Canagliflozin REnal Distribution Intervention Trial (CREDIT); A feasibility study for the use of 18F-canagliflozin to quantify individual differences in target-site exposure in diabetes patients

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

Summary

ID

NL-OMON50114

Source
ToetsingOnline

Brief title
CREDIT

Condition

- Diabetic complications
- Diabetic complications
- Nephropathies

Synonym
Diabetes

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: European Association for the Study of Diabetes/European Foundation for the Study of Diabetes

Intervention

Keyword: PET imaging, Receptor occupancy, SGLT2 inhibitor, Type 2 diabetes mellitus

Outcome measures

Primary outcome

The main study parameters are dynamic PET data and images and radiation count

measurement, and free plasma concentrations of canagliflozin.

Secondary outcome

The secondary study parameters are (estimated) Glomerular Filtration Rate,

plasma glucose and urine glucose excretion

Study description

Background summary

Recently, a novel class of glucose lowering drugs, the SGLT2 inhibitors, is approved as second-line therapy in the treatment of DM2. These drugs have shown to improve glycemic control, slow progression of diabetic kidney disease and show beneficial effects on cardiovascular end points, in particular reduction of heart failure (Neal et al., 2017). However, the response to SGLT2 inhibitors in markers of kidney function (albuminuria, eGFR) varies between individuals such that approximately 20% of patients does not show improvement in glycemic control (Petrykiv, de Zeeuw, et al., 2017; Petrykiv, Laverman, et al., 2017). The underlying mechanisms of drug response variability for SGLT2 inhibitors, but also other drugs used for the prevention and treatment of DKD, are unknown. Understanding these mechanisms should lead to more effective treatment strategies for these high-risk individuals. The ultimate aim of this study is to determine the underlying mechanisms and determinants of the variability in drug response. This will lead to the identification of previously unknown

factors that determine therapy response and provide the potential to improve the treatment of microvascular complications of type 2 diabetes in the future. We hypothesize that the underlying mechanisms of the varying response in multiple parameters within an individual can be attributed to variability in the causal path between drug administration, drug tissue distribution, and tissue receptor interaction.
To test this hypothesis we have synthesized an 18F PET radiotracer of the SGLT2 inhibitor canagliflozin, retaining the original molecular structure and therefore pharmacodynamic properties are not changed. This drug class was selected for several reasons. First, it represents an established blood glucose lowering drug in the treatment of type 2 diabetes and given the positive effects on cardiovascular outcomes and good tolerability it is likely that in the near future SGLT2 inhibitors will form the guideline recommended therapy for patients that do not respond well on diet and/or metformin. The advantage of canagliflozin over other SGLT2 inhibitors is that it is particular suitable for PET imaging since it carries an F-atom which can be replaced for 18F without changing the molecular structure of the compound and thus retains its pharmacodynamics properties.
In this clinical feasibility study we will assess 18F-canagliflozin pharmacokinetic characteristics and determine specific receptor binding, receptor occupancy and optimal scanning time in 9 selected subjects with type 2 diabetes.

Study objective

The main objectives are:
• To assess canagliflozin target (i.e. receptor) specific binding in vivo
• To assess receptor occupancy of canagliflozin in vivo
• To determine optimal scanning time in vivo

To explore the relationship between canagliflozin disposition and changes in the following parameters: (estimated) Glomerular Filtration Rate, plasma glucose and urine glucose excretion

Study design

A randomized open label feasibility study will be conducted in subjects with Type II diabetes. The study will consist of a screening visit and 2 treatment days. On the first study day, after IV radiotracer administration, a baseline dynamic PET scan will be taken to measure selective uptake and accumulation in the region of interest (ROI; kidney, aorta and part of the liver).
On the second study day, after oral canagliflozin administration, a second IV radiotracer dose will be administered followed by a second 90-minute dynamic PET scan (post-drug). In this second scan, receptor binding sites are occupied by canagliflozin, hence the reduction of radiotracer uptake compared to the baseline scan can be used to determine the receptor occupancy based on the

binding potentials obtained from both scans. In all patients arterial plasma samples will be taken after radiotracer administration, to quantify radiation measure and free plasma concentrations of canagliflozin and its metabolites. Subjects will receive one of 3 dosages of oral canagliflozin, 50, 100 or 300 mg canagliflozin, with 3 patiens per dosage.

Intervention

A single oral dose of 50, 100, 300mg of canagliflozin (see also study design).

Study burden and risks

Patients will be subjected to physical examination by the principal investigator or delegate before inclusion. This physical examination entails a routine investigation of heart, lungs and abdomen. A pregnancy test will be performed in female participants of the study. Blood pressure will be monitored during screening and on both study days. Body weight will be measured during screening and both study days. On the first study day, a CT topogram will be performed. At time=0 hours, patients will receive an intravenous (IV) diagnostic dose of 18F-canagliflozin radiotracer followed by a 90-minute dynamic PET scan. On the second study day, a CT topogram will be performed and three dose groups will receive an oral dose of canagliflozin. At the approximate time of maximal plasma canagliflozin concentration (tmax, 2.5h) a second IV radiotracer dose will be administered immediately followed by a second 90-minute dynamic PET scan. During the two treatment periods, 24-hour urine will be collected. At screening and on both study days (prior to dosing) a blood sample will be drawn by venepuncture for laboratory measurement (10 mL each). During the two study days, in all patients, arterial plasma samples (10 samples of ~50 microlitre) will be taken after radiotracer administration, to quantify radiation measure of 18F canagliflozin and its metabolites. For this procedure an anaesthesiologist will place an arterial cannula under local lidocain anaesthesia on both study days. Also, on the second study day, plasma samples (10 samples of 4 mL) will be taken to quantify unlabelled plasma concentrations of canagliflozin for the purpose of determining the pharmacokinetic parameters (e.g clearance and volume of distribution) for each subject. Over the entire duration of the study an amount of 285ml of blood will be taken.
The total radiation exposure is 7.4 mSv over the entire duration of the trial. This is classified as category 2B according to ICRP 62 and comparable to 3 times the background radiation dose per year.
There is no direct benefit to the patient*s health be expected from this study. 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 wil only minor risks, if any at all.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Type 2 diabetes
Age >= 40 years <75 years
Written informed consent

Exclusion criteria

• Subjects who participated in a trial with exposure to radiation before, are only
allowed to participate if the total cumulative radiation burden in their life does not
exceed 1 mSv per year, counting from the age of 18 years.

• Pregnant women and women of child-bearing potential who are not using reliable
contraception
• eGFR < 30 mL/min/1.73 m2
• Subjects on diuretics are allowed to participate but the dose should be stable for at least 4 weeks prior to screening
• Subjects already on a SGLT2 inhibitor are allowed to participate, but the drug should be interrupted 1 week prior to the first study day till the end of the second study day
• Subjects using a sulphonylurea.
• Established peripheral arterial disease
• Cardiovascular disease: myocardial infarction, angina pectoris, percutanous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, heart failure (NYHA I-IV) < 3 months before inclusion
• History of hypersensitivity to canagliflozin or another SGLT2 inhibitor
• Active malignancy
• 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.
• 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
• Severe claustrophobia

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-02-2021

Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	18F-Canagliflozin
Generic name:	18F-Canagliflozin
Product type:	Medicine
Brand name:	Invokana
Generic name:	Canagliflozin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-11-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-01-2021
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: 26995
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-001835-29-NL
CCMO	NL70157.042.19
Other	NL7707
OMON	NL-OMON26995