A randomized, sponsor open, site and subject double blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of LHW090 after 4 weeks treatment in patients with resistant hypertension

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

Summary

ID

NL-OMON43264

Source
ToetsingOnline

Brief title
CLHW090X2202

Condition

- Vascular hypertensive disorders

Synonym
resistant hypertension / difficult-to-treat hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor / verrichter van dit onderzoek)

Intervention

Keyword: efficay, LHW090, resistant hypertension, safety

Outcome measures

Primary outcome

The primary efficacy variable will be the change in the 12 hour average of

systolic blood pressure measured by ambulatory blood pressure monitoring (ABPM)

28 days following the start of treatment.

Safety endpoints (adverse events, serious adverse events) up to and including

end of study assessments

Secondary outcome

PK parameters on Day 28 (Cmax, Tmax, AUClast, AUC0-t)

Study description

Background summary

The adequate and timely control of blood pressure in patients diagnosed with hypertension is an important public health goal. Hypertension is a major risk factor for heart disease, kidney disease and stroke. Patients with resistant hypertension are even more likely to display the sequelae of uncontrolled hypertension such as an enlarged heart or kidney damage.

Clinically, NEP inhibitors given in combination with an angiotensin receptor blocker (ARB) have been shown to reduce blood pressure in patients with essential hypertension (Bavishi et al 2015). NEP inhibition in combination with an ARB may represent an attractive therapeutic option for patients with

resistant hypertension.

LHW090 is an orally administered prodrug, which upon ester hydrolysis is metabolized to LHV527, a highly potent and specific inhibitor of NEP. LHW090 was safe and well-tolerated when administered to healthy subjects and subjects with baseline chronic renal insufficiency.

Study objective

The purpose of the current study is to determine whether LHW090 displays the clinical safety and efficacy profile to support further development for resistant hypertension.

Study design

This is a non-confirmatory, randomized, sponsor open, site and subject blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of 4 weeks treatment with LHW090 in patients with resistant hypertension.

Patients with resistant hypertension will be randomized to either placebo or 1 of 2 dose regimens of LHW090, i.e. LHW090 100 mg once daily or LHW090 200 mg once daily, as an add-on to their anti-hypertensive regimen at baseline.

Each subject will participate in an up to 3 week screening period, a 2-week single blind placebo run-in period, baseline assessments, a 4 week treatment period, and an end of study assessment. At the end of this run-in period, patients who demonstrate >= 80% compliance with placebo will be randomized.

On Day -2, patients will commence 24 hour ABPM monitoring and return the next day (Day -1) to have the ABPM device removed and the data collected. Upon collection of satisfactory baseline ABPM assessment, subjects will then return for baseline pharmacodynamic assessments on Day -1 and then begin active treatment on Day 1. Patients will be randomized to either:
• LHW090 100 mg once daily for 28 days
• LHW090 200 mg once daily for 28 days
• Matching placebo for 28 days

Subjects will then be monitored for at least 8 hours for vital signs, PK and PD assessments. If, in the opinion of the Investigator, the patient is stable for discharge, the patient will be discharged after this monitoring period. Subjects will return on Day 3 for vital sign and physical examination. Subjects will then visit the clinic at weekly intervals (Day 7, 14 and 21) for safety, PK, and PD assessments. On visit days, subjects will be instructed to take their medications at the site. On Day 27, patients will commence a final 24 hour ABPM assessment and then return the next day to have the device removed and then begin collection of Day 28 steady-state PK and PD assessments.

Patients will be asked to return after approximately 1 week for end of study (EOS) assessments.

Intervention

medication (double blind) in addition of patients' own anti-hypertensive medication

Study burden and risks

Disadvantages of participation for the patient could be the chance on side effects of LHW090 and burden of the study assessments.

Possible side effects of the study medicine may include: diarrhea, abdominal pain, dry mouth, nausea, vomiting, dizziness and headache. Possible risks may also include damage to the kidneys and anemia.

The risks of taking blood may include fainting, pain and/or bruising. Rarely, there may be a small blood clot or infection where the needle punctures the skin. The blood pressure cuff may also cause discomfort or bruising of the upper arm.
The blood pressure cuff applied for the ambulatory blood pressure measurement (ABPM) will inflate several times each hour for 24 hours. This can be disturbing.

There are 2 long study visits where the patients need to stay in the hospital for at least 8 hours.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Written informed consent must be obtained before any assessment is performed.
- Male and female patients, age 40 to 85 years inclusive.
- Demonstrating a >= 80% medication compliance rate during the singleblind run-in period.
- Patients with uncontrolled hypertension (here defined as having a daytime systolic BP >= 135 mmHg by ABPM at screening) despite treatment with a stable (at least 1 month) regimen that includes an optimal doses of an ARB plus a diuretic (thiazide or loop) plus at least one class of anti-hypertensive medication.
- Subjects must weigh at least 45 kg to participate in the study and must have a body mass index
(BMI) within the range of 18-40 kg/m2.;See protocol for more details and other inclusion criteria that may apply.

Exclusion criteria

- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 halflives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
- Patients with an estimated GFR <60 ml/min/1.73m2 at screening using the MDRD equation.
- Use of angiotensin converting enzyme inhibitors (ACE-inhibitors).
- History of angioedema, drug related or otherwise, as reported by the patient.
- Clinically significant ECG abnormalities at screening as determined by the Investigator.
- Severe hypertension as defined by an office systolic blood pressure >= 180 mmHg or diastolic blood pressure >=110 mmHg at screening or baseline.
- A history of secondary hypertension of any etiology including but not limited to unilateral or bilateral renal artery stenosis, polycystic kidney disease, coarctation of the aorta, primary hyperaldosteronism, Cushing's disease, pheochromocytoma, and drug-induced

hypertension. If the patient has not been evaluated for secondary HT, investigators are responsible to evaluate all potential secondary causes of hypertension considering clinical history, physical examination, laboratory investigations or other relevant diagnostic measures in accordance with current practices and clinical guidelines before entering the patient into the study.
- Known current significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or significant severe valvular disease (on prior or current echocardiogram).
- History within the previous 6 months of myocardial infarction, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), hypertensive encephalopathy, stroke, or transient ischemic attack (TIA).
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 1 year
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential.
- Sexually active males must use a condom during intercourse while taking drug and for 1 week after stopping study medication and should not father a child in this period.;See protocol for more details and other exclusion criteria that may apply.

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):	07-09-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LHW090
Generic name:	LHW090

Ethics review

Approved WMO Date:	11-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2016
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:	06-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	04-07-2017
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	EUCTR2015-001890-42-NL
ClinicalTrials.gov	NCT02515331
CCMO	NL56779.018.16