A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ 28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus

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In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:Primary Objectives*to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by...

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

Summary

ID

NL-OMON36405

Source
ToetsingOnline

Brief title
The CANVAS Trial: CANagliflozin CardioVascular Assessment Study

Condition

- Diabetic complications

Synonym
diabetes, Diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag B.V.

Intervention

Keyword: Cardiovascular Outcomes, type 2 diabetes mellitus

Outcome measures

Primary outcome

The hypothesis of CV risk reduction for canagliflozin will be evaluated based upon the events in the CV composite endpoint of MACE (CV death, nonfatal MI, nonfatal stroke). An independent Endpoint Adjudication Committee will assess all events that could potentially be in the specified CV endpoint and only those events where the committee, using methodology and definitions defined in the committee*s charter, determines a specified endpoint has occurred will be included in the primary analysis.

Secondary outcome

Secondary Efficacy Endpoints: HbA1c, FPG, systolic and diastolic blood pressure, body weight, albuminuria, eGFR, and fasting plasma lipids. The change from baseline in HbA1c, FPG, systolic and diastolic blood pressure, body weight, albuminuria, and eGFR and percent change in fasting plasma lipids will be evaluated. Urinary albumin/creatinine ratio (from first morning void) will be measured and classified. The proportion of subjects with progression of albuminuria will be evaluated. Measurements to assess HOMA B and the proinsulin/insulin ratio will be collected in a subset of subjects of approximately 1,200 subjects (at designated sites) who are not receiving

insulin at baseline.

Safety and tolerability will be evaluated on the basis of the overall incidence of adverse events and incidence of specific adverse events, discontinuation rate due to adverse experiences, incidence of CV events, incidence of clinically important changes in clinical laboratory tests, ECGs, vital signs, physical examination, and body weight.

Study description

Background summary

Canagliflozin (JNJ-28431754) is an orally active inhibitor of the sodium-glucose transporter 2 (SGLT2) that is being developed as an oral antihyperglycemic agent (AHA) for the treatment of patients with type 2 diabetes mellitus (T2DM). The goals of this study (CANVAS) are to assess the overall safety and tolerability of canagliflozin and to demonstrate a reduction in major adverse cardiovascular events (MACE) with canagliflozin treatment. Prior clinical studies of canagliflozin in patients with T2DM have demonstrated improvements in glycemic control and fasting plasma glucose, reduction in body weight, and trends towards improvements in other cardiovascular disease risk factors, with generally good tolerance and appropriate safety to support continued clinical development of this medication. With improved glycemic control, which itself may provide a benefit in CV risk (Ray 2009), and the trends towards benefit on other CV risk factors including body weight, the potential for a benefit of long-term treatment with canagliflozin on CV disease is raised.

Study objective

In subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease:
Primary Objectives
*to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on CV risk as measured by the hazard ratio (HR) for a composite endpoint (MACE including CV death, nonfatal MI, and nonfatal stroke)
*to assess the safety and tolerability of canagliflozin plus standard of care relative to placebo plus standard of care
Secondary Objectives

*to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care on: fasting measures of beta-cell function (homeostasis model assessment [HOMA]-B and the proinsulin/insulin ratio); the proportion of subjects with progression of albuminuria (progression defined as *1 step, ie, no albuminuria to micro- or macro-albuminuria or from micro-albuminuria to macro-albuminuria); the urinary albumin/creatinine ratio; renal function (as measured by the change from baseline in estimated glomerular filtration rate [eGFR])
*to assess the effect of canagliflozin plus standard of care relative to placebo plus standard of care at 18 weeks and at the end of the treatment period on: glycemic efficacy (HbA1c and FPG); body weight; blood pressure; fasting plasma lipids (triglycerides, HDL-C, low-density lipoprotein cholesterol [LDL-C], total cholesterol, and the ratio of LDL-C to HDL-C

Study design

This is an adaptively-designed, randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM, on a wide range of current AHAs, who have either a history or high risk of CV disease. Up to 18,500 subjects may be enrolled, in 2 cohorts, with study duration for individual subjects of up to approximately 8 years. The study will recruit an initial 4,500 subjects who will be randomized to treatment with 1 of 2 doses of canagliflozin (100 or 300 mg) or placebo, in a 1:1:1 randomization ratio. An interim analysis will be conducted (after approximately 4 years) by an Independent Data Monitoring Committee (IDMC) to assess study feasibility in achieving the primary hypothesis of CV benefit.
In this study, investigators will be counseled to assure appropriate management of CV risk factors according to standard guidelines or other local diabetes guidelines for the care of patients with T2DM.

Intervention

Upon successful completion of the initial screening, all potentially eligible individuals will enter a 2-week run in period, during which they will receive single-blind placebo tablets (to be administered once-daily).
Subjects in the initial cohort will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. Based upon the Phase 3 canagliflozin program evaluation (using dose efficacy and tolerability assessments), one or the other dose may not be continued in development, and therefore not continued in this study. In addition, based upon the results of the planned interim analysis of the initial cohort, the study IDMC may recommend continuing only one dose in this study after re-opening of enrollment. The randomization of subjects when enrollment is re-opened will be based upon allocation to placebo and the dose(s) of

canagliflozin continuing with a distribution between placebo and canagliflozin dose group(s) considered by the IDMC to maximize study power.

Study burden and risks

Burden:
1. 37 visits during 8 years
2. 25 bloodsampling during 8 years

Risks:
1. Adverse events standard of care
2. Adverse events Canagliflozine
3. Side effects from testing (bllodsampling, ecg)
4. Unknown risks.

While the subject is participating in this study, the studyteam will follow on his condition very closely. The subject may benefit from the health information provided to him/her as a result of study procedures such as blood and urine tests, ECG, physical exams and other follow up.
The subject will be allowed to keep the blood glucose meter that is provided to him/her.
The subject will receive diet and exercise counseling and materials which will support his/her treatment.

Contacts

Public
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Janssen-Cilag

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria at Screening Visit
Man or woman with a diagnosis of T2DM with HbA1c level > or <= 7.0% to < or <= 10.5% at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved class of agents: eg, sulfonylurea, pioglitazon, metformin, PPAR agonist, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.
*History or high risk of CV disease defined on the basis of either:
*Age > or <= 30 years with documented symptomatic atherosclerotic CV disease: 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
*Age > or <= 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 on at least one blood pressure-lowering treatment, current daily cigarette smoker, documented micro- or macro¬-albuminuria, or documented HDL-C of <1 mmol/L (<39 mg/dL).
Note: an overall 70%:30% target ratio for CV history (first category):risk factors (second category) will be implemented (with max 40% in 2nd category); this ratio is intended to be a global ratio and may vary by region.The proportion of subjects in these categories will be monitored centrally.
*Women must not be or get pregnant during their participation at the trial.
*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
*To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.
Inclusion Criterion for Randomization: Subjects must have taken >80% of their single-blind placebo tablets during the 2 week run-in period at Day 1 to be eligible for randomization.

Exclusion criteria

Diabetes-Related/Metabolic
*History of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
*On an AHA and not on a stable regimen (ie, agents and doses) for at least 8 weeks before the screening visit
Note: a stable dose of insulin is defined as no change in the insulin regimen (ie, type[s] of insulin) and < or = 10% change in the average total daily dose of insulin.
*Fasting fingerstick glucose at home or investigational site >270 mg/dL (>15 mmol/L) at Baseline/Day 1
*For patients on a sulphonylurea agent or on insulin: fasting fingerstick glucose at home or investigational site <110 mg/dL (<6 mmol/L) at Baseline/Day 1
Note: at the investigator*s discretion, based upon an assessment of recent SMBG values, subjects meeting either of these fingerstick glucose exclusion criteria may return to the investigational site within 14 days and be randomized if the repeat fasting fingerstick value no longer meets the criterion. Subjects with fingerstick glucose >270 mg/dL (>15 mmol/L) may have their AHA regimen adjusted, and be rescreened once on a stable regimen for at least 8 weeks.
*History of one or more severe hypoglycemic episode within 6 months before screening
*History of hereditary glucose-galactose malabsorption or primary renal glucosuria
*Run-in visit thyroid stimulating hormone [TSH] value that is <0.2 or >10 mIU/L. Subjects taking a thyroxine supplementation for thyroid disorder should be on a stable dose for at least 6 weeks before baseline
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; refer to Attachment 3, New York Heart Association Classification of Cardiac Disease, for a description of the classes
*Findings on 12-lead ECG that would require urgent diagnostic evaluation or intervention (eg, new clinically important arrhythmia or conduction disturbance)
Gastrointestinal
*History of hepatitis B surface antigen or hepatitis C antibody positive (unless associated with documented persistently stable/normal range aspartate aminotransferase [AST] and ALT levels), or other clinically active liver disease
*Any history of or planned bariatric surgery
Laboratory
*Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 at screening (provided by the central laboratory)
*For subjects taking metformin: serum creatinine > or = 1.5 mg/dL (133 *mol/L) for men and > or = 1.4 mg/dL (124 µmol/L) for women, at screening; or eGFR <60 mL/min/1.73m2, at screening
*ALT levels >2.0 times the ULN or total bilirubin >1.5 times the ULN, at screening, 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
*Current use of a disallowed therapy:Any other SGLT2 inhibitor or use of rosiglitazone within 8 weeks before screening
Subjects may be rescreened on one additional occasion after a period of 30 days from the time that treatment with the allowed therapy was initiated.
*Known allergies, hypersensitivity, or intolerance to canagliflozin or its excipients

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	05-01-2010
Enrollment:	300
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not yet known.
Generic name:	Canagliflozin

Ethics review

Approved WMO Date:	06-11-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date: 17-04-2012

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 12-07-2012

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 16-11-2012

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 13-05-2013

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 29-07-2013

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 21-01-2014

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: 25-03-2015

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 14-07-2015

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:	07-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2016
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:	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

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	EUCTR2009-012140-16-NL
CCMO	NL30079.018.09