severe hypersensitivity or contraindications to dapagliflozin
- Unable to monitor blood pressure / body weight or handle digital technologies
- History of non-adherence to medical regimens or unwillingness to comply with the study protocol
- Participation in any clinical investigation within 3 months prior to initial dosing
- Unstable or rapidly progressing renal disease
- Severe hepatic impairment (Child-Pugh class C) as determined by the treating physician.
- Active malignancy
- 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 as decided by the treating physician
o Pancreatitis within the last six months.
o Evidence of serious hepatic disease as determined by the treating physician
o Evidence of urinary obstruction or difficulty in voiding at screening.
- Confirmed lactose intolerance demonstrated with a lactose intolerance test.
- Donation or loss of 400 mL 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
- 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.
- Current pregnancy or breast feeding / attempting to conceive.
- Women of childbearing potential (WOCBP):
o WOCBP who are unwilling or unable to use 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 the risk of pregnancy is minimized.
o WOCBP must have a negative serum or urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent of HCG) within 0 to 72 hours before the first dose of study drug.

WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or

bilateral oophorectomy) or who are not post-menopausal (see definition below).
The following women are WOCBP:
- Women using the following methods to prevent pregnancy: oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).
- Women who are practicing abstinence.
- Women who have a partner who is sterile (e.g. due to vasectomy).

Post-menopause is defined as:
- Women who have had amenorrhea for >12 consecutive months (without another cause) and who have a documented serum follicle-stimulating hormone (FSH) level >35 mIU/mL.
- Women who have irregular menstrual periods and a documented serum FSH level >35 mIU/mL.
- Women who are taking hormone replacement therapy (HRT).

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 11-05-2021 |
| Enrollment: | 20 |
| Type: | Actual |

## Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Forxiga |

| | |
|---|---|
| Generic name: | Dapagliflozin |
| Registration: | Yes - NL outside intended use |

## Ethics review

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| Approved WMO Date: | 21-12-2020 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 14-04-2021 |
| Application type: | First submission |
| 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

ID: 26308
Source: NTR
Title:

### In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2020-004929-23-NL |
| CCMO | NL75914.042.20 |
| Other | NL9060 |
| OMON | NL-OMON26308 |