A multicenter, international, randomized, parallel group, double-blind, placebo-controlled, cardiovascular safety and renal microvascular outcome study with linagliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA

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

Summary

ID

NL-OMON44703

Source
ToetsingOnline

Brief title
CARMELINA

Condition

- Diabetic complications

Synonym
Diabetes T2DM

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim International GmbH

Intervention

Keyword: Cardiovascular risk, Linagliptine, Type 2 Diabetes Mellitus

Outcome measures

Primary outcome

The primary endpoint in this trial is time to the first occurence of any of the

following by adjudication confirmed components of the primary composite

endpoint (3-point MACE): CV death, non-fatal MI or non fatal stroke.

Secondary outcome

Time to first occurance of any of the following by adjudication confirmed

components: Composite renal endpoint (renal death,

sustained end stage renal disease [ESRD], sustained decrease of 40% or more in

eGFR

Study description

Background summary

The DPP-4 inhibitor compound linagliptin was discovered by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. Linagliptin is a potent inhibitor of DPP-4 activity and prolongs the half-life of GLP-1. Its efficacy and safety are well-known through extensive data collection. The aim of the present study is to investigate the long*term impact on CV morbidity and mortality of treatment with linagliptin in a selected population of patients with T2DM and compare outcomes against placebo, on a background of standard of care. To date, this

has not been tested in long-term trials of linagliptin.

Study objective

The primary objective is to demonstrate non-inferiority (by means of comparing the upper limit of a two-sided 95% confidence interval with the non-inferiority margin of 1.3) of treatment with linagliptin in comparison to placebo (as add-on therapy on top of standard of care) with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint (i.e. cardiovascular (CV) death
[including fatal stroke, fatal MI and sudden death], non-fatal stroke, non-fatal myocardial infarction (MI) (excluding silent MI) and hospitalisation for unstable angina pectoris) in patients with type 2 diabetes mellitus (T2DM). If non-inferiority has been demonstrated, then the primary composite endpoint will be tested for superiority and the other objective, to assess the impact of treatment with respect to the composite renal endpoint (i.e. renal death, sustained end-stage renal disease (ESRD), sustained loss in estimated global filtration rate (eGFR) * 50% from baseline), will be investigated separately with a test on superiority.

Study design

This randomized, double-blind, placebo controlled, parallel group study compares treatment with linagliptin (5 mg once daily) to treatment with placebo (matching tablets once daily) as add-on therapy to standard of care.

Intervention

Treatment with linagliptin (5 mg once daily) or placebo treatment (matching tablets once daily) as add-on
therapy to standard antidiabetic treatment.

Study burden and risks

Potential general benefits for study participants in this trial irrespective of investigational drug received are 1) improvements in glycaemic control, 2) improvements of other CV risk factors and 3) general medical benefit from careful and close monitoring by medical
personnel and home blood glucose monitoring during the study. General risks associated with participating are related to trial specific procedures such as blood sampling that can be associated with bruising and pain. The amount of blood taken during the whole course of the trial is not believed to be associated with any discomfort for the patients.

Linagliptin from its clinical phase III testing has shown a safety profile similar to placebo. It carries a low risk for inducing hypoglycaemia and is

generally weight neutral. Safety will be ensured by monitoring the patients for AEs both clinically and by laboratory testing. If any investigator should have a clinical concern, the safety of the patients will be of paramount importance. Given the large safety margin derived from the toxicology studies, the wide therapeutic window of linagliptin (120-fold recommended clinical dose), the high tolerability observed in previous trials in subjects with T2DM, and the monitoring throughout the trial the sponsor is of the opinion that the risks for the participating patients are minimal and justified.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Documented diagnosis of T2DM before visit 1(screening).

2) Male or female patients who are drug-naïve or pre-treated with any antidiabetic background medication, excluding treatment with GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors if * 7 days.
3) Stable antidiabetic background medication (unchanged daily dose) for at least 8 weeks prior to randomization. If insulin is part of the background therapy, the average daily insulin dose should not have changed by more than 10% within the 8 weeks prior to randomization compared with the daily insulin dose at randomization.
4) HbA1c of * 6.5% and * 10.0% at Visit 1 (screening)
5) Age * 18 years at Visit 1(screening).
6) Body Mass Index (BMI) < of gelijk aan 45 kg/m2 at Visit 1 (screening)
7) Signed and dated written informed consent by date of Visit 1(screening) in accordance with Good Clinical Practice (GCP) and local legislation prior to any study related procedure
8) High risk of CV events

Exclusion criteria

1) Type 1 diabetes mellitus.
2) Treatment (=> 7 consecutive days) with GLP-1 receptor agonists, other DPP-4 inhibitors or SGLT-2 inhibitors prior to informed consent. Note: This also includes clinical trials where these antidiabetic drugs have been provided to the patient.
3) Active liver disease or impaired hepatic function, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase (AP) =>; 3 x upper limit of normal (ULN) as determined at Visit 1.
4) eGFR <15 ml/min 1.73 m2 (severe renal impairment or ESRD, MDRD formula), as determined during screening at Visit 1 and/or the need for maintenance dialysis.
5) Any previous (or planned within next 12 months) bariatric surgery (open or laparascopic) or intervention (gastric sleeve).
6) Pre-planned coronary artery re-vascularisation (PCI, CABG) or any previous PCI and/or CABG <= 2 months prior informed consent

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:	Recruitment stopped
Start date (anticipated):	27-08-2014
Enrollment:	165
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Trajenta
Generic name:	Linagliptin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	25-07-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	28-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	28-05-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	27-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-06-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-08-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-11-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-09-2016

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-04-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2011-004148-23-NL
ClinicalTrials.gov	NCT01897532
CCMO	NL44998.068.13