# A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus ('CANVAS-R')

Published: 20-12-2013
Last updated: 24-04-2024

Primary objectiveIn subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevatedrisk of cardiovascular (CV) events to assess the effect of canagliflozin compared to placebo onprogression of albuminuria.Secondary...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Cardiac disorders, signs and symptoms NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON45079

**Source**
ToetsingOnline

**Brief title**
Canagliflozine cardiovasculair outcome trial - renal

### Condition

- Cardiac disorders, signs and symptoms NEC
- Diabetic complications
- Nephropathies

**Synonym**
diabetes, Diabetes mellitus

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Janssen-Cilag
**Source(s) of monetary or material Support:** bedrijf - Janssen-Cilag BV

## Intervention

**Keyword:** Albumineria, Cardiovascular Outcomes, Diabetes Mellitus Type 2, SGLT2- inhibitor

## Outcome measures

**Primary outcome**

Progression is the development of microalbuminuria or macroalbuminuria in a

subject with baseline

normoalbuminuria or the development of macroalbuminuria in a subject with

baseline microalbuminuria,

accompanied by an ACR value increase of greater than or equal to 30% from

baseline.

The primary outcome is progression of albuminuria (as defined above). If the

ACR at a visit meets the

definition of progression described above, a repeat ACR collection

approximately 1 to 2 months later (or

sooner under unusual circumstances, eg, subject is stopping study drug) must

confirm progression of

albuminuria (ie, confirmed progression). If the last on-treatment value meets

the definition of progression

and no repeat ACR collection can be made, the subject will also be deemed to have progressed.

ACR assessments will be based upon values obtained from first morning void urines analyzed by the central laboratory. In this study, duplicate urine specimens will be collected for all ACR measurements.

**Secondary outcome**

The secondary outcomes are:

* Regression of albuminuria is the development of normoalbuminuria in a subject with baseline microalbuminuria or macroalbuminuria or the development of microalbuminuria in a subject with baseline macroalbuminuria, accompanied by a decrease in the urinary ACR value of greater than or equal to 30% from baseline. If the ACR at a visit meets the definition of regression described above, a repeat on-treatment ACR collection approximately 1 to 2 months later (or sooner under unusual circumstances, eg, subject is stopping study drug), must confirm regression of albuminuria (ie, confirmed regression). If the last on-treatment value meets the definition of regression and no repeat ACR collection can be made, the subject will also be deemed to have regressed.

* Change in eGFR from baseline to the last off-treatment value done

approximately 30 days post study

drug discontinuation.

* Urinary albumin/creatinine ratio at last on-treatment visit.

Safety outcomes

The data from this study will be combined with the data from another

large-scale study of the effects of

canagliflozin compared to placebo (CANVAS) in a pre-specified meta-analysis of

cardiovascular safety

outcomes to satisfy the US FDA Post Marketing Requirements.

# Study description

**Background summary**

Canagliflozin (JNJ-28431754) is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2) that has been developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). In March 2013, canagliflozin was approved for marketing by the United States (US) Food and Drug Administration (FDA). An ongoing clinical program designed to continue research on the effects of the agent on renal and cardiovascular outcomes is underway. The goal of this study is to assess the effects of canagliflozin compared to placebo on the progression of albuminuria, an important intermediate marker of renal injury and progression of diabetic nephropathy.

**Study objective**

Primary objective

In subjects with T2DM receiving standard of care but with inadequate glycemic control and at elevated
risk of cardiovascular (CV) events to assess the effect of canagliflozin compared to placebo on
progression of albuminuria.

Secondary objectives
In subjects with T2DM receiving standard care but with inadequate glycemic control and at elevated risk
of CV events to assess the effect of canagliflozin compared to placebo on:
* Regression of albuminuria
* Change in glomerular filtration rate (eGFR) from baseline to the last off-treatment value done
approximately 30 days post study drug discontinuation
* Urinary albumin/creatinine ratio (ACR)

Exploratory objectives
In subjects with T2DM receiving standard care but with inadequate glycemic control and at elevated risk
of CV events to assess the effect of canagliflozin compared to placebo on:
* Change in eGFR determined from a between group comparison of the eGFR slopes using all
on-treatment measures of eGFR made from the first on-treatment measurement to the final
on-treatment measurement
* Changes in HbA1c
* Utilization of AHA therapy

Safety objective
Cardiovascular safety data from this study will be combined with the data from the other large-scale study
of the effects of canagliflozin compared to placebo (CANVAS; 28431754DIA3008; A Randomized,
Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on
Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus; NCT01032629) in a
pre-specified meta-analysis of cardiovascular safety outcomes.

**Study design**

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the
effects of canagliflozin compared to placebo on progression of albuminuria, an important intermediate
marker of renal injury and progression of diabetic nephropathy. The study will be conducted in subjects

with T2DM, receiving standard of care for hyperglycemia and CV risk factors, who have either a history
or high risk of CV events. A total of 5,700 subjects will be recruited into the study. The study*s last
subject last visit is targeted to occur when the last subject randomized has approximately 78 weeks of
follow-up or when 688 major adverse cardiovascular events (MACE) events (ie, CV death, nonfatal
myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R
(DIA4003) studies, whichever comes later (estimated to occur between January 2017 and April 2017).
The effects of canagliflozin will be evaluated against a background of standard of care for the treatment
of hyperglycemia and CV risk factors with study investigators counseled to assure appropriate
management according to applicable national guidelines for the care of patients with T2DM with
treatment individualized as clinically appropriate.

**Intervention**

Upon successful completion of screening, all potentially eligible individuals will enter a 2-week run-in
period, during which they will receive single-blind placebo capsules (one capsule to be taken once-daily)
to assess compliance.
Individuals that meet inclusion/exclusion criteria and that are compliant during run-in will be randomly
assigned in a 1:1 ratio to canagliflozin or matching placebo to be taken once daily, before the first meal of
the day. Canagliflozin will be provided at the dose of 100 mg/day through Week 13 and then increased at
the discretion of the investigator at Week 13 or a subsequent visit to the dose of 300 mg/day, if the subject
requires additional glycemic control and is tolerating the 100 mg dose (see Protocol Section 3.1). All study drug
after randomization will be provided in a double-blind manner.
During the study, the subjects will visit maximum 11 times research centre. In addition there are six telephone contacts. During the visits, blood and urine will be collected for analysis and the vital signs of the patient are measured.

**Study burden and risks**

Burden:
1. Up to 11 visits spread over 3.5 years;

2. Up to 6 telephone contacts / email contacts about 3.5 years;
3. 11 blood samples (including 6 times sober) and 10 times urine collection over 3.5 years

Risks:
1. Side effects of canagliflozine;
2. Risks from side effects of testing (eg bloodsampling)
3. Unknown risks

## Contacts

**Public**
Janssen-Cilag

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**Scientific**
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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

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

### Inclusion criteria

- Man or woman with a diagnosis of T2DM with HbA1c level * 7.0% to * 10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination

therapy with any approved agent: eg, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.;- History or high risk of CV events defined on the basis of either:
Age *30 years with documented symptomatic atherosclerotic CV events:
including stroke; MI; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented hemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease.
2) age * 50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic blood pressure >140 mmHg (average of 3 readings) recorded at the Screening Visit, while the subject is on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria (see Section 3.2, Study Design Rationale, for definition) within one year of screening, or documented HDL-C of <1 mmol/L (<39 mg/dL) within one year of screening.
Note: An overall target ratio of approximately 70%:30% for CV history (first category):risk factors (second category) will be implemented (with a maximum of approximately 40% in the second category). This target is intended to be a global ratio and may vary by region. The proportion of subjects in these categories will be monitored centrally.
Note: the term *documented* in the above paragraphs refers to the required information being clearly noted in hospital/clinical records or in physician-referral documents, copies of which should be retained in the subject*s study files.;- Women must be: postmenopausal, defined as
o >45 years of age with amenorrhea for at least 18 months, or
o >45 years of age with amenorrhea for at least 6 months and less than 18 months and a known serum follicle stimulating hormone (FSH) level >40 IU/L, or
o surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal occlusion), or otherwise be incapable of pregnancy, or
o heterosexually active and practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for the duration of their participation in the study, or
o not heterosexually active.
Note: subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.;- Women of childbearing potential (ie, those subjects who do not meet the postmenopausal
definition above, regardless of age) must have a negative urine pregnancy test at baseline (Day 1) and at screening if required by local regulations (Note: a serum pregnancy test is acceptable in lieu of a urine pregnancy test if required by local regulations).;- Willing and able to adhere to the prohibitions and restrictions specified in this protocol
- Subjects must have signed an informed consent document indicating that they understand

the purpose of and procedures required for the study and are willing to participate in the study;Inclusion Criterion for Randomization
- Subjects must have taken *80% of their single-blind placebo doses during the 2-weeks prior to randomization on Day 1 to be eligible for randomization.

## Exclusion criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:;Diabetes-Related/Metabolic
- History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- History of one or more severe hypoglycemic episodes within 6 months before screening
Note: a severe hypoglycemic episode is defined as an event that requires the help of another person.
- History of hereditary glucose-galactose malabsorption or primary renal glucosuria
- Ongoing, inadequately controlled thyroid disorder
Note: subjects on thyroid hormone replacement therapy must be on a stable dose for at least 6 weeks before Day 1.;Renal/Cardiovascular
- Renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant. Note: subjects with a history of treated childhood renal disease, without sequelae, may participate.
- Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident within 3 months before screening, or a planned revascularization procedure, or history of New York Heart Association (NYHA) Class IV cardiac disease (The Criteria Committee of the New York Heart Association).
- Known ECG findings within 3 months before screening that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance);Gastrointestinal
- Known history of hepatitis B surface antigen or hepatitis C antibody positive (unless known to be associated with documented persistently stable/normal range aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), or other clinically active liver disease
- Any history of or planned bariatric surgery;Laboratory
- eGFR <30 mL/min/1.73m2 at screening visit
- ALT levels >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN, unless in the opinion of the investigator and as agreed upon by the sponsor*s medical officer, the findings are consistent with Gilbert*s disease;Other conditions
- History of malignancy within 5 years before screening (exceptions: squamous and basal cell carcinomas of the skin and carcinoma of the cervix in situ, or a malignancy that in the opinion of the investigator, with concurrence with the sponsor*s medical monitor, is considered cured with minimal risk of recurrence)
- History of human immunodeficiency virus (HIV) antibody positive
- Subject has a current clinically important hematological disorder (eg, symptomatic anemia, proliferative bone marrow disorder, thrombocytopenia)
- Investigator*s assessment that the subject*s life expectancy is less than 1 year, or any

condition that in the opinion of the investigator would make participation not in the best interest of the subject, or could prevent, limit, or confound the protocol-specified safety or efficacy assessments
- Major surgery (ie, requiring general anesthesia) within 3 months of the screening visit or any
surgery planned during the subject*s expected participation in the study (except minor surgery, ie, outpatient surgery under local anesthesia)
- Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or prevent the subject from meeting or performing study requirements
Medications/Therapies
- Current or prior use of an SGLT2 inhibitor.
- Prior or current participation in another canagliflozin study.
- Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients (refer to Section 14.1, Physical Description of Study Drug[s])
- Current use of a corticosteroid medication or immunosuppressive agent, or likely to require treatment with a corticosteroid medication (for longer than 2 weeks in duration) or an immunosuppressive agent. Note: subjects using inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses may participate
- Received an active investigational drug (including vaccines) or used an investigational medical device within 3 months before Day 1/baseline;General
- History of drug or alcohol abuse within 3 years before screening
- Pregnant or breast-feeding or planning to become pregnant or breast-feed during the study
- Employees of the investigator or study center, with direct involvement in the proposed study
or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator
Note: Investigators should assure that all study enrollment criteria have been met and determine that the subject has not had any interval change in clinical status since screening. Before randomization, subjects whose status changes after screening, such that they now meet an exclusion criterion, should be excluded from participation.

# Study design

## Design

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|---|---|
| Study phase: | 4 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |

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|---|---|
| Primary purpose: | Prevention |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 02-04-2014 |
| Enrollment: | 250 |
| Type: | Actual |

### Medical products/devices used

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

## Ethics review

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|---|---|
| Approved WMO Date: | 20-12-2013 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 12-02-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 13-03-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 17-03-2014 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 10-04-2014 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 15-04-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 23-04-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 08-05-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-05-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 22-07-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 31-07-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-09-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 10-09-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 13-03-2015 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 25-03-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 10-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 11-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 07-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 26-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-11-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 09-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-03-2016 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 10-05-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-05-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 13-06-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 08-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 12-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 04-11-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 10-11-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

## 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 | EUCTR2013-003050-25-NL |
| CCMO | NL47109.018.13 |