

# 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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<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Diabetic complications
<b>Study type</b>	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 occurrence 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 occurrence 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

### Public

Boehringer Ingelheim

Binger Stra e 173  
Ingelheim am Rhein 55216  
DE

### Scientific

Boehringer Ingelheim

Binger Stra e 173  
Ingelheim am Rhein 55216  
DE

## 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).

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- 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/m<sup>2</sup> 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 m<sup>2</sup> (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 laparoscopic) 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