TECOS: A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control

Published: 17-04-2009
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To compare the impact of adding sitagliptin to usual care vs. usual care without sitagliptin with regard to the risk of developing cardiovascular events.

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

Summary

ID

NL-OMON39187

Source
ToetsingOnline

Brief title
TECOS

Condition

- Cardiac disorders, signs and symptoms NEC
- Autoimmune disorders

Synonym
diabetes

Research involving

Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck & Co.;Inc.

Intervention

Keyword: cardiovascular outcomes, sitagliptin, type 2 diabetes mellitus

Outcome measures

Primary outcome

Objective: To compare the impact of including sitagliptin as part of usual care

vs. usual

care without sitagliptin on CV outcomes as measured by the primary CV composite

endpoint of CV-related death, nonfatal MI, nonfatal stroke, or unstable angina

requiring

hospitalization.

Hypothesis a:

Sitagliptin, when used as part of usual care, is noninferior to usual care

without sitagliptin with regard to the risk of developing a confirmed1 event in

the primary

CV composite endpoint. (Criteria for determining non-inferiority can be found

in the

Statistical Methods Section, Section 8.3).

Hypothesis b:

If hypothesis a is satisfied: Sitagliptin, when used as part of usual care, is superior to usual care without sitagliptin with regard to the risk of developing a confirmed event in the primary CV composite endpoint. (Criteria for determining superiority can be found in Section 8.3)

Secondary outcome

To compare the impact of including sitagliptin as part of usual care vs. usual care without sitagliptin on:

(1) A secondary composite CV endpoint of CV-related death, nonfatal MI, and nonfatal stroke.

(2) Each of the components of the primary composite endpoint (i.e., confirmed CVrelated death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization).

(3) All-cause mortality.

(4) Hospital admissions for congestive heart failure as reported by the investigator.

(5) Change from baseline in HbA1c over time.

(6) Change in renal function (based on estimated glomerular filtration rate [eGFR] using the Modification of Diet in Renal Disease [MDRD] method) and albuminuria (based on urinary albumin to creatinine ratio) over time.

(7) Time to initiation of long-term insulin therapy. Long-term insulin therapy is defined as a continuous period of insulin use of more than 3 months.

(8) Time to addition of first co-interventional agent (i.e., next oral AHA or long term insulin, where long-term insulin therapy is defined as a continuous

period of insulin use of more than 3 months).

(9) Medical resource utilization during the trial (e.g., hospitalizations and outpatient physician visits).

Amendment related to Protocol Amendement 3 dd. 05-Sep-2013:

Rationale for this amendment is to update the secondary objective related to the analysis of each of the components of the primary composite endpoint that has been revised to include fatal myocardial infarctions and fatal strokes when analysing the time to these individual categories of events.

For a summary/list of changes made to the previous version/edition kindly refer to Summary of Changes section in the protocol document (page 5).

Study description

Background summary

Patients with type 2 diabetes mellitus (T2DM) have high rates of vascular disease involving the coronary, cerebral, and peripheral arteries. The potential impact of T2DM treatment regimens on cardiovascular (CV) outcomes is a key consideration in long-term treatment of the disease. Several studies have assessed CV outcomes associated with various antihyperglycemic therapies, but no trials to date have shown definitively that lowering glucose levels reduces macrovascular risk.

In light of the above, and the well known fact that the majority of patients with T2DM die of CV disease, it is clearly important to assess the impact of any antihyperglycemic regimen on CV event rates in a long-term outcomes trial. The current study is a randomized, double-blind, placebo-controlled trial designed to assess the impact of sitagliptin therapy on cardiovascular event rates when used as part of a usual care regimen.

Study objective

To compare the impact of adding sitagliptin to usual care vs. usual care

without sitagliptin with regard to the risk of developing cardiovascular events.

Study design

Integrated study design with no interruption in usual care. Sitagliptin/Placebo will be added to the ongoing care regimen.
Patients need to be on stable doses of
* metformin, pioglitazone, or a sulfonylurea as monotherapy or any dual combination of metformin, pioglitazone, or a sulfonylurea continuously without alteration in dose for at least 3 months
Note: Patients who have received insulin for only a short period (i.e., less than 14 days) during a hospitalization or for the management of acute illness will not be excluded for that reason.
OR
* a stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months. The use of supplemental/sliding scale insulin during the prior three months is permissible, as long as the total daily insulin dose is within ±20% of the scheduled total daily insulin dose.
Note: Patients who have required modification of their usual insulin daily dose for a short period (i.e., less than 14 days) during a hospitalization or for the management of acute illness will not be excluded for that reason.

Intervention

Treatment 1:
Sitagliptin tablet taken orally once daily in the morning.

Treatment 2:
Matching placebo tablet taken orally once daily in the morning.

Both groups will undergo a venipuncture 7 times.

Study burden and risks

Drawing blood is a routine procedure which may cause tempory discomfort or slight bruising at the site of blood dwaing or fainting.
The blood pressure cuff may cause discomfort or bruising of the upper arm.

Contacts

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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

a. Patient has T2DM with HbA1c of * 6.5% (48 mmol/mol) and * 8.0% (64 mmol/mol) (HbA1c must be documented within 3 months prior to study enrollment) while receiving metformin, pioglitazone, or a sulfonylurea as monotherapy or any dual combination of metformin, pioglitazone, or a sulfonylurea continuously without alteration in dose for at least 3 months OR a stable dose of insulin (±20% of the scheduled total daily insulin dose) either alone or in combination with a stable dose of metformin for at least 3 months;b. Patient is able to see a usual care provider at least twice a year;c. Patient is * 50 years of age with preexisting vascular disease, defined as having any one of the following:;c.1 History of a major clinical manifestation of coronary artery disease (i.e., myocardial infarction, surgical or percutaneous [balloon and/or stent] coronary revascularization procedure, or coronary angiography showing at least one stenosis * 50% in a major epicardial artery or branch vessel);;c.2 Ischemic cerebrovascular disease, including:;c.2.1 History of ischemic stroke. Strokes not known to be hemorrhagic will be allowed as part of this criterion;;c.2.2 History of carotid arterial disease as documented by * 50 % stenosis documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography, with or without symptoms of neurologic deficit.;c.3 Atherosclerotic peripheral arterial disease, as documented by objective evidence such as amputation due to vascular disease, current symptoms of intermittent claudication confirmed by an ankle-brachial pressure index or toe brachial pressure index less than 0.9 or

history of surgical or percutaneous revascularization procedure.;d. Female patients agree to use an effective method of contraception or must not otherwise be at risk of becoming pregnant.;e. Patient understands the study procedures, alternative treatments available, and the risks involved with the study, and voluntarily agrees to participate by providing written informed consent.;f. Patient agrees to provide permission to obtain all medical records necessary for complete data ascertainment during the follow-up period.

Exclusion criteria

a. Patient has a history of type 1 diabetes mellitus or a history of ketoacidosis.;b. Patient has a history of *2 episodes of severe hypoglycemia during the 12 months prior to enrollment. Severe hypoglycemia (hypoglycemia requiring assistance) refers to instances in which the patient was sufficiently disoriented or incapacitated as to require help from either another individual or from medical personnel (whether or not this assistance was actually provided).;c. Patient has taken an approved or investigational DPP-4 inhibitor agent (e.g., sitagliptin, alogliptin, saxagliptin, or vildagliptin), or GLP-1 analogue (e.g., exenatide, exenatide LAR, or liraglutide), or a thiazolidinedione other than pioglitazone within the past 3 months.;d. Patient has cirrhosis of the liver, as assessed by medical history.;e. Patient is enrolled in another experimental protocol which involves the use of an investigational drug or device, or an intervention that would interfere with the conduct of the trial.;f. Patient has a planned or anticipated revascularization procedure.;g. Pregnancy or planned pregnancy during the trial period.;h. Patient has medical history that indicates a life expectancy of < 2 years or might limit the individual*s ability to take trial treatments for the duration of the study.;i. Patient has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance which, in the opinion of the investigator or coordinator, might pose a risk to the patient, make participation not in the patient*s best interest, confound the results of the study (e.g., if patient cannot comply with requirements of the study), or interfere with the patient*s participation for the full duration of the study.;j. Patient has an estimated GFR (calculated based on serum creatinine via the MDRD formula) of < 30 mL/min/1.73 m2.;k. Patient has a known allergy or intolerance to sitagliptin.;l. Patient has previously been enrolled in this 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):	03-12-2009
Enrollment:	449
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sitagliptin
Generic name:	Januvia
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-04-2009
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	13-10-2009
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	15-10-2009
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	08-07-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Approved WMO Date:	21-10-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	22-10-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	03-01-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	04-01-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	24-02-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	18-03-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	06-05-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	17-05-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	10-06-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO	

Date:	22-06-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	10-10-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	17-10-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	20-02-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	23-03-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	11-09-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO	

Date:	27-11-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	29-11-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	11-06-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	22-10-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	26-11-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

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	EUCTR2008-006719-20-NL
ClinicalTrials.gov	NCT00790205
CCMO	NL26805.094.09