Perindopril arginine/Amlodipine versus Valsartan/Amlodipine antihypertensive startegies: Efficacy and safety in mild to moderate hypertensive patients. A randomised, double blind 6-month study followed by 8-month open label long-term follow-up with Perindopril arginine/Amlodipine.

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To assess the efficacy of blood pressure lowering and the safety of increasing doses of perindopril and amlodipine combination and to compare them to another validated antihypertensive strategy using valsartan and valsartan combined to amlodipine.

Ethical review	Approved WMO
Status	Pending
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON34436

Source
ToetsingOnline

Brief title
Efficacy/safety of Perindoprilarg./Amlodipine versus Valsartan/Amlodipine

Condition

- Vascular hypertensive disorders

Synonym
arterial hypertension, high blood pressure

Research involving
Human

Sponsors and support

Primary sponsor: Servier R&D Benelux
Source(s) of monetary or material Support: Institut de Recherches Internationales Servier

Intervention

Keyword: Hypertension, Perindopril+Amlodipine, Treatment strategy

Outcome measures

Primary outcome

Primary efficacy end point

Mean change from baseline to M3 of supine systolic BP measured at trough in the

investigator*s office using an automatic validated device.

Primary Safety End Points

* Emergent Adverse Events occurring during the double blind period of the study

(until M6)

* Leg oedema assessment by the investigator

* Clinically significant orthostatic hypotension evaluation

* Clinically significant biochemical and haematological abnormalities

Secondary outcome

Office blood pressure

Mean changes from baseline in:

- Mean Supine Diastolic blood pressure

- Controlled blood pressure

- Response rate to treatment

Definitions are provided in section 11 Efficacy measurements.

Ambulatory blood pressure monitoring

Change from baseline for the following parameters:

-mean systolic blood pressure over 24 hours (main ABPM criterion).

Tertiary end points see protocol p26

Study description

Background summary

It is estimated that hypertension affects as many as a billion people worldwide and that each year over 7 million deaths may be attributable to hypertension. Many large randomised intervention trials have shown that blood presssure (BP) lowering over prolonged durations of up to 5 years, using one or more of several drug classes is associated with large and significant reductions in all major cardiovascular endpoints and deaths.
The most recent European and American guidelines have recommended that fixed dose combinations of 2 drugs may be suitable as first line agents for marked BP elevation or high risk patients.

Combination of Perindopril and Amlopdipine (P/A)
S05985, is a combination of perindopril(an ACE inhibitor) and amlodipine (a dihydropyridine calcium channel antagonist) used in the treatment of hypertension. Both drugs have been in common clinical use for treating hypertension in many countries worldwide for more than 15 years.
The fixed combination is a good candidate to improve the benefit risk ratio and to meet the recommended target BP values for more patients.
This drug combination has been developed in a single tablet form and three possible dose combinations will be used in the trial (Perindopril arginine/Amlodipine: 3.5/2.5; 7.0/5 and 14.0/10 mg).

Study comparator

Doses of Valsartan/Amlodipine combinations (V/A)
Valsartan (Angiotensine II Receptor Blocker) is available worldwide and indicated for the treatment of essential hypertension.
The combination of valsartan and amlodipine is available in Europe and in many other countries for the treatment of essential hypertension in 3 doses (80/5, 160/5, 160/10mg).
The combination and up-titration steps used in the trial are 80/0, 160/0, 160/5 and 160/10mg.

Study objective

To assess the efficacy of blood pressure lowering and the safety of increasing doses of perindopril and amlodipine combination and to compare them to another validated antihypertensive strategy using valsartan and valsartan combined to amlodipine.

Study design

This is a Phase III prospective, international, multicentre, comparative double-blind randomised versus active treatment, study.1.600 mild to moderate hypertensive patients will be enrolled and randomised into one of the treatment strategies. The total duration of the study treatment for the patients will be of 14 months.
The study will be divided into following periods:
- Placebo run-in period of 2 weeks (max 4 weeks)
- M00: patients will randomly receive the starting dose of the P/A or V/A strategy.
- M01, M02, M03: patients with uncontrolled BP will follow a titration scheme with increasing doses step by step, of each treatment strategy until their BP is controlled. Controlled BP is defined as systolic blood pressure (SBP) < 140 Hg and diastolic blood pressure (DBP) < 90mmHg. When controlled BP is achieved, the patient will continue at the same dose. Patients not controlled with the upper dose will receive indapamide 1.5mg slow-release as add on therapy or a higher dose of the valsartan/amlodipine combination according to the treatment strategy arm.
- M06: patients with controlled BP will enter in a open label follow-up period for 8 months, and will only receive the P/A combination at the same step of dose than the one reached at M6 for patients previously receiving P/A strategy or at the equivalent or closest step of dose for patients previously receiving V/A strategy. No up-titration will be allowed during the long-term follow-up period. Patients whose blood pressure becomes uncontrolled during this open label period at 2 consecutive visits or whose SBP/DBP is above 160/100 mmHg (confirmed with 2 measurements within15 days) will be withdrawn from the study.

Intervention

Blood samples will be taken during the study for haematology and biochemistry at selection (+ * GCH test, for non-menopausal women only), M3, M6, M7 (only simplified biochemistry) and M14. Approximately 70 ml blood will be taken in total during the whole trial.
The lab results need to be available before inclusion. An ECG will be performed at selection, M6 and M14. In those centres equipped with ambulatory blood pressure monitoring (ABPM) material, ABPM will be proposed to the patients before M0, M3 and M6 visits.
Two substudies are applicable but not in all centres:
- Home blood pressure monitoring (at all visits, morning and evening, 9 days)
- Applanation tonometry at M0, M3, M6

Study burden and risks

Cfr.E2 and E9

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

Selection
Patients women and men of at least 18 years with BMI*30:
For untreated patients: 150*SBP<180 mmHg and 95mmHg*DBP <110mmHg
For treated patients with no more than2 antihypertensive drugs and who in the investigator*s opinion require a change in medication either because of insufficient efficacy or poor tolerability: SBP <160 mmHg and DBP<100 mmHg.;Inclusion visit
After two weeks placebo run-in period 150*SBP<180 mmHg and 95mmHg*DBP <110mmHg
Tablet compliance *70%and* 130%during placebo period

Exclusion criteria

Selection
Patients treated with more than 2 antihypertensive drugs at the selection visit or treated with Perindopril arginine/Amlodipine or Valsartan/Amlodipine free or fixed combination at the highest available doses (P10/A 10 mg or V160/A10 mg).
History of intolerance with one or several study drugs
Contraindication for using the study drugs
History of acute episode of cerebrovascular disease, acute episode of heart disease alcholism or drug abuse
Secondary hypertension , known symptomatic orthostatic hypotension
Pregnancy, breastfeeding or possibilty to become pregnant during the study;Inclusionvisit
Presence on the selection ECG of ventricular rhytm disorders: twisting spikes, ventricular tachycardia, ventricular extra-systoles (except for isolated occurence) or atrial fibrillation or atrial flutter or other cardiac rhytm disorders leading to important beat-to-beat variations in blood pressure
Positive orthostatic test at inclusion
Selection Laboratory result unavailable
Hyponatraemia (<135 mmol/L) or hypernatraemia (>150 mmol/L), hypokalaemia (<3.5 mmol/L) or hyperkalaemia (>5.8 mmol/L).
Creatinine clearance <30ml/min,using Cockcroft*s formula
ALAT or ASAT upper than 3 times the upper limit of normal laboratory range
Positive pregnancy test (beta GCH) performed at selection visit

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:	Pending
Start date (anticipated):	15-11-2010
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Coveram
Generic name:	perindopril arginine+amlodipine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Diovan
Generic name:	Valsartan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Exforge
Generic name:	Valsartan+amlodipine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fludex
Generic name:	Indapamide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-10-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2013
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	EUCTR2010-020945-28-NL
CCMO	NL33736.018.10