A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of LCZ696 on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction

Published: 18-10-2017
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The primary objectives of this study are:- To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in reducing NT proBNP from baseline after 12 weeks of treatment in patients with HFpEF.- To demonstrate that LCZ696...

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

Summary

ID

NL-OMON46419

Source
ToetsingOnline

Brief title
CLCZ696D2302 (PARALLAX)

Condition

- Heart failures

Synonym
heartfailure

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: Heart failure, LCZ696, NT-proBNP, preserved ejection fraction

Outcome measures

Primary outcome

- NT-proBNP at Week 12

- Exercise capacity by the six-minute walk test (6MWT) at Week 24

Secondary outcome

- Mean change from baseline in Kansas City Cardiomyophathy Questionnaire (KCCQ)

clinical summary score (CSS) at week 24

- Proportion of patients with equal or larger than 5 points change in KCCQ CSS

at week 24

- Improvement in NYHA functional class at week 24

- Improvement in symptoms as assessed by the SF-36 physical component summary

(PCS) score at week 24.

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%. 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 (CAO). 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 CAO.
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.

Study objective

The primary objectives of this study are:
- To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in reducing NT proBNP from baseline after 12 weeks of treatment in patients with HFpEF.
- To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in improving exercise capacity as assessed by the six-minute walk test (6MWT) at Week 24 in a subset of patients

Secundary:
To compare LCZ696 to individualized medical therpay for comorbidities for:
- Mean change from baseline in Kansas City Cardiomyophathy Questionnaire (KCCQ) clinical summary score (CSS) at week 24
- proportion of patients with equal or larger than 5 points change in KCCQ CSS at week 24
- improvement in NYHA functional class at week 24
- Improvement in symptoms as assessed by the SF-36 physical component summary (PCS) score at week 24.

Study design

Multi-center ,randomized, double-blind, parallel group phase Ill study with active comparator.
Screening period of up to 2 weeks.
Randomisation is determined by the treatment, which the patient receives before start of the study:
When previously treated with ACE, randomisation will be between enalapril/LCZ696.
When previously treated with valsartan/ARB, then valsartan/LCZ696
When no previous treatment with ACE or ARB has been given, it will be between LCZ/placebo.
Blinding will be maintained because all parties involved will not know whether LCZ or comparator will be provided.

Treatment will be twice daily:
LCZ696: 200 mg
Valsartan: 160 mg
Enalapril: 10 mg
Matching Placebo

Back-titration if dose is not tolerated.
Continuation of reguiar treatment against heart failure (except ACE-, angiotensin - and renin inhibitors)
Total study duration estimated at 26 weeks
Approx 2500 patients.

No added risk will be applicable for subjects in the Placebogroup, since regular therapy will be continued. When subjects will be placed in the placebogroup, no risk of undertreatment is applicable, since their treatment will be continued. When the subjects are placed in the LCZ696 group, a treatment will be added.
At this timepoint, no study has proven ACE/ARB to be of additional value for HF-pEF. ACE/ARB is routinely prescribed for other reasons (mainly hypertension). When this is not applicable, a more conservative treatment with diuretics etc is chosen.

Intervention

Treatment with LCZ696, enalapril, valsartan or placebo.

Study burden and risks

Adverse effects of study medication and study procedures.
Change of HF medication.

- Physical examination 9x
- Vital signs: 9x

- Blood draw (10-12 ml}:9x
- Pregnancy test, if applicable (in urine/plasma): 9x
- ECG: 3x
- Echocardiogram:1x
- Completion of questionnaires: 6x
- 6MWT: 4x

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Left ventricular ejection fraction (LVEF) >40% by echo within 6 months prior to study entry or during the screening epoch
- Symptom(s) of heart failure (HF) requiring treatment with diuretics (including loop, or thiazide diuretics, or mineralocorticoid antagonist [MRAs]) for at least 30 days prior to study

entry
- NYHA class II-IV
- Structural heart disease (left atrial enlargement or left ventricular hypertrophy) documented by echocardiogram.
- NT-proBNP > 220 pg/mL for patients with no atrial fibrillation/atrial flutter (AF) or >600 pg/mL for patients with AF
- KCCQ clinical summary score < 75
- Patients on ACEi or ARB therapy must have a history of hypertension;Other protocol-defined inclusion criteria may apply.

Exclusion criteria

- Any prior measurement of LVEF *40% under stable conditions
- Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery within 3 months , or urgent percutaneous coronary intervention (PCI) within 3 months or an elective PCI within 30 days prior to study entry
- Any clinical event within the 6 months prior to Visit 1 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 > 40%
- Current (within 30 days from visit 1) acute decompensated HF requiring therapy.
- Current (within 30 days from visit 1) use of renin inhibitor(s), dual RAS blockade or LCZ696
- History of hypersensitivity to LCZ696 or its components
- Patients with a known history of angioedema
- Walk distance primarily limited by non-cardiac comorbid conditions at visit 1
- Alternative reason for shortness of breath such as: significant pulmonary disease or severe COPD, hemoglobin (Hgb) <10 g/dL males and < 9.5 g/dL females, or body mass index (BMI)> 40 kg/m2.
- Systolic blood pressure (SBP) * 180 mmHg at study entry, or SBP >150 mmHg and <180 mmHg at study entry unless the patient is receiving 3 or more antihypertensive drugs, or SBP <110 mmHg at study entry.
- Patients with HbA1c >7.5% not treated for diabetes
- eGFR<15 ml/min/1.73 m2 as measured by MDRD at screening
- Serum potassium > 5.2 mmol /L (or equivalent plasma potassium value) at study entry
- History or presence of any other disease with a life expectancy of <3 years
- Pregnant or nursing women or women of childbearing potential unless they are using highly effective methods of contraception.
Other protocol-defined exclusion criteria may apply.

Study design

Design

Study phase:	3
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):	27-03-2018
Enrollment:	60
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
Product type:	Medicine
Brand name:	Renitec
Generic name:	enalapril
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	18-10-2017

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-01-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-01-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-04-2018
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:	15-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-04-2019
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	EUCTR2016-003410-28-NL
ClinicalTrials.gov	NCT03066804
CCMO	NL62777.100.17