A randomized, double-blind, placebo-controlled, parallel-group study to determine whether, in patients with type 2 diabetes at high risk for cardiovascular and renal events, aliskiren, on top of conventional treatment, reduces cardiovascular and renal morbidity and mortality

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

Summary

ID

NL-OMON37199

Source
ToetsingOnline

Brief title
Aliskiren Trial In Type 2 diabetes with cardio-renal Endpoints

Condition

- Cardiac disorders, signs and symptoms NEC
- Diabetic complications

- Nephropathies

Synonym
cardiovascular and renal events in patients with diabetes type 2

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutisch industrie

Intervention

Keyword: aliskiren, cardiovascular, diabetes II, renal

Outcome measures

Primary outcome

Time to the first event of the primary composite endpoint consisting of cardiovascular death, resuscitated sudden death, non-fatal MI, non-fatal stroke, unplanned hospitalization for heart failure, onset of end stage renal disease, renal death, and doubling of serum creatinine concentration from baseline, sustained for at least one month.

Secondary outcome

- Time to first onset of cardiovascular complications, defined as the first event of the following composite endpoint: cardiovascular death, resuscitated sudden death, non-fatal MI, non-fatal stroke, and unplanned hospitalization for heart failure.

- Time to first onset of renal complications, defined as the first even of the following composite endpoint: doubling of baseline serum creatinin concentration sustained for at least one month, onset of end stage renal

disease and renal death.

Study description

Background summary

In this study, aliskiren is investigated on top of conventional treatment in patients with type II diabetes. Aliskiren is a new drug, a renin antagonist. Aliskiren blocks renin (a peptide) in one of the body's systems regulating the blood pressure, the renin-angiotensin-aldosteron system, or RAAS. By blocking renine, aliskiren may delay or prevent cardiovascular and renal complications. This is investigated in this phase III study.

Examples of cardiovascular and renal complications which are investigated in this study are MI, stroke, unplanned hospitalization for heart failure, doubling of baseline serum creatinin concentration and renal failure

Study objective

The purpose of this study is to determine whether, in patients with type II diabetes at high risk for cardiovascular and/or renal events, aliskiren at a target dose of 300 mg o.d. compared to placebo, on top of conventional treatment, reduces cardiovascular and renal morbidity and mortality.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, two-arm, long-term morbidity and mortalility study that comprises 2 study phases:

Phase 1, pre-randomization period (4-12 weeks): during the 4-12 weeks screening period the patient's eligibility for randomization into the trial will be evaluated. The patient should be on conventional therapy according to the national guidelines and concomitant treatment must include an ACEI or an ARB. If this is not already the case at Visit 1, the first 4 weeks of the screening period should be used to stabilize the patient on the forementioned therapy. Investigators should strive to achieve a blood pressure target 135/85 mmHg or less. Patients' antihypertensive treatment must be stable for at least 4 weeks prior to randomization.

Phase 2, double-blind study treatment period: at randomization, patients who fulfill all eligibility criteria will be randomized to receive aliskiren 150 mg o.d. or placebo on top of their conventional treatment. 4 weeks after randomization, patients will be uptitrated to aliskiren target dose of 300mg o.d. or placebo. Patients can be downtitrated to aliskiren 150 mg o.d. or placebo at any time of the study in case of intolerance or other reasons. Throughout the trial investigators should strive to achieve a blood pressure target of 135/85 mmHg or less.

The study will continue until 1620 patients have reached a primary endpoint. Total follow-up is estimated to be four years.

Intervention

Patients are treated in two treatment groups. Depending on the group, patients will receive:

Aliskiren: week 1-4, 150 mg o.d.; week 5- study end, 300 mg o.d.

Placebo: week 1- 4, placebo o.d. matching aliskiren 150mg; week 5-study end, placebo o.d. matching aliskiren 300mg

Study burden and risks

Tests performed during the study are all standard medical tests.

Burden: at least 23-25 visits to the clinic; at least 23-25x blood collection (if study gets extended these numbers become higher)

Risks:
In general, aliskiren is well tolerated. The following side effects of aliskiren have been reported in research studies to date.
Hyperkalemia and minor increases in blood urea nitrogen or serum creatinin (in < 7% of the patients)
Gastro-intestinal side effects (diarrhea, abdominal pain, indigestion, nausea, acid regurgitation, heartbrun), cough, rash, headache, inflammation of the nasal passage, dizziness, fatigue, upper respiratory tract infection, back pain, increase in creatinin kinase (in < 3% of the patients)
Elevated uric acid values, gout and renal stones, small decreases in hemoglobin and hematocrit values (leading to anemia in some cases), angiodema, hypotension, tonic-clonic seizures with loss of consciousness (in <1% of the patients)

The risks of taking blood may include pain and/or bruising, or fainting. In rare cases, there may be a small blood clot or infection at the site of the

needle puncture.

The cuff of the 24-hours blood pressure device may cause an unpleasant feeling, feeling of pressure or bruising.

Contacts

Public
Novartis

Raapopseweg 1
6824 DP
NL
Scientific
Novartis

Raapopseweg 1
6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion criteria at visit 1:
1. Patients with type 2 diabetes.
2. Male or female patients, at least 35 years of age
3. Patients who provide written informed consent to participate in the study after the purpose and nature of the investigation have been clearly explained to them
Additional inclusion criteria at visit 3:

4. - Persistent macroalbuminuria
- Persistent microalbuminuria and a mean eGFR of at least 30 and less than 60 mL/min/1.73m2
- A history of cardiovascular disease and a mean eGFR of at least 30 and less than 60 mL/min/1.73m2
5. Patient's concomitant treatment must include an ACEI or an ARB. Patient should be on conventional therapy according to the guidelines. Patients must not have had any adjustments to their concomitant antihypertensive therapy for at least four (4) weeks prior to randomization (visit 3).

Exclusion criteria

Patients with any of the following at Visit 1 through 3 will be excluded from participation in the study:
1. Serum potassium > 5.0 mmol/L (at the visit directly preceeding Visit 3). If the investigator has reason to believe the serum potassium result is invalid, one repeat test may be done
2. History of any cardiovascular event (stroke, transient ischemic cerebral attack, MI, instable angina, CABG, PCI, hospitalization due to HF) during the 3 months prior to Visit 1
* If a patient experiences such an event between Visit 1 and randomization at Visit 3, he/she should be withdrawn from the screening phase. If suitable, the patient can be re-screened at a later stage
3. Hypertension (at Visit 3): any patient with a mean sitting systolic blood pressure (msSBP) of at least 135 and less than 170 mmHg or msDBP of at least 85 and less than 110 mmHg unless treated with at least 3 anti-hypertensive medications
4. Hypertension (at Visit 3): Any patient with msSBP of at least 170 mmHg or msDBP of at least 110 mmHg
5. Congestive heart failure NYHA class III or IV
6. Concomitant treatment with two (2) or more renin-angiotensin-aldosterone system blocking agents apart from the study drug, e.g. ACEI, ARB or aldosterone-antagonist or any renin inhibitor
7. Unstable serum creatinine: defined as equal to or more than 20% difference between 2 consecutive serum creatinine measurements before Visit 3. A maximum of 4 measurements will be allowed. If the difference between the first two measurements is equal to or more than 20% of the higher value, a third measurement should be performed at the next visit. If the difference between the last 2 measurements is equal to or more than 20% of the higher value, a fourth measurement should be performed at the next visit. If the difference between the last two measurements performed is equal to or more than 20%, the patient is excluded
8. Second or third degree heart block without a pacemaker
9. Concurrent potentially life threatening arrhythmia or other uncontrolled arrhythmia
10. Clinically significant valvular disease
11. Known renal artery stenosis
12. Type I diabetes mellitus (defined as onset of disease before the age of 35 and need of permanent insulin treatment within one year of diagnosis)
For other general exclusion criteria, see study protocol pages 26/27

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):	10-10-2007
Enrollment:	350
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet geregistreerd voor de te bestuderen indicatie
Generic name:	aliskiren

Ethics review

Approved WMO Date:	18-06-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	29-11-2007
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-01-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-04-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-10-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2009

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-03-2009
Application type:	Amendment
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Approved WMO Date:	16-04-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-04-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-10-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-11-2009
Application type:	Amendment
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Approved WMO Date:	11-11-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	12-10-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-10-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-08-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-09-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-09-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2012
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-02-2014
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2007-000860-25-NL
ClinicalTrials.gov	NCT00549757
CCMO	NL17684.003.07