A multicentre, international, randomised, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The CAROLINA Trial.

Published: 05-10-2010
Last updated: 04-05-2024

CAROLINA studyThe aim of the present study is to investigate the long*term impact on CV morbidity and mortality and relevant efficacy parameters (HbA1c, fasting plasma glucose, treatment sustainability) of treatment with linagliptin in a relevant...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON43615

Source
ToetsingOnline

Brief title
CAROLINA

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Diabetes mellitus type 2

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cardiovascular risk, DDP-4 inhibitor, Diabetes Mellitus Type II, Linagliptin

Outcome measures

Primary outcome

CAROLINA study

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 glimepiride (as monotherapy or as add-on therapy) with respect to time to first occurrence of any of the adjudicated components of the primary composite endpoint (i.e. cardiovascular
death, non-fatal stroke and non-fatal myocardial infarction) in patients with type 2 diabetes mellitus.
If the noninferiority hypothesis with margin 1.3 has revealed a significant result, then secondly, the primary composite endpoint will be tested with a superiority hypothesis.
If the superiority test has revealed a significant result, then thirdly the first key secondary endpoint will be tested hierarchically. If the test of the first key secondary hypothesis has revealed a significant result, then fourthly

the second key secondary endpoint will be tested hierarchically.

See also section 2.2 of the protocol.

Continuous Glucose Monitoring substudy of CAROLINA

The primary end-point of this sub-study will be the degree to which these medications mimic normal glycemic patterns represented by ambulatory glucose profile (AGP) analysis captured using continuous glucose monitoring (CGM), and expressed as glucose variability.

See also page 7 of the substudy protocol.

Cognition II substudy of CAROLINA

The CAROLINA Cognition study II will address the following primary research questions:

1. Does Linagliptin improve cognitive performance (primary end-points mental flexibility and psychomotor speed) relative to Glimepiride from baseline till 32 weeks?

2. Is such an improvement of cognitive performance by Linagliptin relative to Glimepiride at 32 weeks maintained during follow up?

See also page 11 of the substudy protocol.

Secondary outcome

CAROLINA study

The key secondary efficacy endpoints are:

* composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c * 7.0%) without need for rescue medication (between end of titration [Visit 6] and Final Visit) and patients without any moderate/severe hypoglycaemic episodes (between Visit 6 and Final Visit) and without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))

* composite endpoint of (treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycaemic control (HbA1c * 7.0%) without need for rescue medication (between Visit 6 and Final Visit) and patients without > 2% weight gain at Final Visit (between Visit 6 and Final Visit))

Additionally secondary efficacy endpoints are the change from baseline of HbA1c, FPG, proportion of patients that at Final Visit maintain glycaemic control without need for rescue medication (between end of titration [Visit 6] and Final Visit) to obtain HbA1c * 7.0% or that obtain HbA1c * 7.0% overall.

See also section 5.1 of the protocol.

Continuous Glucose Monitoring substudy of CAROLINA

Secondary end-points will include glucose exposure and stability, impact on other parameters of glycemic variability; i.e. the mean amplitude of glycemic excursions (MAGE) and standard deviation (SD) of mean glucose as derived from the CGM as well as from verified home blood glucose monitoring (HBGM).

See also page 8 of the substudy protocol.

Cognition II substudy of CAROLINA

Secondary research questions in the CAROLINA Cognition Sub study II are:
1. Is there a difference in psychological well-being between the Linagliptin and the Glimepiride treated groups after 32 weeks and is this maintained during follow-up?
2. Is there a relation between glycaemic variability and cognitive performance (primary endpoints mental flexibility and psychomotor speed) or psychological well-being?
3. In further exploratory analyses we can address other predictors such inflammatory, oxidative and endothelial function parameters (see flow chart).

See also page 11 of the substudy protocol.

Study description

Background summary

CAROLINA study

T2DM is a chronic metabolic disease defined by elevated glucose levels that is associated with an increased risk for acute and/or late complications related to the micro- and macrovascular circulation. The latter is primarily related to increased athero-thrombosis that leads to increased morbidity and premature mortality from cardiovascular (CV) disease.Studies suggest that 70-75% of all deaths in people with diabetes can be attributed to CV complications. Since hyperglycaemia in itself probably plays a causal role in this, strategies aiming at improving glycaemic control, could contribute in reducing complications and thereby also societies cost.

See also section 1.1 of the protocol.

Continuous Glucose Monitoring substudy of CAROLINA

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia and glucose fluctuations due to inappropriate insulin levels caused by a combination of defects in insulin secretion and action, and incretin dysfunction. Subjects with T2DM are prone to end organ damage due to microvascular and macrovascular changes caused by chronic elevations in glucose levels. Recently, glucose fluctuations have been implicated in the cascade of events that lead to vascular complications, as well as, considered significant contributors to *-cell dysfunction.

See also page 7 of the substudy protocol.

Cognition II substudy of CAROLINA

Cross-sectional studies in non-demented patients with type 2 diabetes (T2DM) consistently show mild to moderate
decrements in cognitive functioning. These decrements are primarily found in learning and memory, speed of information
processing and mental flexibility. It has also been noted that cognitive performance may vary with daily fluctuations in
blood glucose levels and that post-meal glucose fluctuations may relate to

cognitive symptoms and mood. Longitudinal
observational studies however show that for the majority of patients, cognitive decrements do not show a marked decline
over time, that is, only a proportion of these patients show severe cognitive decline that may progress towards dementia.

See also page 7 of the substudy protocol.

Study objective

CAROLINA study

The aim of the present study is to investigate the long*term impact on CV morbidity and mortality and relevant efficacy parameters (HbA1c, fasting plasma glucose, treatment sustainability) of treatment with linagliptin in a relevant population of patients with T2DM and compare outcome against one compound of the second most used OAD class, i.e., SU (glimepiride).

See also section 2.1 of the protocol.

Continuous Glucose Monitoring substudy of CAROLINA

Although a small number of studies have addressed the impact of various pharmacologic treatments on glucose variability, there is a dearth of prospective randomized controlled studies comparing different treatment modalities. Since DPP-IV inhibitors enhance glucose-induced insulin secretion, decrease glucagon secretion, enhance *-cell responsiveness and reduce postprandial glycemic excursions, they may effectively reduce blood glucose variability. This hypothesis will be tested in a sub-study of the CAROLINA trial.

See also page 7 of the substudy protocol.

Cognition II substudy of CAROLINA

In this Cognition sub-study II we will assess:
The ability of the different drug regimens to improve mental flexibility and psychomotor speed and psychological well-being over a short period, i.e. 32 weeks and whether these effects are maintained during follow-up (32 weeks to 6-8 years).

See also page 7 of the substudy protocol.

Study design

CAROLINA study

This randomised, double-blind, parallel groups study compares treatment with linagliptin (5 mg once daily) to treatment with glimepiride (1-4 mg).

The trial is event driven and will run with a minimum of 6000 patients for 432 weeks, beginning with the randomisation of the first patient. In the case the number of events is not or may not be reached within this period the trial duration and/or the number of patients enrolled will be increased until the defined number of adjudicated primary events is reached.

Patients will enter open-label placebo (add-on) run-in period up to 4 weeks before randomisation. Patients who successfully complete at least two weeks of the placebo-run and who still meet the inclusion/exclusion criteria (including treatment compliance between 80% and 120%) will be randomised to receive either linagliptin or glimepiride. Patients who not successfully complete at least two weeks of the placebo run-in, may
continue the placebo run-in phase up to four weeks to meet the compliance.

See also section 3.1 of the protocol.

Continuous Glucose Monitoring substudy of CAROLINA

This research will be undertaken as a six-eight year substudy within the planned CAROLINA trial. The substudy will measure glucose exposure, variability and stability in a sample of 220 patients. These patients will employ continuous glucose monitoring (CGM) to obtain unbiased glucose data in order to ascertain to what degree the two medications differ in terms of alteration of diurnal glycemic patterns. Specifically, diurnal glucose exposure, variability and stability will be measured and compared between and within groups during a two-week baseline period and subsequently for two weeks immediately prior to the 32nd, 64th, 160th, 208th and 256th study weeks as well as for 2 weeks immediately prior to the last study month of the trial (i.e., the 14 days just before the end of the study visit); hence in principle a total of 7 two weeks CGM periods will be registered during the trial.

See also page 8 of the substudy protocol.

Cognition II substudy of CAROLINA

Cognition and well-being will be tested at the beginning of placebo-run-in (for a so called *familiarisation test*), at randomization (visit 2; before drug initiation, this will be the *true baseline*), after 32 weeks, after 160 weeks and at the end of the study, (see flow chart). Treatment will commence at the time of randomization. It is expected that by 32 weeks all patients will have

obtained stable glycemic control.

See also page 9 of the substudy protocol.

Intervention

CAROLINA study

Patients will continue with their antidiabetic background therapy at the same dose throughout the entire study . Patients on previous SU or glinide treatment will discontinue this SU or glinide treatment at Visit 2.

Patients will be randomly assigned to linagliptin 5 mg or glimepiride. Medication will be dispensed in a double-blind and double-dummy manner as either 5 mg linagliptin or an initial dose of 1 mg /day of glimepiride. After the starting dose of 1 mg/day, glimepiride has to be uptitrated to the next dose to a potential maximum dose of 4 mg/day. In 4 weeks intervals during the first 16 weeks of
treatment, glimepiride is to be uptitrated if the fasted HBGM values are > 110 mg/dl (6.1 mmol/L).

Patients on previous glimepiride may continue on their previous glimepiride dose up to V2.

See also section 4.1 of the protocol.

Continuous Glucose Monitoring substudy of CAROLINA

The substudy will be carried out over a period of approximately six-eight years. During this time seven periods of CGM will be conducted. The two-week baseline CGM will be completed immediately prior to randomization to active treatment; the second CGM will be completed during the 2 weeks immediately prior to the 32nd week of treatment. The third to seventh CGM assessments will be conducted, respectively, during the 2 weeks immediately prior to the 64th, 160th, 208th, 256th week and the last month of the study (i.e., the 14 days prior to the study visit). Each CGM period will encompass 14 consecutive days. The 14 days of CGM are ideal as they account for the natural variation due to sleep/wake, eating and activity patterns. To guarantee unbiased data, CGM real time values will be blinded to the patient. To assure device accuracy, HBGM will be requested of the patients at least four times each day (using a random time logbook) during CGM usage (also for calibration purposes). In addition, for each of the 14 days of CGM the participating patients will indicate on the CGM device, according to further instruction, when breakfast, lunch and dinner were ingested.

See also page 12 and the flow charts of the substudy protocol.

Cognition II substudy of CAROLINA

Patients participating in the Cognition sub study II will also take part in the CGM substudy [16]. For the cognition part, all tests will be administrated electronically utilising a touch screen. The tests are to be executed at the site of the investigators and the whole test procedure is expected to last approximately 45 minutes.
Participating centres will be trained at the occasion of regional or national study initiation meetings as well as web-based training provided by CANTAB.

See also page 13 of the substudy protocol.

Study burden and risks

CAROLINA study

Considering a treatment period of 7 years and 9 months (32 visits), the burden for patients will be:
- Physical Exam - 11 times
- Urine sampling - 30 times
- Blood sampling - 34 times
- Pregnancy test (if applicable) - 29 times
- Blood pressure and pulse - 33 times
- Length - 1 times
- Weight - 30 times
- Waist circumference - 12 times
- Diet- and exercise counselling - 32 times
- ECG - 11 times
- Questionnaires - 3 times
- HBGM test - visit 1b till 2, at least once a week
- HBGM test - from visit 2 onwards, only with symptoms

Continuous Glucose Monitoring substudy of CAROLINA

- Two-week CGM - 7 times
- HBGM - four times each day during CGM usage
- 8 point HBGM - one time during CGM usage
- Additional blood sampling - 5 times

Cognition II substudy of CAROLINA

Cognition tests - 5 times 45 minutes in total devided in
- CANTAB test including Paired Associate Learning (10 min), Spatial Working memory (8 min), Reaction time (5 min), Rapid Visual Information Processing (7 min), Attention Shifting Test (AST; 7 min)

- Diabetes Symptom Checklist-revised (DSC-r), 34 items
- WHO-5 Well-being Index, 5 items

Contacts

Public
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Scientific
Boehringer Ingelheim

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NL

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 and concurrently 2) insufficient glycaemic control and a high risk of CV events 3) prior to informed consent.;2) Insufficient glycaemic control (at Visit 1a) defined as:;a) HbA1c 6.5 - 8.5% (48 - 69 mmol/mol) while patient is treatment naïve (if intolerant or contraindicated to first line anti-diabetic treatment) or treated with:
- metformin monotherapy, or
- alpha-glucosidase inhibitor monotherapy (e.g. acarbose, voglibose), or
- metformin + alpha-glucosidase inhibitor (e.g. acarbose, voglibose), or;b) HbA1c 6.5 - 7.5% (48 - 58 mmol/mol) while patient is treated with

- sulphonylurea (SU) monotherapy, or
- glinide monotherapy (e.g. repaglinide, nateglinide), or
- metformin + SU (combination maximal up to 5 years), or
- metformin + glinide (combination maximal up to 5 years), or
- sulphonylurea + alpha-glucosidase inhibitor (combination maximal up to 5years), or
- glinide + alpha-glucosidase inhibitor (combination maximal up to 5 years);3) High risk of CV events defined as any one (or more) of A), B), C) or D):;A) Previous Vascular Disease:
- Myocardial infarction (> 6 weeks prior to informed consent)
- Documented coronary artery disease (*50% luminal diameter narrowing of left main coronary artery or * 50% in at least two major coronary arteries in angiogram)
- Percutaneous Coronary Intervention (PCI) > 6 weeks prior informed consent
- Coronary Artery By-pass Grafting (CABG) > 4 years prior to informed consent or with recurrent angina following surgery
- Ischemic or hemorrhagic stroke (> 3 months prior to informed consent)
- Peripheral occlusive arterial disease (previous limb bypass surgery, stenting or percutaneous transluminal angioplasty; previous limb or foot amputation due to circulatory insufficiency, angiographic or ultrasound detected significant vessel stenosis (>50%) of major limb arteries
(common iliac artery, internal iliac artery, external iliac artery, femoral artery, popliteal artery), history of intermittent claudication, with an ankle: arm blood pressure ratio < 0.90 on at least one side).;B) Evidence of vascular related end-organ damage:
- Moderately impaired renal function (as defined by modified diet of renal disease (MDRD) formula) with estimated glomerular filtration rate [eGFRF]) 30-59 mL/min/1.73 m2
- Random spot urinary albumin:creatinine ratio * 30 *g/mg (* 3.4 mg/mmol) in two of three unrelated specimens in previous 12 months prior Visit 1a
- Proliferative retinopathy defined as retinal neovascularisation or previous retinal laser coagulation therapy.;C) Age * 70 years (at Visit 1a);D) At least two of the following CV risk factors:
- Type 2 diabetes mellitus duration > 10 years at Visit 1a.
- Current* systolic blood pressure (SBP) > 140 mmHg (or on at least one blood pressure lowering treatment at Visit 1a)
- Current daily cigarette smoking
- Current* LDL cholesterol * 135 mg/dL (3.5 mmol/lL) (or specific current treatment for this lipid abnormality at Visit 1a).
* Current <= Blood pressure or LDL cholesterol measurement < 6 months
prior V1a.;4) Body Mass Index (BMI) * 45 kg/m2 at Visit 1b.;5) Age * 40 and * 85 years at Visit 1a;6) Signed and dated written informed consent at the latest by the date of Visit 1a, in accordance with GCP and local legislation;7) Stable anti-diabetic background medication (unchanged daily dose) for at least 8 weeks prior V1a and without short term use of insulin. Background medication should be stable during screening/run-in phase to allow randomisation.

Exclusion criteria

1) Type 1 diabetes mellitus;2) Any history and/or current treatment with other antidiabetic

drugs (e.g. rosiglitazone, pioglitazone, GLP-1 analogue/agonists, DPP-IV inhibitors or any insulin) prior to informed consent.;3) Treatment with anti-obesity drugs 3 months prior to informed consent;4) Uncontrolled hyperglycaemia with a glucose level >240 mg/dl (>13.3 mmol/L) after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day).;5) Active liver disease or impaired hepatic function, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x upper limit of normal (ULN) as determined at Visit 1a.;6) Any previous (or planned within next 12 months) bariatric surgery (open or laparascopic) or intervention (gastric sleeve);7) Pre-planned coronary artery re-vascularisation (PCI, CABG) within next 6 months after V1a or any previous PCI and/or CABG * 6 weeks prior informed consent;8) Known hypersensitivity or allergy to the investigational product or its excipients, or glimepiride (or the SU class).;9) Inappropriateness of glimepiride treatment for renal safety issues or other issues (e.g. allergy) according to local prescribing information ;10) Congestive heart failure of NYHA class III or IV;11) Acute or chronic metabolic acidosis (present condition in patient history);12) Hereditary galactose intolerance;13) Alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation;14) Current treatment with systemic corticosteroids at time of informed consent or preplanned initiation of such therapy. Note: inhaled use of steroids (e.g. for asthma/COPD) is no exclusion criterion, as this does not cause systemic steroid action.;15) Change in dose of thyroid hormones within 6 weeks prior informed consent;16) Participation in another trial with an investigational drug given within 2 months prior to informed consent;17) Pre-menopausal women (last menstruation * 1 year prior to informed consent) who:
- are nursing or pregnant,
- or are of child-bearing potential and are not practicing an acceptable method of birth control (acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems (IUDs/IUSs), oral, implantable or injectable contraceptives, sexual abstinence (if allowed by local authorities), double barrier method and vasectomised partner) or do not plan to continue using acceptable method of birth control throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial.;18) Patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, has a life expectancy less than 5 years for non-CV causes, or has cancer other than nonmelanoma skin cancer within last 3 years, or has any other condition than mentioned which in the opinion of the investigator, would not allow safe participation in the study;19) Acute coronary syndrome * 6 weeks prior to informed consent;20) Stroke or TIA * 3 months prior to informed consent

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-12-2010
Enrollment:	210
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Amaryl
Generic name:	glimepiride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Trajenta
Generic name:	linagliptin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-10-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2010
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:	14-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2018
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	EUCTR2009-013157-15-NL
ClinicalTrials.gov	NCT01243424
CCMO	NL33817.018.10