NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Sacubitril/valsartan (LCZ696)

Trial Indication(s)

Heart failure with reduced ejection fraction

Protocol Number

CLCZ696BDE01

Protocol Title

A randomized, double-blind, active-controlled study to assess the effect of LCZ696 compared with enalapril to improve exercise capacity in patients with heart failure with reduced ejection fraction (HFrEF).

Clinical Trial Phase

Phase 4

Phase of Drug Development

Phase 4

Study Start/End Dates

Study Start Date: July 2016 (Actual)
Primary Completion Date: November 2019 (Actual)
Study Completion Date: November 2019 (Actual)

Study Design/Methodology

This study was a randomized, double-blind, double-dummy, parallel-group, active-controlled, two-arm trial to compare LCZ696 200 mg twice daily (bid) to enalapril 10 mg bid in improving exercise capacity, daily physical activity and quality of life in patients with stable chronic heart failure (New York Heart Association III) and reduced left ventricular ejection fraction (LVEF ≤ 40%).

The study consisted of a screening period of 2 weeks during which the subject's eligibility for the study was assessed followed by a double blind treatment period of 12 weeks. Eligible subjects were randomized 1:1 to receive either LCZ696 or enalapril during the double-blind period. Treatment was initiated with LCZ696 100 mg bid or enalapril 5 mg bid (enalapril 10 mg bid for patients at a stable daily dose of enalapril above 10 mg per day or corresponding doses of other angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) prior first screening visit), respectively. Dose was up-titrated after 2 weeks to the final dose of LCZ696 200 mg bid or enalapril 10 mg bid.

Patients continued to take their background medications for chronic heart failure during the study, with the exception of ACEI or ARBs which were replaced by investigational treatment and had to be discontinued before first dose of study drug.

Centers

Germany(34)

Objectives:

The primary objective was to demonstrate the superiority of LCZ696 200 mg bid compared to enalapril 10 mg bid in improving exercise tolerance (peak respiratory oxygen uptake (VO2peak), adjusted to body weight) as assessed by cardio-pulmonary-exercise testing (CPET) in patients with stable chronic heart failure (NYHA III) and reduced ejection fraction (LVEF ≤ 40%) after 3 months treatment.

Secondary objectives were:

- To demonstrate the superiority of LCZ696 versus enalapril regarding the improvement of exercise tolerance (VO2peak, adjusted to body weight) as assessed by CPET in patients with CHF after 6 weeks of treatment (key secondary objective).
- To compare LCZ696 versus enalapril on the following CPET parameters:
  - Change of VE/VCO2 slope after 6 weeks and after 3 months
  - Change in exercise capacity (watt) at VAT after 6 weeks and after 3 months
  - Rate of perceived exertion during exercise (Borg scale) after 3 months
- To assess the safety and tolerability of LCZ696 in patients with stable CHF with NYHA class III and reduced ejection fraction (LVEF ≤ 40%)

Test Product (s), Dose(s), and Mode(s) of Administration

LCZ696 (sacubitril/valsartan) was supplied as tablets at dose strength of 50 mg, 100 mg and 200mg. Participants received LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.

Enalapril was supplied as tablets of 2.5 mg, 5 mg and 10 mg dose strengths. Participants received enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.

Statistical Methods

The primary analysis was performed comparing treatments with respect to the primary efficacy variable in an analysis of covariance (ANCOVA) model with the factors treatment and center and baseline VO2 peak as a covariate. The raw as well as the adjusted (Least Squares) group means were presented. Additionally, a 95% confidence interval and a p-value were given for the treatment contrast.

The key secondary endpoint was analyzed using the same model that was used for the primary endpoint. The significance level was not adjusted for multiplicity, the result of the test for Week 6 was regarded as providing confirmatory evidence, only if the test of the primary hypothesis (Month 3) was also significant (a-priori ordered hypotheses).

Secondary efficacy variables were analyzed using ANCOVA models analogous to the analysis of the primary endpoint.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Patients with a diagnosis of chronic heart failure (NYHA class III) and reduced ejection fraction (LVEF ≤ 40%)
- Reduced ability to exercise, evidenced by VO2peak ≤ 18 ml/min per kg
- Patients had to be on an ACEI or an ARB at a stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks prior to the screening visit and until randomization visit.

Exclusion Criteria:
-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 the study drugs
- Previous history of intolerance to recommended target doses of ACEIs or ARBs
- Known history of angioedema
- Requirement of treatment with both ACEIs and ARBs
- Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy)
- Symptomatic hypotension
- Impaired renal function
- Pregnant or nursing (lactating) women

Participant Flow Table

Overall Study

	LCZ696	Enalapril	Total
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.	
Started	103	98	201
Completed	99	91	190
Not Completed	4	7	11
Adverse Event	1	4	5
Death	2	1	3
Non-compliance with study treatment	0	1	1
Subject/guardian decision	1	0	1
Withdrawal of informed consent	0	1	1

Baseline Characteristics

	LCZ696	Enalapril	Total
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.	
Number of Participants [units: participants]	103	98	201
Age Continuous (units: Years) Mean ± Standard Deviation			
	66.1±10.792	67.6±9.961	66.9±10.396
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	17	21	38
Male	86	77	163
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)			
Caucassian	101	96	197
Black	0	1	1
Other	2	1	3

Primary Outcome Result(s)

Change from baseline in peak respiratory oxygen uptake (VO2peak) adjusted to body weight) after 3 months of treatment

(Time Frame: Baseline, 3 months)

	LCZ696	Enalapril
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Number of Participants Analyzed [units: participants]	98	90
Change from baseline in peak respiratory oxygen uptake (VO2peak) adjusted to body weight) after 3 months of treatment (units: mL/kg/min) Least Squares Mean ± Standard Error		
	0.51 ± 0.180	0.19 ± 0.188

Statistical Analysis

Groups	LCZ696, Enalapril
P Value	0.2327
Method	ANCOVA
Other Least Squares (LS) Mean	0.32
Standard Error of the mean	0.268

95 % Confidence Interval 2-Sided	-0.21 to 0.85

Secondary Outcome Result(s)

Change from baseline in peak respiratory oxygen uptake (VO2peak) adjusted to body weight) after 6 weeks of treatment

(Time Frame: Baseline, 6 weeks)

	LCZ696	Enalapril
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Number of Participants Analyzed [units: participants]	97	88
Change from baseline in peak respiratory oxygen uptake (VO2peak) adjusted to body weight) after 6 weeks of treatment (units: mL/kg/min) Least Squares Mean ± Standard Error		
	0.28 ± 0.185	0.42 ± 0.195

Statistical Analysis

Groups	LCZ696, Enalapril
P Value	0.6247
Method	ANCOVA

Other LS Mean	-0.14
Standard Error of the mean	0.277
95 % Confidence Interval 2-Sided	-0.68 to 0.41

Change from baseline in the minute ventilation (VE) to carbon dioxide output slope (VE/VCO2 slope)

(Time Frame: Baseline, 6 weeks, 3 months)

	LCZ696	Enalapril
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Number of Participants Analyzed [units: participants]	103	98
Change from baseline in the minute ventilation (VE) to carbon dioxide output slope (VE/VCO2 slope) (units: no units) Least Squares Mean ± Standard Error		
6 weeks	-1.05 ± 0.597	0.18 ± 0.629
3 months	0.76 ± 0.542	-0.07 ± 0.575

Statistical Analysis

Groups	LCZ696, Enalapril	6 weeks
P Value	0.1678	
Method	ANCOVA	
Other LS Mean	-1.23	
Standard Error of the mean	0.888	
95 % Confidence Interval 2-Sided	-2.98 to 0.52	

Statistical Analysis

Groups	LCZ696, Enalapril	3 months
P Value	0.3052	
Method	ANCOVA	
Other LS Mean	0.83	
Standard Error of the mean	0.809	
95 % Confidence Interval 2-Sided	-0.77 to 2.43	

Change from baseline in exercise capacity (watt) at ventilatory anaerobic threshold (VAT)

(Time Frame: Baseline, 6 weeks, 3 months)

	LCZ696	Enalapril
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Number of Participants Analyzed [units: participants]	103	98
Change from baseline in exercise capacity (watt) at ventilatory anaerobic threshold (VAT) (units: Watt) Least Squares Mean ± Standard Error		
6 weeks	1.71 ± 1.168	0.83 ± 1.234
3 months	2.45 ± 1.436	-0.83 ± 1.483

Statistical Analysis

Groups	LCZ696, Enalapril	6 weeks
P Value	0.6181	
Method	ANCOVA	
Other LS Mean	0.87	
Standard Error of the mean	1.744	
95 % Confidence Interval 2-Sided	-2.58 to 4.32	

Statistical Analysis

Groups	LCZ696, Enalapril	3 months
P Value	0.1254	
Method	ANCOVA	
Other LS Mean	3.28	
Standard Error of the mean	2.124	
95 % Confidence Interval 2-Sided	-0.93 to 7.48	

Change from baseline in rate of perceived exertion (perceived dyspnea and perceived fatigue) during exercise assessed by Borg scale

(Time Frame: Baseline, 3 months)

	LCZ696	Enalapril
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Number of Participants Analyzed [units: participants]	103	98
Change from baseline in rate of perceived exertion (perceived dyspnea and perceived fatigue) during exercise assessed by Borg scale (units: Score on scale) Least Squares Mean ± Standard Error		
Borg value perceived dyspnea	-0.19 ± 0.212	0.11 ± 0.223

Borg value perceived fatigue	-0.04 ± 0.167	-0.20 ± 0.178

Statistical Analysis

Groups	LCZ696, Enalapril	Borg value dyspnea
P Value	0.3432	
Method	ANCOVA	
Other LS Mean	-0.30	
Standard Error of the mean	0.317	
95 % Confidence Interval 2-Sided	-0.93 to 0.33	

Statistical Analysis

Groups	LCZ696, Enalapril	Borg value fatigue
P Value	0.5319	
Method	ANCOVA	
Other LS Mean	0.16	
Standard Error of the mean	0.251	
95 % Confidence Interval 2-Sided	-0.34 to 0.65	

Safety Results

All-Cause Mortality

	LCZ696 N = 103	Enalapril N = 98
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Total participants affected	2 (1.94%)	1 (1.02%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days (16 weeks on average).
Additional Description	Any signs or symptoms that occurs during study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment

	LCZ696 N = 103	Enalapril N = 98
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per

		day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Total participants affected	12 (11.65%)	14 (14.29%)
Cardiac disorders		
Acute myocardial infarction	1 (0.97%)	0 (0.00%)
Angina pectoris	1 (0.97%)	0 (0.00%)
Aortic valve incompetence	1 (0.97%)	0 (0.00%)
Atrial fibrillation	2 (1.94%)	1 (1.02%)
Atrial flutter	0 (0.00%)	1 (1.02%)
Atrial tachycardia	0 (0.00%)	1 (1.02%)
Atrial thrombosis	0 (0.00%)	1 (1.02%)
Bradycardia	0 (0.00%)	1 (1.02%)
Cardiac failure	1 (0.97%)	2 (2.04%)
Cardiogenic shock	0 (0.00%)	1 (1.02%)
Coronary artery disease	1 (0.97%)	0 (0.00%)
Tachycardia	1 (0.97%)	0 (0.00%)
Ventricular tachycardia	2 (1.94%)	0 (0.00%)
Gastrointestinal disorders		
Pancreatitis	0 (0.00%)	1 (1.02%)
General disorders and administration site conditions		
Non-cardiac chest pain	0 (0.00%)	1 (1.02%)

Vascular stent occlusion	0 (0.00%)	1 (1.02%)
Infections and infestations		
Appendicitis	1 (0.97%)	0 (0.00%)
Gastroenteritis norovirus	1 (0.97%)	0 (0.00%)
Pneumonia	2 (1.94%)	0 (0.00%)
Septic shock	1 (0.97%)	0 (0.00%)
Injury, poisoning and procedural complications		
Contusion	0 (0.00%)	1 (1.02%)
Investigations		
Angiocardiogram	0 (0.00%)	1 (1.02%)
International normalised ratio abnormal	1 (0.97%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Glioblastoma	0 (0.00%)	1 (1.02%)
Nervous system disorders		
Seizure	0 (0.00%)	1 (1.02%)
Syncope	0 (0.00%)	2 (2.04%)
Renal and urinary disorders		
Renal failure	0 (0.00%)	1 (1.02%)

Respiratory, thoracic and mediastinal disorders		
Dyspnoea	1 (0.97%)	1 (1.02%)
Pleural effusion	0 (0.00%)	1 (1.02%)
Vascular disorders		
Hypotension	1 (0.97%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days (16 weeks on average).
Additional Description	Any signs or symptoms that occurs during study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LCZ696 N = 103	**Enalapril N = 98**
Arm/Group Description	LCZ696 100 mg oral twice daily (bid) for 2 weeks followed by LCZ696 200 mg oral bid for 10 weeks.	Enalapril 5 mg oral twice daily (bid) for 2 weeks followed by enalapril 10 mg oral bid for 10 weeks. Patients who prior Screening were at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) started the study at a dose of enalapril 10 mg bid.
Total participants affected	52 (50.49%)	36 (36.73%)

General disorders and administration site conditions		
Fatigue	2 (1.94%)	7 (7.14%)
Infections and infestations		
Nasopharyngitis	9 (8.74%)	3 (3.06%)
Metabolism and nutrition disorders		
Hyperkalaemia	9 (8.74%)	3 (3.06%)
Nervous system disorders		
Dizziness	14 (13.59%)	6 (6.12%)
Respiratory, thoracic and mediastinal disorders		
Cough	3 (2.91%)	9 (9.18%)
Dyspnoea	2 (1.94%)	6 (6.12%)
Vascular disorders		
Hypotension	27 (26.21%)	11 (11.22%)

Conclusion:

The primary endpoint of this study, the increase in VO2peak (adjusted to body weight) was numerically higher in the LCZ696 group compared to the enalapril group at month 3. However, this difference was not large enough to reach statistical significance, therefore, the study did not meet its primary endpoint.

The treatment difference in VO2peak (adjusted to body weight) at week 6 was not statistically significant, therefore, the study did not meet the key secondary endpoint. There was also no statistically significant treatment difference in the change from baseline for VE/VCO2 slope or for exercise capacity (watt) at VAT at either time point. Perceived exertion (fatigue and dyspnea based on the Borg scale) during the assessment was similar in the LCZ696-treated and the enalapril-treated groups at baseline and at both time points.

The overall safety of LCZ696 in this study was consistent with the well-established safety profile in patients with heart failure with reduced ejection fraction in previous studies. No new or unexpected safety signals or changes in the known frequency of AEs were identified that would alter the current benefit-risk assessment of LCZ696.

Date of Clinical Trial Report

13-Aug-2020