A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction (CLCZ696D2301)

Published: 12-08-2014
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The primary objective:To compare LCZ696 to valsartan in reducing the rate of the composite endpoint of cardiovascular death andtotal (first and recurrent) heart failure (HF) hospitalizations, in HF patients (NYHA Class II-IV) with preserved EF (LVEF...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON47866

Source
ToetsingOnline

Brief title
CLCZ696D2301 (PARAGON)

Condition

- Heart failures

Synonym
heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: heart failure, LCZ696, morbidity, mortality

Outcome measures

Primary outcome

Cumulative number of primary composite events of cardiovascular (CV) death and

total (first and recurrent) HF hospitalizations.

Secondary outcome

- Change in KCCQ clinical summary score from baseline to Month 8.

- Change from baseline to Month 8 in New York Heart Association (NYHA)

functional class.

- Time to composite renal endpoint.

- Time to all-cause mortality.

Study description

Background summary

Heart failure (HF) prevalence in Europe ranges between 2 and 3% and between 10 and 20% in the elderly.
Studies in HF with normal ejection fraction (EF) have defined preserved EF (pEF) with a cut-off of 40-50%, with 45% being the most common cut-off. HFpEF accounts for approximately half of HF cases, and is associated with substantial

morbidity and mortality. Compared with HFrEF (HF with reduced EF), patients with HFpEF are older, predominantly female, more likely to have hypertension and atrial fibrillation (AF), and less likely to have coronary artery disease (CAD). Mechanisms implicated in HFpEF include abnormal diastolic function with resultant increase in ventricular filling pressures, increased vascular stiffness, and abnormal systolic function despite preserved EF. Recently, these individuals have also been shown to have an impaired natriuretic and renal endocrine response to acute volume expansion early in the development. Unlike HFrEF, no pharmacologic therapies have shown benefit in HFpEF. Current guidelines focus on treating co-morbid conditions, such as diabetes mellitus, hypertension, renal insufficiency, AF and CAD.
LCZ696 is a first-in-class, angiotensin receptor neprilysin inhibitor. Following ingestion, LCZ696 provides systemic exposure to AHU377, a neprilysin (NEP) inhibitor and valsartan, an angiotensin receptor blocker. Prior research had suggested that the potential clinical benefits from NEP inhibition can only be leveraged if the RAS system is inhibited concomitantly. It is anticipated that LCZ696 may provide clinical benefits to patients with CV disease, including HF and hypertension, in which vasoconstriction, volume expansion, and target organ damage play a key role in pathophysiology.
The primary objective of the current study is to compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations, in HF patients (NYHA Class II-IV) with EF *45%.

Study objective

The primary objective:
To compare LCZ696 to valsartan in reducing the rate of the composite endpoint of cardiovascular death and
total (first and recurrent) heart failure (HF) hospitalizations, in HF patients (NYHA Class II-IV) with preserved EF (LVEF *45%). The
treatment arm with the lower rate of events will be deemed as having a successful response.

The secondary objectives:
- Evaluation of the changes in the clinical summary score for HF symptoms and physical limitations (as assessed by Kansas
City Cardiomyopathy Questionnaire [KCCQ]) at 8 months.
- Evaluation of change from baseline to Month 8 in NYHA functional class.
- Evaluation of the time to onset of first composite renal endpoint.
- Evaluation of the time to all cause death.

Study design

Multi-center, randomized, double-blind, parallel group phase III study with active comparator.
Screening period of up to 2 weeks. Single-blind, run-in period 3-8 weeks

(treatment with LCZ696 and valsartan separately).
Thereafter randomization (1:1) to:
1. LCZ696 200 mg bid,
2. Valsartan 160 mg bid.
Back-titration if dose is not tolerated.
Continuation of regular treatment against heart failure (except ACE-, angiotensin - and renin inhibitors)
Event-driven study.
Total study duration estimated at 24-57 months (depending on time point of study start).
Approx 4.600 patients.

Intervention

Treatment with LCZ696 or valsartan.

Study burden and risks

Risk:
Adverse effects of study medication. Change of HF medication.

Burden:
Up to treatment month 1 (5-7 visits):
- physical examination 3x
- vital signs: 3-5x
- blood draw (5-10 ml): 5x
- urine test: 3x
- pregnancy test: 4-6x
- ECG: 3x
- Echocardiogram:1x
- 2 questionnaires: 1 and 2x
- MMSE: 1x

After treatment month 1 (visit every 16 weeks (1st year) to 24 weeks (after 1st year):
- physical examination each visit
- vital signs: each visit
- blood draw (5-10 ml): each visit
- urine test: annually
- pregnancy test: first year 4x, bi-annually thereafter
- ECG: annually
- 2 questionnaires: first year 3x, annually thereafter
- MMSE: annually and at final visit

Optional Biomarker Substudy: Blood- and urine tests, 5x (30 ml in total) combined with other blood draws.

Optional Pharmacogenetic and Pharmacogenomic substudy:
Farmacogenetic: blood test 1x (10 ml)
Farmacogenomic: blood test 2x (13 ml)

Contacts

Public
Novartis Pharma B.V.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- * 55 years of age, male or female.
- Left ventricular ejection fraction (LVEF) *45% by echo during the screening epoch, or within 6 months prior to Visit 1.
- Symptom(s) of heart failure (HF) and requiring treatment with diuretic(s) for HF *30 days prior to Visit 1.
- Current symptom(s) of HF (NYHA Class II-IV) at Visit 1.
- Structural heart disease (left atrial enlargement or left ventricular hypertrophy) documented

by echocardiogram.
- A HF hospitalization within 9 months prior to Visit 1 and/or an elevated NT-proBNP at Visit 1.
- See protocol for details and more inclusion criteria.

Exclusion criteria

- Any prior echocardiographic measurement of LVEF < 40%.
- Acute coronary syndrome (including myocardial infarction (MI)), cardiac surgery, other major cardiovascular surgery within 3 months, or urgent percutaneous coronary intervention (PCI) within 30 days of Visit 1.
- Any clinical event within 6 months that could have reduced the LVEF (e.g., MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be * 45%.
- Current acute decompensated HF requiring therapy.
- Patients who require treatment with 2 or more of the following: angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB) or a renin inhibitor.
- Alternative reason for shortness of breath such as: significant pulmonary disease or severe COPD, hemoglobin (Hgb) <10 g/dl, or body mass index (BMI) > 40 kg/m2.
- Hyper- or hypotension.
- See protocol for details and more exclusion criteria.

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):	22-12-2014
Enrollment:	100

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:	Entresto
Generic name:	sacubitril/valsartan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-08-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-10-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2015

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-04-2019
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-001747-31-NL
ClinicalTrials.gov	NCT01920711
CCMO	NL45785.060.13