A double blind placebo controlled study to evaluate the effects of bexagliflozin on hemoglobin A1c in patients with type 2 diabetes and increased risk of cardiovascular adverse events

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Primary Efficacy Objectives:The primary efficacy objective of this trial is to evaluate the placebo-adjusted change in HbA1c from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects with increased risk of cardiovascular...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON47856

Source
ToetsingOnline

Brief title
Theracos study THR-1442-C-476

Condition

- Heart failures
- Glucose metabolism disorders (incl diabetes mellitus)
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Type 2 diabetes and increased risk of cardiovascular adverse events

Research involving

Human

Sponsors and support

Primary sponsor: Theracos Sub, LLC
Source(s) of monetary or material Support: Theracos Sub LLC;225 Cedar Hill St.;Suite 200;Marlborough;MA 01752;USA

Intervention

Keyword: Bexagliflozin, Double blind study, Effects on cardiovascular events, Type 2 diabètes

Outcome measures

Primary outcome

Primary efficacy endpoint:

* Change in HbA1c from baseline to week 24, compared to placebo

Secondary outcome

Secondary efficacy endpoints:

* Change in body weight from baseline to week 48 in subjects with a BMI * 25

kg/m2

* Change in SBP from baseline to week 24 in subjects with baseline systolic

blood pressure * 140 mmHg

Exploratory efficacy end points:

* Change in HbA1c from baseline over time

* Change in FPG from baseline over time

* Change in body weight from baseline over time

* Change in SBP over time

* Requirement of additional anti-diabetic medications, including insulin, over

time

* Requirement of reduced anti-diabetic medications, including insulin, over time
* Incidence of hospitalization for heart failure among all subjects and among subjects who have a history of heart failure

Other endpoint:

Samples for population PK analysis will be collected and the plasma concentration of bexagliflozin determined. The PK parameters will be assessed separately as part of the population PK analysis. Biomarker samples will be collected. The biomarker analysis will be performed separately.

Safety Assessments:

The safety endpoints will include:

* A 5-point composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization
* A 6-point composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, coronary revascularization or hospitalization for heart failure
* Individual events including all-cause mortality, CV death, fatal and non-fatal MI, fatal and non-fatal stroke, hospitalization for unstable angina, hospitalization for CHF, or coronary revascularization. Both first events and total events, taking account of repeat events will be examined
* Change in eGFR from baseline
* Change in UACR from baseline

* Incidence of adverse events of interest. Adverse events of interest including urinary tract infections including urosepsis and pyelonephritis, genital mycotic infections, diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders, and renal failure events

Other safety assessments:

**Adverse events

**Clinical laboratory events

**Physical examinations

**Vital signs including orthostatic blood pressure

**Use of concomitant medications

Study description

Background summary

(See protocol point 1)
Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality worldwide, affecting an estimated 382 million people in 2013 (IDF, 2014). More than 95% of people with diabetes have type 2 diabetes, and more than 80% of those with T2DM are overweight or obese. In Western societies, individuals with diabetes have at least twice the risk of hypertension and major cardiovascular complications compared to individuals without diabetes (Bhatt et al., 2010; Preis et al., 2009; Sarwar et al., 2010) and the major cause of death among patients with T2DM is cardiovascular disease (Go et al., 2013). In addition, congestive heart failure is highly prevalent among men and women with T2DM, and T2DM increases the occurrence of heart failure independently of underlying coronary disease (Boudina and Abel, 2007; Domanski et al., 2003; Kannel and McGee, 1979).

Although glycemic control clearly reduces microvascular diabetic complications (ADA, 2013), it is less clear whether any specific approach to reducing blood

glucose concentration, particularly among patients with long standing T2DM or established cardiovascular risk factors, confers additional risk with respect to cardiovascular events (Duckworth et al., 2009; Patel et al., 2008). As a result of this uncertainty, both FDA and European Medicines Agency (EMA) require demonstration of long-term cardiovascular safety prior to the approval of new drugs for treatment of T2DM (FDA Guidance 2008, ucm071627.pdf).

The renal Na+/glucose transport protein (SGLT2) actively transports extracellular glucose into cells using the driving energy of the transmembrane electrochemical potential for sodium ions. Individuals with disruptions in SLC5A2, the gene encoding SGLT2, exhibit prominent glucosuria in the absence of significant co-morbidities (Santer et al., 2003; van den Heuvel et al., 2002). The excretion of glucose in the urine of diabetic subjects in amounts comparable to or greater than that seen in individuals harboring loss of functions mutations in SLC5A2 has the potential to improve both fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia. Several SGLT2 inhibitors have demonstrated these clinical benefits as a mono- or combination therapy with other oral anti-diabetic medications including insulin (Nauck, 2014). Studies of the three SGLT2 inhibitors licensed in the US, dapagliflozin, canagliflozin, and empagliflozin, have demonstrated that long term use of an SGLT2 inhibitor does not increase the incidence of major adverse cardiovascular events (MACE). Because heart failure is exacerbated by fluid retention, the development of diuretic oral antidiabetic agents is potentially attractive for the treatment of diabetic patients with comorbid heart failure and may be similarly attractive in patients with both diabetes and hypertension.

Study objective

Primary Efficacy Objectives:
The primary efficacy objective of this trial is to evaluate the placebo-adjusted change in HbA1c from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects with increased risk of cardiovascular adverse events.

Secondary Efficacy Objectives:
The key secondary efficacy objectives are:
* To evaluate the effect of bexagliflozin on the change in body weight from baseline to week 48 in randomized subjects with a BMI * 25 kg/m2 compared to placebo
* To evaluate the effect of bexagliflozin on the change in systolic blood pressure (SBP) from baseline to week 24 in subjects with Baseline systolic blood pressure * 140 mmHg compared to placebo

Additional exploratory efficacy objectives are:
* To assess the effect of bexagliflozin treatment on the change in HbA1c versus

placebo over time
* To evaluate the effect of bexagliflozin treatment on the change in fasting plasma glucose (FPG) versus placebo over time
* To measure the proportion of subjects requiring an intensification of antidiabetic regimen versus placebo over time
* To measure the proportion of subjects requiring a relaxation of their antidiabetic regimen versus placebo over time
* To measure the incidence of hospitalization for heart failure among all subjects and among subjects with a history of heart failure at baseline

Safety Objectives:
The primary safety objective of this study is the contribution of at least 134 major adverse cardiovascular events (MACE+) to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo. MACE+ is defined as cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina.

An additional objective is the evaluation of the safety of exposure to bexagliflozin for a minimum of 52 weeks in a treatment population that is at elevated risk for major adverse cardiovascular events.

Other Objectives:
Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled) will be conducted at 30 sites and will include approximately 240 subjects.
Measurement of cardiovascular biomarkers at baseline and week 12 in an exploratory study to increase the understanding of bexagliflozin treatment effect on the biomarkers that are relevant in the CV disease diagnosis and prognosis

Study design

THR-1442-C-476 is a multi-center, randomized, double-blind, placebo-controlled, parallelgroup study. Approximately 1650 subjects with sub-optimally controlled T2DM and elevated risk for cardiovascular adverse events will be randomized to bexagliflozin tablets, 20 mg, or placebo in a 2:1 ratio as an add-on therapy to background anti-diabetic medications

Intervention

* Protocol scheduled subject visits
* Diet & exercise counseling (at visit 2)
* Diary & glucometer records (reviewed at each visit)
* PK sampling (visits 5 & 6)

Study burden and risks

Possible risks of bexagliflozin:
Bexagliflozin has been tested in animals and humans (A total of 10 studies have been conducted in healthy volunteers and subjects with type 2 diabetes).

Overall, bexagliflozin has been well tolerated by subjects. A very common side effect that is associated with bexagliflozin use is headache (one in ten patients). Common side effects include sore throat, muscle pain, and frequent urination (occurred between one in ten and one in a hundred patients). There have been a few patients that discontinued participation of a clinical trial due to adverse events that the study doctor considered to be related to bexagliflozin treatment. These adverse events were skin rash, temporary blurry vision, and creatinine increase (indicating a decrease in kidney function). You must tell the study doctor or study staff about all side effects that you have. If you are not honest about your side effects, it may not be safe for you to stay in the study.

Before experimental drugs are given to human subjects they are given to animals at doses much higher than used in humans to see what kind of bad effects they may produce. Not all of the bad effects seen in animals may be seen in humans, and some bad effects may occur in humans that were never seen in animals. Animals given doses much higher than what will be given during this study have experienced effects on the digestive system, such as diarrhea and stomach irritation, and effects on the liver, kidney, and heart. No such reactions have been observed in humans receiving up to 100 mg doses of bexagliflozin.

Studies have been conducted in humans with other drugs similar to bexagliflozin. These drugs have been generally well tolerated. The possible side effects of SGLT2 inhibitors include dehydration, kidney problems, low blood sugar when this class of medicines is combined with other prescription medicines used to treat diabetes, increased cholesterol in the blood, and yeast infection. A rare side effect called ketoacidosis has been experienced in some diabetic patients who have taken SGLT2 inhibitors. Ketoacidosis is a condition when the body produces high levels of blood acids. If you experience difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness, you must contact your study doctor. The number of events is only slightly higher than the number of side effects in people taking a placebo. Side effects that were not included as risks in the previous consent form are bronchitis, influenza, back pain, upper respiratory tract infection, muscle spams, dizziness and hypertension.

Unforeseen risks: Since the study medication is experimental, there may be other side effects (risks) that are not known. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening.

Side effects of other study-related medication
It is important to know that there may be other side effects that are not yet known. Side effects may go away after the treatment is stopped, but it is also possible that side effects may last a long time or may never go away. They may range from mild to life threatening and/or fatal.
It is important to tell the study doctor or study nurse right away about any changes in health that may have happened even if you do not think they are related to the study or to the medication. Your study doctor may give you treatment to help control side effects.

Pregnancy risks for Female Participants
The effects of the study drug on an unborn child and on a breast-fed baby are not known. Because of this, it is very important that you are not pregnant and are not breast-feeding and you do not become pregnant during the course of the study. You will not be allowed to take part in the study if you are pregnant, trying to become pregnant or are breast-feeding.
* If you can become pregnant, the study doctor will ask you to have a urine pregnancy test before you start the study, and during the study to make sure that you are not pregnant.
* If you can become pregnant, you must practice abstinence or use a reliable birth control method(s) for the duration of the study. Your study doctor will let you know which birth control methods are acceptable. The following birth control methods are recommended: oral contraceptives, intrauterine device, Depo-Provera, Norplant, hormonal contraceptive implants, bilateral tubal ligation, partner with vasectomy, condom or diaphragm plus contraceptive sponge, foam, or jelly.
* If you become pregnant while taking part in the study you should let your study doctor know right away. Your study doctor will remove you from the study and talk to you about the need for further medical attention if appropriate.
If you become pregnant, we ask that you allow us to collect information on your pregnancy and your child for at least 6 months after your child*s birth.

What are the possible benefits and disadvantages of taking part in this research study?
Possible benefits from taking part in this study may include:
* Your health problem may get better from taking part in this study. In this study you may get placebo which means you may not be taking bexagliflozin during the study.
* Taking part in this study will help doctors to learn more about bexagliflozin. This may help others with your health problem in the future.

Contacts

Public

Theracos Sub, LLC

255 Cedar Hill St. Suite 200
Marlborough MA 01752
US
Scientific
Theracos Sub, LLC

255 Cedar Hill St. Suite 200
Marlborough MA 01752
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

The study population will include:
1. Male or female adult subjects with an age *40 years
2. Subjects with a diagnosis of T2DM
3. Subjects with HbA1c values of 7.5 * 11%, inclusive
4. Subjects with fasting plasma glucose (FPG) * 250 mg/dL at screening
5. Subjects who have a regimen for treatment of T2DM that has been stable for the past 3 months. A stable regimen is defined as: no changes in dose or frequency of OHAs or GLP-1 agonists, or <20% variability in total daily insulin dose
6. Subjects who present with at least one of the following 3 histories:
Group 1: A history of atherosclerotic vascular disease as defined by one or more of the following:
a) myocardial infarction (MI) or ischemic (non-hemorrhagic) stroke > 3 months but * 5 years prior to screening or
b) documented history of coronary, carotid, or peripheral arterial revascularization (coronary artery bypass grafting must have occurred * 5 years

prior to screening)
Group 2: A history of NYHA class II or class III heart failure at the time of screening with a left ventricular ejection fraction (LVEF) * 40% and no subsequent LVEF > 40% documented within 6 months of screening. No more than 200 subjects with class II NYHA heart failure will be randomized in the study
Group 3: Age * 55 years with 2 or more of the following:
a) diabetes duration of * 10 years
b) uncontrolled hypertension defined as SBP > 140 mmHg despite 3 or more anti-hypertensive medications
c) current smoking
d) urine albumin:creatinine ratio (UACR) > 30 mg/g
e) eGFR of 45 to 60 mL/min/1.73 m2, or
f) HDL < 1 mmol/L (38 mg/dL)
7. Female subjects of childbearing potential who are willing to use an adequate method of contraception and to not become pregnant for the duration of the study. Adequate contraceptive measures include, but are not limited to, oral contraceptives, intrauterine devices, Depo-Provera, Norplant, hormonal contraceptive implants, bilateral tubal ligation, partner with vasectomy, condom or diaphragm plus contraceptive sponge, foam, or jelly, and abstinence
8. Subjects who are willing and able to return for all clinic visits and to complete all study required procedures, including self-monitored blood glucose (SMBG) measurement, and take run-in medication, missing no more than one dose
9. Subjects who receive anti-hypertensive medications at a stable dosage for * 2 weeks prior to randomization
10. Subjects who receive lipid modifying therapy on a stable regimen for 6 weeks prior to randomization
11. Subjects who have seated SBP < 170 mmHg and DBP < 110 mmHg at screening

Exclusion criteria

Patients who exhibit any of the following characteristics will be excluded from the study:
1. Diagnosis of type 1 diabetes mellitus or maturity*onset/diabetes of the young (MODY)
2. Hemoglobinopathy that affects HbA1c measurement
3. Frequent symptomatic hypoglycemia (greater than one episode per week on average)
4. Genitourinary tract infection within 6 weeks of screening or history of * 3 genitourinary infections requiring treatment within the last 6 months
5. Cancer, active or in remission for < 3 years (Non-melanoma skin cancer or basal cell carcinoma or carcinoma in situ of the cervix will not be grounds for exclusion)
6. History of alcohol or illicit drug abuse in the past 2 years
7. Evidence of abnormal liver function tests (total bilirubin or alkaline phosphatase > 1.5 x upper limit of normal (ULN) with the exception of isolated

Gilbert*s syndrome); or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 x ULN
8. History of MI, stroke or hospitalization for heart failure in the prior 3 months
9. Evidence of NYHA class IV heart failure at screening or randomization
10. Presently scheduled for percutaneous coronary intervention, coronary artery bypass grafting or any surgical procedure
11. Previous treatment with bexagliflozin or EGT0001474
12. Currently or within 3 months of taking any SGLT2 inhibitors
13. Any condition, disease, disorder, or clinically relevant laboratory abnormality that, in the opinion of the PI, would jeopardize the subject*s appropriate participation in this study or obscure the effects of treatment
14. Prior renal transplantation or evidence of nephrotic syndrome, defined as a urine albumin: creatinine ratio (UACR) > 2000 mg/g, at screening
15. Implantation of a cardiac resynchronization therapy device within 3 months prior to screening or intent to implant a cardiac resynchronization therapy (CRT) within 6 months following screening
16. Diagnosis of peripartum or chemotherapy-induced cardiomyopathy within 12 months prior to screening
17. Symptomatic bradycardia or second or third degree atrioventricular block without a pacemaker
18. eGFR, as calculated by the modification of diet in renal disease study equation (MDRD), < 45 mL/min/1.73 m2 or requiring dialysis
19. Pregnant or nursing
20. Currently participating in another interventional trial

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-09-2016
Enrollment:	132
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not applicable
Generic name:	Bexaglifozin

Ethics review

Approved WMO Date:	22-12-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-07-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-09-2016
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-06-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2015-001760-19-NL
ClinicalTrials.gov	NCT02558296
CCMO	NL55821.028.15