A multicenter study to evaluate safety and tolerability in patients with chronic heart failure and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696

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The primary objective of this study is to continue to evaluate the safety and tolerability of LCZ696 in heart failure patients from PARADIGM-HF receiving open-label investigational drug.There are no secondary objectives for this study.

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

Summary

ID

NL-OMON42095

Source
ToetsingOnline

Brief title
CLCZ696B2317 / Open-label Paradigm HF extension

Condition

- Heart failures

Synonym
Heart Failure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: LCZ696, Open-label, safety, tolerability

Outcome measures

Primary outcome

The primary assessments for safety is the reporting of all (S)AEs.

The assessment of safety will be based primarily on the frequency of adverse

events of special interest, sitting systolic and diastolic blood pressure,

heart rate, and serious adverse events suspected by the investigators to be

related to LCZ696.

Secondary outcome

N/A

Study description

Background summary

In Europe, the prevalence of HF is between 2 and 3%, and in the elderly is estimated between 10 to 20%. Medical therapies targeted at improving outcomes in HF with a low EF have been well studied over the past two decades, leading to an improvement in survival as well as a decrease in morbidity, mostly in the form of decreased re-hospitalization for HF. These medical therapies include angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), *-blockers and mineralocorticoid antagonists. However, despite advances in therapies, the outlook remains poor. Overall, 50% of patients die within 4 years and 40% of patients admitted to the hospital with HF die or are readmitted within 1 year. Thus, HF still represents a major cause of cardiac mortality and morbidity with a clear need for better therapy.

LCZ696 is a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI)

being developed for the treatment of heart failure.
The PARADIGM-HF study (protocol CLCZ696B2314) was a randomized, double-blind, Phase III outcome trial that evaluated the efficacy and safety of LCZ696 versus enalapril in 8,436 heart failure patients with reduced ejection fraction. The primary endpoint was time to first occurrence of either cardiovascular (CV) death or heart failure hospitalization, and the trial was also designed to be able to detect a significant
difference in CV death alone.
On March 28, 2014 the Data Monitoring Committee (DMC) for PARADIGM-HF reviewed efficacy and safety data for the third interim analysis with approximately 1,027 CV death events and concluded that LCZ696 was superior to enalapril in delaying the time to first occurrence of the primary composite endpoint and most importantly, in delaying the time to the CV death component as well. Based on these results and an acceptable safety profile, the DMC unanimously recommended early closure of the study, which was agreed by the study Executive Committee and Sponsor of the trial.
In order to provide patients the opportunity to receive life-saving treatment with LCZ696 and to collect safety data, this open-label, safety and tolerability study will offer enrollment to all surviving, eligible patients that had been randomized in PARADIGM-HF.

Study objective

The primary objective of this study is to continue to evaluate the safety and tolerability of LCZ696 in heart failure patients from PARADIGM-HF receiving open-label investigational drug.
There are no secondary objectives for this study.

Study design

This trial is a multicenter, open-label follow-up to PARADIGMHF, which evaluated the morbidity, mortality and safety of LCZ696 compared to enalapril in patients with chronic heart failure and reduced ejection fraction. Prior to enrollment in this trial, all patients will have been enrolled and treated with double-blind study medication in the PARADIGM-HF study and most will have transitioned to an ACEI or ARB. Investigators will be offered the option to initiate open-label treatment with LCZ696 for any PARADIGM-HF patient that meets the eligibility criteria. Consenting patients will undergo a washout period, if necessary (36 hr for patients on ACEIs only), be up-titrated to the maximally tolerated dose of LCZ696 and scheduled for visits to dispense study drug and assess safety and tolerability at 6-month intervals until the conclusion of the trial.

Intervention

Treatment with LCZ696.

Study burden and risks

Burden and risks of participation is the chance of side effects from the study medication and inconveniences of blood sampling.

The known most common side effects of the study medication include: Dizziness, and postural dizziness (get dizzy when you stand up), vertigo, syncope (transient loss of consciousness), headache, cough, diarrhea, and nausea, worsening kidney function, fatigue, feeling of physical weakness, hypersensitivity (such as skin rushes, urticaria, etc.), liver disorder, hypokalemia and hyperkalemia (decreased and increased blood potassium levels, respectively) hypotension, and orthostatic hypotension (lowering of blood pressure when you stand up). Angioedema (localized swelling of the head, neck, throat, tongue, genitalia and/or intestines) have also been reported.

Assessments:
Length: 1x (visit 1)
Weight: Every visit (max 9x).
Physical examination: Every visit (max 9x)
Blood pressure and pulse: Every visit (max 9x)
Urinalysis: 5x (in women, pregnancy)
Blood tests: Each visit (max 9x), including 2 x serum preganancy test in women.

During treatment with LCZ696 there is prohibited medication (such as ACE inhibitors, ARBs and renin inhibitors).

Contacts

Public
Novartis Pharma B.V.

Raapopseweg 1
Arnhem 6824DP
NL
Scientific
Novartis Pharma B.V.

Raapopseweg 1
Arnhem 6824DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Written informed consent for the extension must be obtained before any assessment is performed.
2. Patients who have been enrolled and treated with double-blind study medication in the PARADIGM-HF study (protocol CLCZ696B2314) and are able to be safely enrolled into the open-label trial as judged by the investigator.

Exclusion criteria

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
2. History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to LCZ696.
3. Known history of angioedema.
4. Requirement of simultaneous treatment with both ACEIs and ARBs.
5. Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy).
6. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening).
7. Estimated GFR < 30 mL/min/1.73m2 as measured by the simplified MDRD formula at Visit 1 (screening).
8. Presence of bilateral renal artery stenosis.
9. Serum potassium > 5.2mmol/L at Visit 1 (screening).
10. Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 3 x ULN at Visit 1, history of hepatic encephalopathy, history of esophageal varices, or history of portacaval shunt.
11. Pregnant or nursing (lactating) women.
12. Women of childbearing potential.

13. Any condition, not identified in the protocol, that in the opinion of the investigator is likely to prevent the patient from safely tolerating LCZ696 or complying with the requirements of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-01-2015
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LCZ696
Generic name:	LCZ696

Ethics review

Approved WMO

Date:	04-11-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	09-01-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	24-04-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	19-05-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO
Date: 22-07-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 05-08-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 07-08-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 14-08-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 13-10-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 16-10-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 03-12-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 23-12-2015

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 10-05-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 19-05-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 13-06-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 14-06-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

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	EUCTR2014-001971-30-NL
ClinicalTrials.gov	NCT02226120
CCMO	NL50986.098.14