A Study to Assess the Effects of the Endothelin Receptor Antagonist Zibotentan and the SGLT2 Inhibitor Dapagliflozin in Patients elevated Albuminuria: a Randomized Double Blind Cross-Over Trial

Published: 15-06-2021
Last updated: 07-06-2025

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

Summary

ID

NL-OMON54022

Source
ToetsingOnline

Brief title
ZODIAC

Condition

- Diabetic complications
- Nephropathies

Synonym
diabetic kidney disease, diabetic nephropathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Astra Zeneca,Industry: Astra Zeneca funds the study and delivers the study drugs

Intervention

Keyword: albuminuira, diabetic nephropathies, endothelium receptor antagonist, sodium glucose co transporter inhibitor

Outcome measures

Primary outcome

To assess the change from baseline in albuminuria after 4 weeks combined

Zibotentan (ZIBO) and Dapagliflozin (DAPA) treatment versus four weeks

Zibotentan alone in patients with an albumin:creatinine ratio between 100 and

3500 mg/g on stable ACEi or ARB treatment for at least 4 weeks.

Secondary outcome

• To evaluate the effect of a combined zibotentan / dapagliflozin treatment

versus zibotentan only on:

- Extracellular fluid measured by bioimpedance spectroscopy

- Body weight

- NT-proBNP and BNP

Glomerular filtration rate (GFR) and extracellular volume (ECV) using iohexol

clearance techniques.

- Hematocrit

- Systolic and diastolic blood pressure

- fractional lithium excretion

• To assess the effect of zibotentan / dapagliflozin versus zibotentan on

selected neurohormones / biomarkers:

- Renin-angiotensin-aldosterone system markers (plasma and urine)

- Copeptin (surrogate of vasopressin)

Study description

Background summary

Dapagliflozin is a medicine that increases the loss of salt and sugar in the urine. Dapagliflozin reduces urinary protein levels and has been shown to protect heart and kidney function in patients with type 2 diabetes and chronic kidney disease. Albuminuria is an important indicator of kidney damage. A reduction in albuminuria is related to kidney protection.
Zibotentan is a new investigational drug that lowers blood pressure and, similar to dapagliflozin, reduces albuminuria in patients with type 2 diabetes. Zibotentan can cause fluid retention and heart failure. Dapagliflozin may decrease fluid retention due to zibotentan, while the combination of both zibotentan and dapagliflozin may reduce urinary protein levels more, and therefore potentially better protect the kidneys, than zibotentan alone.

Study objective

This study investigates how well the combination of the two drugs, zibotentan and dapagliflozin, works for the treatment of chronic kidney disease in patients. We compare the effect of zibotentan and dapagliflozin with the effect of a placebo. The main aim of the study is to investigate whether a combination of zibotentan and dapagliflozin may have beneficial effects on albuminuria reduction compared to zibotentan alone. The second aim is to investigate whether the combination of zibotentan and dapagliflozin has an effect on water retention compared to zibotentan alone.

Study design

This study has a cross-over design, which means that, depending on the randomisation schedule, patients will receive successively dapagliflozin, zibotentan, a combination of dapagliflozin and zibotentan or placebo. Dapagliflozin is prescribed at a dose of 10 mg/day. Zibotentan is prescribed at a dose of 1.5 mg/day.

The study consists of a screening visit, a 4-week run-in period (up to a

maximum of 16 weeks) for subjects not receiving stable ACEi/ARB treatment, 2 consecutive double-blind 4-week treatment periods each separated by a 4-week washout period. The third treatment period lasts 6 weeks.

Patients are randomly assigned to two strata with the order of medications in periods 1 and 2 within each stratum determined by randomization:
Stratum 1: period 1: zibotentan, period 2: placebo, period 3: dapagliflozin/placebo and finally the combination of zibotentan and dapagliflozin
Stratum 2: period 1: dapagliflozin, period 2: zibotentan, period 3: dapagliflozin/placebo and finally the combination of zibotentan and dapagliflozin

The above means that there are a total of 8 different randomization options: the first two treatment periods in each stratum are random, meaning that a patient can start with zibotentan or placebo in startum 1 and with dapagliflozin or zibotentan in stratum 2. The third treatment period begins with 2 weeks of treatment with either dapagliflozin or placebo, which will also be randomized to place the patient in the dapagliflozin or placebo group. During the remaining 4 weeks of the third period, all patients will receive the combination of both zibotentan and dapagliflozin (open-label).

All patients come to the hospital 10 times in 6 months. A visit takes about 4.5 hours. In addition, each patient is called 6 times by the investigator, twice during each treatment period. The patient is then asked questions about the use of the medication and adverse events. These phone calls last approximately 15 minutes.

Intervention

Addition of dapagliflozin, zibotentan or a combination of both compared to placebo in addition to stable background therapy for at least 4 weeks with an ACEi or ARB according to current guidelines.

Study burden and risks

Patients are at risk for adverse events due to the study drugs dapagliflozin and zibotentan.
The most relevant potential risks due to dapagliflozin are: urinary tract infections, genital infections, hypovolemia, electrolyte disturbances and ketoacidosis. Zibotentan can induce fluid retention, edema, heart failure (in susceptible patients), nausea, vomiting and dilution anemia.
As with all blood sampling, there is a risk of mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site. There is a small risk of light-headedness and/or fainting.
It is possible to have an allergic reaction to the Iohexol kidney function

test, including rashes (hives) and more severe allergic reactions.

It is not expected that the patients will receive treatment benefit from participation in this mechanistic 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 and <=75 years
Urinary albumin:creatinine ratio > 100 mg/g and <= 3500 mg/g in a first morning void urine collection
eGFR >= 30 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

Exclusion criteria

Diagnosis of type 1 diabetes Minimal change disease, unstable rapidly progressing renal disease, and/or renal disease requiring significant immunosuppression, autosomal dominant or autosomal recessive polycystic kidney disease Hba1c > 12.5% Urinary albuminexcretion > 3500 mg/day Heart Failure NYHA Class III or IV NT-proBNP > 600 pg/ml Acute coronary syndrome event within the preceding 6 months Severe peripheral edema according to investigators opinion Women of childbearing potential (WOCBP). WOCBP is defined as 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 Pregnancy or breastfeeding Indication for high dose immunosuppressants as per the treating physician*s judgment. Active malignancy aside from treated squamous cell or basal cell carcinoma of the skin within the last 5 years. Use of the co-interventional treatments within 6 weeks of screening will not be allowed. 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 or difficulty in voiding at screening Severe hepatic impairment History of epilepsy syndrome History of severe hypersensitivity or contraindications to dapagliflozin History of hypersensitivity or contraindications to iodinated contrast media Subject who, in the assessment of the investigator, 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 or according to investigator*s assessment. 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 subject at higher risk from his/her participation in the study, or is likely to prevent the subject from complying with the requirements of the study or completing the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-10-2022
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	15-06-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-09-2021

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-10-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-12-2024
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	EUCTR2021-001324-18-NL
ClinicalTrials.gov	NCT05570305
CCMO	NL77104.042.21