A Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Saxagliptin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischaemic Stroke in Patients whith Type 2 Diabetes

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Primary objectivesEfficacyThe primary efficacy objective is to determine, as a superiority assessment, whether treatment with saxagliptin compared with placebo when added to current background therapy will result in a reduction in the composite...

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

Summary

ID

NL-OMON36559

Source
ToetsingOnline

Brief title
SAVOR

Condition

- Cardiac disorders, signs and symptoms NEC
- Glucose metabolism disorders (incl diabetes mellitus)
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Bristol-Myers Squibb,farmaceutische industrie

Intervention

Keyword: cardiovascular risk, saxagliptin, Type 2 Diabetes

Outcome measures

Primary outcome

Primary efficacy variable

The primary efficacy outcome variable of the study is defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke (time to first event).

Primary safety variable

The primary safety outcome variable of the study is defined as the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke (time to first event).

Secondary outcome

Secondary efficacy variable

The secondary efficacy variable is the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation.

Secondary safety variables

Secondary safety variables includes overall adverse events and adverse events of special interest. These will include assessment of the long-term effects of saxagliptin on decrease in lymphocyte counts, decrease in thrombocyte counts, severe infections, hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions and renal abnormalities

Study description

Background summary

Cardiovascular disease is the leading cause of death in patients with type 2 diabetes mellitus. More than 60% of all patients with type 2 diabetes mellitus die of cardiovascular disease and an even greater percentage have serious cardiovascular related complications. There are compelling data in patients with type 2 diabetes mellitus supporting a reduced risk of microvascular complications with improved long-term glycaemic control. The ability of glucose lowering to impact cardiovascular outcome is not clear.

The results from the 8 studies in the saxagliptin Phase IIb/III programmes in over 4600 patients combined with the results from clinical pharmacology studies support the oral dose of saxagliptin 5 mg once daily in a wide range of patients with type 2 diabetes mellitus, as either monotherapy, add-on combination therapy with metformin, a thiazolidinedione, or a sulphonylurea, or initial combination therapy with metformin.
Currently none of the available antidiabetic agents are indicated for CV risk reduction in patients with type 2 diabetes mellitus. The Phase IIb/III programme has not only established the efficacy and safety of saxagliptin in lowering glucose levels (as assessed by HbA1c) but also created hypothesis-generating data suggesting fewer occurrences of MACE (Major adverse cardiovascular events). This clinical study will test this hypothesis in a rigorous fashion. The potential results of such a study will be of great benefit to all patients with type 2 diabetes mellitus.

Study objective

Primary objectives

Efficacy
The primary efficacy objective is to determine, as a superiority assessment, whether treatment with saxagliptin compared with placebo when added to current

background therapy will result in a reduction in the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke, in patients with type 2 diabetes mellitus.

Safety
The primary safety objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of the composite endpoint of cardiovascular death, non fatal myocardial infarction or non-fatal ischaemic stroke, in patients with type 2 diabetes mellitus, observed with saxagliptin to that observed in the placebo group is less than 1.3.

Secondary efficacy objective
The secondary efficacy objective is to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in patients with type 2 diabetes mellitus will result in a reduction of the composite endpoint of cardiovascular death, non fatal myocardial infarction, non-fatal ischaemic stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris or hospitalisation for coronary revascularisation.

Secondary safety objectives
Safety and tolerability will be evaluated by assessment of overall adverse events and adverse events of special interest. These will include assessment of the long-term effects of saxagliptin on decrease in lymphocyte counts, decrease in thrombocyte counts, severe infections, hypersensitivity reactions, liver abnormalities, bone fractures, pancreatitis, skin reactions and renal abnormalities.

Study design

This is a multicentre, randomised, double-blind, placebo-controlled Phase IV study to evaluate whether treatment with saxagliptin can reduce the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke in patients with T2DM and to definitively exclude unacceptable CV toxicity. The anticipated duration of the study is approximately 5 years, including an anticipated enrolment period of 2 years and follow-up period of 3 years. However, the duration of the trial will be based on accrual of the predetermined number of events, and therefore the study may be shorter or longer.

Intervention

Patients meeting all eligibility criteria will be randomised (1:1) to receive either saxagliptin or placebo. Active treatment will comprise the doses of 5 and 2.5 mg based upon a patient*s renal function. Patients with a estimated GFR >50 mL/min will be randomised to receive 5 mg saxagliptin or placebo and

patients with a estimated GFR *50 mL/min will be randomised to receive 2.5 mg saxagliptin or placebo. Saxagliptin is administered orally, once daily.
Matching placebo, as described above, will be used as comparator.

Patients will return every 6 months for assessment of events related to the objectives of the study, tolerability and safety. Assessment of treatment compliance and provision of study drug will be done at these 6 month visits.
In addition, phone contacts will be performed at a 3 month interval in between regular visits.

Study burden and risks

The study medication may cause some side effects. The taking of a blood sample may cause some discomfort.
It is hoped that saxagliptin treatment will help reducing the risk of experiencing a cardiovascular event. The information we get from this study may help to treat future patients with type 2 diabetes better.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-age * 40 years
-diagnosed with T2DM based on the current ADA guidelines
-HbA1c *6.5%
-high risk for a CV event defined as having either established CV disease and/or multiple risk factors

Exclusion criteria

-current or previous (within 6 months) treatment with an incretin-based therapy such as DPP4 inhibitors and or GLP-1 mimetics
-acute vascular (cardiac or stroke) event < 2 months prior to randomisation
-initiation of chronic dialysis and/or renal transplant and/or serum creatinine >6.0 mg/dL (> 530 µmol/L)
-pregnant or breast-feeding patients

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2010
Enrollment:	600
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Onglyza
Generic name:	saxagliptin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-05-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-09-2010
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:	24-01-2011

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:	17-04-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-04-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2011
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:	12-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2012
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:	31-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2012
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	EUCTR2009-017358-10-NL
CCMO	NL31366.018.10