A multi-center, randomized, double-blind, placebo and active controlled, parallel group, dose range study to evaluate the efficacy and safety of LCZ696 comparatively to valsartan, and to evaluate AHU377 to placebo after 8 week treatment in patients with essential hypertension

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The primary objective of this study is to determine the efficacy and safety of different doses of LCZ696 compared to valsartan. In addition, the efficacy and safety of AHU377 as compared to placebo is evaluated.

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

Summary

ID

NL-OMON31167

Source
ToetsingOnline

Brief title
LCZ696, AHU377 and valsartan in patients with essential hypertension

Condition

- Vascular hypertensive disorders

Synonym
hypertension = high blood pressure, increased arterial pressure

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: AHU377, hypertension, LCZ696, valsartan

Outcome measures

Primary outcome

Change in MSDBP (mean sitting diastolic blood pressure) at trough from baseline

(visit 3) to the endpoint visit. For definitions of MSDP and endpoint visit,

please refer to protocol pg 50, paragraph 10.4.1.

Secondary outcome

- Changes in MSDBP and MSSBP at trough from baseline for each dose of studied

drug

- Successful responder rate in MSDBP (< 90 mmHg or a reduction of at least 10

mmHg from baseline) and successful control rate in MSDBP (<90 mmHg) at wk 8;

successful responder rate in MSSBP (<140 mmHg or a reduction of at least 20mmHg

from baseline) and successful control rate in MSSBP (<140 mmHg) at wk 8;

successful control rate in both MSSBP (<140 mmHg) and MSDBP (<90 mmHg) at wk 8

- Changes in 24-hour, daytime and nighttime ambulatory diastolic and systolic

blood pressure from baseline to wk 8.

Study description

Background summary

Despite the available therapeutic options, approximately 70% of patients with high bloodpressure remain not adequately controlled, and hence many preventable strokes, MI, HF and end-stage renal disease occur unnecessarily. Poorly controlled hypertension can be attributed to multiple factors, including inadequate antihypertensive efficacy of the drug(s) used.

LCZ696 is a new, dual-acting pro-drug, consisting of an angiotensin receptor blocker (ARB) and a NEPi (neutral endopeptidase inhibitor, AHU377).

Preclinical and clinical data with LCZ696 demonstrate that LCZ696 adequately blocks angiotensin II receptors and inhibits NEP, resulting in a decrease in blood pressure. Based on these findings, it is hypothesized that LCZ696 should deliver significant clinical benefits to patients suffering from hypertension.

This phase II, dose ranging trial investigates the efficacy and safety of LCZ696 compared to valsartan in patients with hypertension. In addition, the efficacy of the NEPi in LCZ696, AHU377, is evaluated compared to placebo.

Study objective

The primary objective of this study is to determine the efficacy and safety of different doses of LCZ696 compared to valsartan. In addition, the efficacy and safety of AHU377 as compared to placebo is evaluated.

Study design

This is a multi-center, randomized, double-blind, placebo and active controlled, parallel group, dose range phase II study. During the study period, patients visit their study doctor 7 times in 13 weeks.

The study comprises 3 periods: a 4-week wash-out and placebo run-in (screening period), an 8-week randomized, double-blind monotherapy period and a 1-week randomized, placebo-controlled withdrawal period.
After successful completion of the screening period (visit 1-3), on visit 3 patients will be randomized and treated with 1)LCZ696 100mg, or 2)LCZ696 200mg, or 3)LCZ696 400mg (1 wk treatment with LCZ696 200mg followed by 7 wks treatment with LCZ696 400mg), or 4) valsartan 80mg, or 5) valsartan 160mg, or 6) valsartan 320mg (1 wk treatment with valsartan 160mg followed by 7 wks

treatment with valsartan 320mg), or 7) AHU377, or 8) placebo.
After 8 weeks of treatment (visit 3-6), all patients will enter the randomized, placebo-controlled withdrawal period on visit 6 and will continue on 1) the same study treatment as before or 2) placebo for another week until the final visit (visit 7).

Intervention

All patients are on placebo for 2 weeks.

Subsequently, patients are treated with one of the following treatments during 8 weeks, depending on their treatment group: LCZ696 100mg, LCZ696 200mg, LCZ696 400mg, valsartan 80mg, valsartan 160mg, valsartan 320mg, AHU377 200mg, placebo

Finally, during 1 week, patients are treated as during the study or continue on placebo.

Study burden and risks

Burden: 7 visits of about half an hour during 13 weeks; 2 extra visits for patients participating in the 24-hour ABPM substudy; 6x blood collection (incl. biomarkers in 50% of the patients and pharmacokinetics in 50% of the patients); fasting conditions on V1, V3, and V6.

Risks: The information on the possible side effects in humans is limited since only 2 studies in healthy volunteers have been conducted with LCZ696 to date. In these studies in which 88 healthy volunteers participated, receiving up to now single and/or multiple doses from 2 to 600 mg, only a small number of side effects were reported, which were all mild in severity. No serious side effects or unexpected side effects were reported, and no subject was discontinued due to a side effect or an abnormal result in the safety tests.
Up to now, no serious or noteworthy adverse experiences have been reported in clinical research studies with AHU377. In these studies in which so far 144 healthy volunteers participated receiving doses from 10 to 600 mg AHU377, the mild side effects reported were: dizziness, drowsiness, tiredness, and headache. No serious side effects were reported, and none of the effects reported required drug discontinuation.
Valsartan is studied extensively in other clinical trials before it was approved for market. The most commonly reported side effects that occurred more frequently with valsartan compared to placebo were viral infection, fatigue, and abdominal pain. Headache, dizziness, upper respiratory tract infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more more than 1% rate, but at about the same rate with valsartan and placebo. Other potential risk with valsartan include low blood pressure and increases in blood potassium levels. Rare cases of angioedema (swelling of the face and extremities, and difficulty in breathing)

have also been reported with valsartan.

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

For complete list, please refer to the protocol pg 17;- Male or female patients from 18 up to and including 75 years
- Patients with mild-to-moderate uncomplicated essential hypertension, untreated or currently taking antihypertensive therapy (monotherapy or combination therapy of 2 drugs)
-Untreated patients must have an office MSDBP higher than or equal to 95 mmHg at the randomization visit (V3) and the 2 preceding visits (V1 and V2)
-Pretreated patients must have an office MSDBP higher than or equal to 90 mmHg after washout (V2), and a MSDBP higher than or equal to 95 mmHg at baseline (V3)

Exclusion criteria

For complete list, please refer to protocol pg 17/18;-Severe hypertension (MSSBP equal to or higher than 180 mmHg and/or MSDBP equal to or higher than 110 mmHG)
- Known or suspected contraindications, including history of allergy to ARBs, NEPis or to drugs with a similar chemical structure
- History of angiodema, drug-related or otherwise, as reported by the patient
-Type 1 or Type 2 diabetes mellitus (according to the ADA criteria)
- History or evidence of a secondary form of hypertension, such as renal parenchymal hypertension, renovascular hypertension, coarctation of the aorta, primary hyperaldosteronism, Cushing's disease, drug-induced hypertension, unilateral or bilateral renal artery stenosis, pheochromocytoma, polycystic kidney disease (PKD), etc.
- History of angina pectoris, myocardial infarction, coronary bypass surgery, ischemic heart disease, surgical or percutaneous arterial intervention of any kind (coronary, carotid or peripheral intervention), stroke, TIA, carotid artery stenosis, aortic aneurysm or peripheral arterial disease
- Women of child-bearing potential, unless they are post-menopausal or use predefined acceptable methods of contraception

Study design

Design

Study phase:	2
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):	28-09-2007
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diovan
Generic name:	valsartan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n.v.t., niet geregistreerd
Generic name:	AHU377
Product type:	Medicine
Brand name:	n.v.t., niet geregistreerd
Generic name:	LCZ696

Ethics review

Approved WMO Date:	08-08-2007
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	04-10-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	04-10-2007
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	18-10-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	29-03-2008

Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	31-03-2008
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	EUCTR2007-001360-76-NL
CCMO	NL18934.003.07